Canadian Journal of Diabetes

Canadian Diabetes Association
2008 Clinical Practice Guidelines
for the Prevention and Management
of Diabetes in Canada

A Publication of the Professional Sections of the Canadian Diabetes Association

Canadian
Diabetes
Association

Canadian Journal of Diabetes

Canadian Diabetes Association
2008 Clinical Practice Guidelines
for the Prevention and Management
of Diabetes in Canada

TABLE OF CONTENTS

Canadian Diabetes Association 2008 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada

Diabetes in Children

Diabetes in Special Populations

Appendices

NOTES TO READERS

Overview
The Canadian Diabetes Association 2008 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada are intended to guide practice and are not intended to serve as a comprehensive text of diabetes management, nor are they intended to set criteria for research protocols. These guidelines are intended to inform general patterns of care. These guidelines are also intended to enhance diabetes prevention efforts in Canada and to reduce the burden of diabetes complications in people living with this disease.

As per the Canadian Medical Association *Handbook on Clinical Practice Guidelines* (Davis D, et al. Ottawa, ON: Canadian Medical Association; 2007), guidelines should not be used as a legal resource in malpractice cases as "their more general nature renders them insensitive to the particular circumstances of the individual cases." Healthcare professionals must consider the needs, values and preferences of individual patients, use clinical judgement, and work with available human and healthcare service resources in their settings. These guidelines were developed using the best available evidence. It is incumbent upon healthcare professionals to stay current in this rapidly changing field.

Unless otherwise specified, these guidelines pertain to the care of adults with diabetes. Two chapters – "Type 1 Diabetes in Children and Adolescents" and "Type 2 Diabetes in Children and Adolescents" – are included to highlight aspects of care that must be tailored to the pediatric population.

Suggested Citation
Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. *Can J Diabetes.* 2008;32(suppl 1): S1-S201.

Reproduction of the Guidelines
Reproduction of the Canadian Diabetes Association 2008 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada in whole or in part is prohibited without written consent of the publisher.

Extra Copies
Copies of this document may be ordered, for a nominal fee, from the Canadian Diabetes Association. Please dial 1-800-BANTING or visit orders.diabetes.ca.

Website
These guidelines are available at http://www.diabetes.ca.

2008 Clinical Practice Guidelines Committees

The Canadian Diabetes Association 2008 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada were developed under the auspices of the Clinical & Scientific Section of the Canadian Diabetes Association. The following committee members contributed to these guidelines. Committee members were volunteers and received no remuneration or honoraria for their participation.

Executive Committee

Lori D. Berard RN CDE
Advisor
Nurse Manager, Health Sciences Centre, Diabetes Research
  Group, Winnipeg, Manitoba

Gillian Booth MD MSc FRCPC
Sub-group Chair, Methods
Division of Endocrinology and Metabolism and Li Ka Shing
  Institute, St. Michael's Hospital and University of
  Toronto, Toronto, Ontario

Sarah Capes MD MSc FRCPC
Staff, Vancouver Island Health Authority, Victoria,
  British Columbia

Karie Quinn RD CDE
Grand Prairie, Alberta

Vincent Woo MD FRCPC *(Chair)*
Health Sciences Centre, University of Manitoba,
  Winnipeg, Manitoba

Steering Committee

Alice Y.Y. Cheng MD FRCPC
Advisor
Division of Endocrinology and Metabolism,
  St. Michael's Hospital and Credit Valley Hospital,
  University of Toronto, Toronto, Ontario

Maureen Clement MD CCFP
Advisor
Medical Director, Diabetes Education,
  Vernon Jubilee Hospital; Assistant Clinical Professor,
  University of British Columbia, Vernon, British Columbia

Keith Dawson MD PhD FRCPC
Advisor
Professor of Medicine (Emeritus), University
  of British Columbia, Vancouver, British Columbia

Amir Hanna MB BCh FRCPC
Sub-group Chair, Management
Professor Emeritus, Department of Medicine, University of
  Toronto, and St. Michael's Hospital, Toronto, Ontario

William Harper MD FRCPC
Advisor
Associate Professor of Medicine, McMaster University,
  Hamilton, Ontario

Stewart B. Harris MD MPH FCFP FACPM
Advisor
Professor of Medicine, Department of Family Medicine,
  University of Western Ontario, London, Ontario

Robyn Houlden MD FRCPC
Sub-group Chair, Management
Professor, Division of Endocrinology,
  Queen's University, Kingston, Ontario

Dereck Hunt MD MSc FRCPC
Methods
Associate Professor, McMaster University,
  Hamilton, Ontario

Helen Jones RN MSN CDE
Advisor
Clinical Nurse Specialist/Manager, Leadership
  Sinai Centre for Diabetes, Mount Sinai Hospital
  and University of Toronto, Toronto, Ontario

Margaret L. Lawson MSc MD FRCPC
Sub-group Chair, Diabetes in Children and Adolescents
Associate Professor of Pediatrics, University of Ottawa;
  Division of Endocrinology and Metabolism, Children's
  Hospital of Eastern Ontario, Ottawa, Ontario

Lawrence A. Leiter MD FRCPC FACP
Sub-group Chair, Macrovascular Complications
Professor of Medicine and Nutritional Sciences, University
  of Toronto; Head, Division of Endocrinology and
  Metabolism, St. Michael's Hospital, Toronto, Ontario

David M. Thompson MD FRCPC
Sub-group Chair, Diabetes and Pregnancy
  Diabetes in Pregnancy Clinic, BC Women's Hospital,
  Vancouver, British Columbia

Ehud Ur MB FRCP
Sub-group Chair, Definition, Classification,
Diagnosis of Diabetes and Other Dysglycemic Categories
Professor of Medicine, University of British Columbia,
  Vancouver, British Columbia

Jean-François Yale MD CSPQ
Sub-group Chair, Microvascular Complications
Professor of Medicine, McGill University, Montreal,
  Quebec

Expert Committee

Filiberto Altomare MD FRCSC
Department of Ophthalmology and Vision Sciences,
  St. Michael's Hospital, University of Toronto,
  Toronto, Ontario

J. Malcolm O. Arnold MD FRCPC FRCP FACC
Professor of Medicine, Physiology, Pharmacology,
  University of Western Ontario, London Health Sciences
  Centre, London, Ontario

Nicole Aylward RD CDE
Winnipeg, Manitoba

Richard Bebb MD ABIM FRCPC
Clinical Assistant Professor, University of British Columbia,
  Vancouver, British Columbia

Ian Blumer MD FRCPC
Sub-group Chair, Dissemination Committee
Charles H. Best Diabetes Centre, Ajax, Ontario

Keith Bowering MD FRCPC FACP
Clinical Professor of Medicine, Division of Endocrinology,
  University of Alberta, Edmonton, Alberta

Shelley R. Boyd MD FRCSC DABO
Clinician-Scientist, Assistant Professor, Department of
  Ophthalmology & Vision Sciences, St. Michael's Hospital,
  University of Toronto, Toronto, Ontario

Sharon Brez RN BScN MA(Ed) CDE
Advanced Practice Nurse, Endocrinology and Metabolism,
  The Ottawa Hospital, Ottawa, Ontario

Vera Bril MD FRCPC
Professor of Medicine, Head, Division of Neurology,
  University Health Network / Mount Sinai Hospital,
  University Health Network, University of Toronto,
  Toronto, Ontario

Gerald Brock MD FRCPC
Professor of Surgery, University of Western Ontario,
  London, Ontario

Jean-Louis Chiasson MD
Professor of Medicine, Université de Montréal,
  Montreal, Quebec

Bruce Culleton MD FRCPC
Clinical Associate Professor, Foothills Hospital,
  Calgary, Alberta

David Dannenbaum MD CCFP
Medical Advisor, Chronic Disease Prevention,
  Cree Board of Health and Social Services of James Bay,
  Montreal, Quebec

Jean-Pierre Després PhD
Director of Research, Cardiology,
  Hôpital Laval Research Centre, Quebec, Quebec

Denis Drouin MD
Consultant in Public Health, Clinical Professor of Family
  Medicine, Laval University Faculty of Medicine, Associate
  Director of the Continuing Professional Development
  Centre, Quebec, Quebec

Peggy Dunbar MEd PDt CDE
Coordinator, Diabetes Care Program of Nova Scotia,
  Halifax, Nova Scotia

Alun Edwards MB MRCP(UK) FRCPC
Associate Professor and Head, Division of Endocrinology
  and Metabolism, University of Calgary and Calgary
  Health Region, Calgary, Alberta

Jean-Marie Ekoé MD CSPQ
Professor of Medicine, Endocrinology, Metabolism,
  Nutrition, CHUM, Hôtel-Dieu Hospital,
  Montreal, Quebec

Denice Feig MD MSc FRCPC
Associate Professor, University of Toronto, Staff
 Endocrinologist, Mount Sinai Hospital, Toronto, Ontario

David Fitchett MD FRCPC
Associate Professor of Medicine, University of Toronto,
 Toronto, Ontario

Jacques Genest MD FRCPC
Montreal, Quebec

Jeannette Goguen MD FRCPC
Assistant Professor, University of Toronto, St. Michael's
 Hospital, Toronto, Ontario

Réjeanne Gougeon PhD
Associate Professor, McGill Nutrition and Food Science
 Centre, Montreal, Quebec

Peter Hall PhD
Assistant Professor, University of Waterloo, Waterloo,
 Ontario

Elisabeth Harvey RNEC MScN
London, Ontario

Michael D. Hill MD
University of Calgary, Calgary, Alberta

Maryann Hopkins BSP CDE
Clinical Pharmacist, The Ottawa Hospital, Ottawa, Ontario

S. Ali Imran MBBS FRCP(Edin) FRCPC
Halifax, Nova Scotia

Jacqueline James MD MEd FRCPC
Associate Professor of Medicine, Division of Endocrinology
 and Metabolism, Mount Sinai Hospital, Toronto, Ontario

Jeffrey A. Johnson PhD
Department of Public Health Sciences, School of Public
 Health, University of Alberta, Edmonton, Alberta

Tina Kader MD FRCPC CDE
Assistant Professor Endocrinology and Internal Medicine,
 Jewish General Hospital, Montreal, Quebec

Timothy P. Kalla BSc DPM FACFAS
Clinical Instructor, University of British Columbia; BC's
 Foot & Ankle Clinic, Providence Health Care, Vancouver,
 British Columbia

Erin Keely MD FRCPC
Chief, Division of Endocrinology and Metabolism, Ottawa
 Hospital; Professor, University of Ottawa, Department of
 Medicine / Obstetrics and Gynecology, Ottawa, Ontario

Glen Kenny PhD
Full Professor and University Research Chair, University
 of Ottawa, Faculty of Health Sciences School of Human
 Kinetics, Affiliate Investigator, Ottawa Health Research
 Institute, Associate Investigator: Institute of Population
 Health, Ottawa, Ontario

Sharon E. Kozak BSN
Vancouver, British Columbia

Maria Kraw MD MHSc FRCPC
Assistant Professor, St. Michael's Hospital, Toronto, Ontario

Pierre LaRochelle MD PhD FRCPC
Director, Clinical Research, Institut de Recherches
 Cliniques de Montreal; Professor, Department of
 Pharmacology, Université de Montréal; Chief, Internal
 Medicine Service, Centre Hospitalier de l'Université de
 Montréal, Montreal, Quebec

David Lau MD PhD FRCPC
Departments of Medicine, Biochemistry and Molecular
 Biology and Julia McFarlane Diabetes Research Centre,
 University of Calgary, Calgary, Alberta

Gary Lewis MD FRCPC
Professor, Departments of Medicine and Physiology,
 University of Toronto, Toronto General Hospital,
 Toronto, Ontario

Sora Ludwig MD FRCPC
Associate Professor, Section of Endocrinology and
 Metabolism, Department of Internal Medicine, University
 of Manitoba, Medical Advisor, Diabetes and Chronic
 Diseases Branch, Manitoba Health, Winnipeg, Manitoba

Lori MacCallum BScPharm PharmD
Assistant Professor, Leslie Dan Faculty of Pharmacy,
 University of Toronto, Clinical Pharmacy Specialist,
 Diabetes Comprehensive Care Program, St. Michael's
 Hospital, Toronto, Ontario

Charlotte McDonald MD FRCPC
Assistant Professor, University of Western Ontario,
 London, Ontario

Philip McFarlane MD PhD FRCPC
Medical Director, Home Dialysis, Division of Nephrology,
St. Michael's Hospital, University of Toronto,
Toronto, Ontario

Ruth McPherson MD PhD FRCPC
Professor, Department of Medicine, University of Ottawa
Heart Institute, Ottawa, Ontario

Graydon Meneilly MD FRCPC FACP
Professor and Head, Department of Medicine, University
of British Columbia, Vancouver, British Columbia

Beth Mitchell PhD
Director, Mental Health Program, London Health Sciences
Centre, London, Ontario

Heather Nichol RN MScN CDE
Clinical Nurse Specialist, British Columbia's Children's
Hospital, Vancouver, British Columbia

Paul Oh MD MSc FRCPC
Toronto Rehabilitation Institute, Toronto, Ontario

Danièle Pacaud MD FRCPC
Pediatric Endocrinologist, Associate Professor, Department
of Pediatrics, University of Calgary, Calgary, Alberta

Constadina Panagiotopoulos MD FRCPC
Assistant Professor, University of British Columbia,
Vancouver, British Columbia

Breay W. Paty MD FRCPC
Clinical Associate Professor, University of British Columbia,
Vancouver, British Columbia

Bruce A. Perkins MD MPH FRCPC
Assistant Professor, Department of Medicine (Division of
Endocrinology), University Health Network and Mount
Sinai Hospital, University of Toronto, Toronto, Ontario

Ronald C. Plotnikoff PhD
Edmonton, Alberta

Paul Poirier MD PhD FRCPC FACC FAHA
Director of Cardiac Prevention/Rehabilitation Program,
Institut de cardiologie et de pneumologie de l'Hôpital
Laval, Quebec City, Quebec

Denis Prud'homme MD MSc
Ottawa, Ontario

Simon Rabkin MD FRCPC FACC
Professor of Medicine, University of British Columbia,
Vancouver, British Columbia

Tom Ransom MD MSc FRCPC
Halifax, Nova Scotia

Cindy Jo Richardson MD FRCPC
Assistant Professor, Section of Endocrinology and
Metabolism, University of Manitoba, Winnipeg, Manitoba

Michael C. Riddell PhD
Associate Professor, School of Kinesiology and Health
Science, Faculty of Science and Engineering, York
University, Toronto, Ontario

Stuart Ross MBCLB RACP FRCPC
Clinical Professor of Medicine, University of Calgary,
Calgary, Alberta

Richard Rowe MBBS MAEd FRCPC
Professor of Medicine, Section of Endocrinology and
Metabolism, University of Manitoba, Winnipeg, Manitoba

Edmond A. Ryan MD FRCPC
Professor, University of Alberta, Edmonton, Alberta

Elizabeth Sellers MD MSc FRCPC
Associate Professor, Pediatrics and Child Health, University
of Manitoba, Winnipeg, Manitoba

Ronald Sigal MD MPH FRCPC
Associate Professor of Medicine, Cardiac Sciences,
Kinesiology and Community Health Sciences,
University of Calgary, Calgary, Alberta

Barry Simon MD FRCP
Assistant Professor of Psychiatry, University of Toronto,
Mount Sinai Hospital, Toronto, Ontario

Scot Simpson BSP PharmD MSc
Assistant Professor, Faculty of Pharmacy and
Pharmaceutical Sciences, University of Alberta,
Edmonton, Alberta

Parmjit Sohal MD PhD CCFP
Surrey, British Columbia

George Steiner MD FRCPC
Toronto General Hospital, University of Toronto, Toronto,
Ontario

Daniel Tessier MD MSc
Professor, Geriatrics, Department of Medicine, Faculty of
  Medicine, Sherbrooke University, Sherbrooke, Quebec

Sheldon Tobe MD FRCPC
Division of Nephrology, Sunnybrook Health Sciences
  Centre, University of Toronto, Toronto, Ontario

Guy Tremblay MD FRCPC
Professeur de clinique Médecine, Université Laval, Quebec,
  Quebec

Diane Wherrett MD FRCPC
Assistant Professor, Hospital for Sick Children and
  University of Toronto, Toronto, Ontario

Dana Whitham MSc RD CDE
Clinical Dietitian, St. Michael's Hospital, Toronto, Ontario

Jay Wortman MD
Senior Medical Advisor, First Nations and Inuit Health,
  Health Canada, Vancouver, British Columbia

Staff

Donna Lillie RN BA
Senior Vice President, Research, Professional Education
  & Government Affairs, Canadian Diabetes Association,
  Toronto, Ontario

Fiona Hendry BA
Director, Publications & Literature, Research, Professional
  Education & Government Affairs Department, Canadian
  Diabetes Association, Toronto, Ontario

Patti Sayle BA
Publications Coordinator, Research, Professional Education
  & Government Affairs Department, Canadian Diabetes
  Association, Toronto, Ontario

Elizabeth Neilly BA
Coordinator, Administrative Services, Research,
  Professional Education & Government Affairs
  Department, Canadian Diabetes Association,
  Toronto, Ontario

Karen Philp DPhil (Oxon)
Vice President, Public Policy & Government Relations,
  Canadian Diabetes Association, Toronto, Ontario

Consultants

Cindy Campbell BA
Executive Editor
Toronto, Ontario

Cynthia N. Lank BSc
Consulting Editor
Halifax, Nova Scotia

Angela Eady MLS
Medical Librarian
Hamilton, Ontario

Comet art + design
Art Direction
Toronto, Ontario

Jeanne McKane MLitt ELS
Copy Editor, Proofreader
Toronto, Ontario

Joanne Auchinachie BA
Proofreader
Brantford, Ontario

Ruth Hanley BJ
Proofreader
Toronto, Ontario

Acknowledgements

Canadian Journal of Diabetes

Official Journal of the Professional Sections of the Canadian Diabetes Association

Mandate
The mission of the Canadian Journal of Diabetes is to promote the sharing of multidisciplinary research and evidence-based knowledge, from clinical science to public health and education, which leads to advances in the care of diabetes.

Introduction

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Vincent Woo MD FRCPC

Since the publication of the 1998 Clinical Practice Guidelines for the Management of Diabetes in Canada, the Clinical & Scientific Section of the Canadian Diabetes Association has published comprehensive, evidence-based recommendations for healthcare professionals to consider in the management of their patients living with diabetes. In the 2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada, the evidence from the 1998 recommendations was completely reviewed, and recommendations on the prevention of type 2 diabetes were enhanced. In developing the 2008 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada, volunteers from the Clinical Practice Guidelines Expert Committee assessed the peer-reviewed evidence published since 2003 relevant to the prevention and management of diabetes, and then incorporated the evidence into revised diagnostic, prognostic and therapeutic recommendations for the care of Canadians living with diabetes, as well as recommendations for preventive measures for populations at high risk of developing type 2 diabetes.

A number of important changes have occurred in the development of the 2008 clinical practice guidelines. The Expert Committee has been expanded to include 76 volunteers, representing a broader variety of healthcare professionals from across Canada. Expert Committee members bring expertise from diverse practice settings, including multiple specialists, family physicians, nurses, dietitians, pharmacists and other healthcare professionals.

In addition to updating previous chapters, a number of new chapters have been added to the 2008 guidelines, widening their scope to other areas of diabetes care and complications. It is hoped that primary care physicians and other healthcare professionals who care for people with diabetes or those at risk of type 2 diabetes will continue to find the evidence compiled in these guidelines a vital aid and resource in their efforts. It is our hope that, ultimately, these guidelines will lead to improved quality of care, reduced morbidity and mortality from diabetes and its complications, and a better quality of life for people living with this chronic disease.

UPDATES

In the past, full updates of these guidelines have occurred every 5 years. However, chapter updates and position statements are produced on an "as needed" basis. These updates are posted on the Canadian Diabetes Association website at http://www.diabetes.ca and published in the *Canadian Journal of Diabetes.*

PATIENT ISSUES

People with diabetes are a diverse and heterogeneous group, and it must therefore be emphasized that treatment decisions must be individualized. Guidelines are meant to aid in decision making, but the therapeutic decisions are made at the level of the patient-physician relationship. Evidence-based guidelines try to weigh the benefit and harm of various treatments; however, patient preferences are not always included in clinical research, although quality-of-life assessments are becoming standard practice. It is important to remind healthcare professionals about the need to incorporate patient values and preferences into decision making (1).

THE CHALLENGE OF DIABETES

Diabetes is a serious condition with potentially devastating complications that affects all age groups worldwide. In 1985, an estimated 30 million people around the world were diagnosed with diabetes; in 2000, that figure rose to over 150 million, and it is projected to rise further to 380 million by 2025 (2). The International Diabetes Federation states that "every ten seconds, two people are diagnosed with diabetes somewhere in this world," and given the current trend, more people will have diabetes in 2025 than the current populations of the United States, Canada and Australia combined (3).

The impact of diabetes is felt in both developed and developing countries. For this reason, the 61st session of the United Nations General Assembly passed a resolution in 2007 recognizing November 14th as World Diabetes Day, and it encouraged all member states to develop national strategies and policies for the prevention, treatment and care of people with diabetes.

The impact of diabetes is also felt in Canada, where 1.8 million adult Canadians – 5.5% of the population – had diagnosed diabetes in 2005 (4). That is an increase from 1998, when the physician-diagnosed prevalence of diabetes in Canada was 4.8% (1 054 000 adult Canadians). Diagnosed diabetes has grown 70% since the publication of the 1998 Canadian Diabetes Association clinical practice guidelines. This number will continue to grow given Canada's demographic trends. An aging population, increasing immigration from high-risk populations and growth in the Aboriginal

population will increase the burden of diabetes over the next 10 years. Researchers project an increase of diagnosed diabetes in Canada to 2.4 million by the year 2016 (5).

The rate of diagnosed diabetes contributes significantly to comorbidity and diabetes complication rates. Diabetes is the leading cause of blindness, end-stage renal failure and non-traumatic amputation in Canadian adults. Cardiovascular disease, the leading cause of death in individuals with diabetes, occurs 2- to 4-fold more often compared to people without diabetes. Approximately one-quarter of Canadians living with diabetes are also diagnosed with depression, and the combination of diabetes and depression is associated with poor compliance with treatment and increased healthcare costs (6,7). Eleven percent of Canadians living with diabetes also have 3 or more chronic health conditions, and compared to the general population, they are 4 times more likely to be admitted to a hospital or a nursing home, 7 times more likely to need home care and 3 to 5 times more likely to see a healthcare provider (8).

Diabetes and its complications increase costs and service pressures on Canada's publicly funded healthcare system. Because of poor compliance to evidence-based recommended management regimens, diabetes and its complications significantly contribute to the cost of primary healthcare, and add to waiting times for treatment in emergency departments and surgeries. Research indicates that 280 330 admissions into Canadian acute care hospitals in 2006 – or 10% of all such admissions – were related to diabetes or its complications (9,10).

Caution is required when identifying direct, indirect and induced costs for treating diabetes, given the differing estimates by different researchers (11-15). Nonetheless, in 2005, federal, provincial and territorial governments spent an estimated $5.6 billion to treat people with diabetes and its complications within the acute healthcare system (5). This amount, equal to 10% of the annual cost of Canada's healthcare system, includes the cost of hospitalization for surgical and emergency care, in-hospital medications, devices and supplies, as well as physician and specialist visits. It does not include the costs of rehabilitation after major surgery or amputation, or the personal costs to the individual and family (e.g. a parent's inability to pay for a child's higher education).

Moreover, the trend of increased hospitalization has gone unchecked in the last 5 years. In Ontario, for example, research shows that little has changed in the rate of complications due to diabetes. Data analysis shows that approximately 4% of newly diagnosed diabetes patients end up in an emergency department or hospital for acute complications of their condition (16). The lack of change in the rate of complications suggests that despite the increasing evidence about the importance of managing diabetes effectively, little progress has been made in ensuring that people living with diabetes get the recommended care, education and management required to lower their risk of developing complications.

PREVENTION OF TYPE 2 DIABETES

Prevention of type 1 diabetes has not yet been successful; however, the evidence indicates that preventing or delaying the onset of type 2 diabetes results in significant health benefits, including lower rates of cardiovascular disease and renal failure; ~30 to 60% of type 2 diabetes may be prevented through early lifestyle or medication intervention (3).

The modifiable risk factors for type 2 diabetes are well known. By 2011, more than 50% of Canadians will be over 40 years of age and at risk for type 2 diabetes. Our lifestyles today contribute to unhealthy eating and physical inactivity. In 2005, 2 of 3 Canadian adults and nearly 1 of 3 children aged 12 to 17 years were overweight or obese (17), and are therefore at high risk of developing type 2 diabetes.

The Diabetes Prevention Program found that people at risk of developing type 2 diabetes were able to cut their risk by 58% with moderate physical activity (30 minutes a day) and weight loss (5 to 7% of body weight, or about 15 lb). For people over age 60, the risk was cut by almost 71% (18).

There remains an urgent and increasing need for governments to invest in research to define effective strategies and programs to prevent and treat obesity and to encourage physical activity. Health promotion and disease prevention strategies should be tailored to specific populations, and should include policies aimed at addressing poverty and other systemic barriers to health.

ADVOCACY AND OPTIMAL CARE

Effective diabetes care is supported by evidence-based clinical practice guidelines; regular monitoring of blood glucose, blood pressure and cholesterol levels; and ongoing feedback among all members of the diabetes health team to lower the risk and potential impact of serious complications for individuals with diabetes. Government investments in chronic disease management approaches offer an interdisciplinary approach recommended for effective diabetes care. A team of healthcare professionals – including physicians, nurses, diabetes educators, pharmacists and other healthcare experts who work together with the individual living with diabetes – is the recommended approach to achieve optimal care.

One of the key challenges of the chronic disease management approach for individuals living with diabetes is the greater level of self-management required in order for this approach to be effective. People with diabetes are asked to have the skills and abilities to reduce the physical and emotional impact of their disease, with or without the collaboration of their healthcare team. There is no question that self-management skills complement the expertise and care provided by members of the diabetes health team; however, the chronic disease management model is a paradigm shift from the traditional primary or acute care model. People with diabetes require training in goal setting, problem solving and planning skills, all of which are critical components of self-management. They also need access to a broad range

of tools, including medications, devices and supplies to help them achieve the recommended blood glucose, cholesterol and blood pressure targets. Health outcomes depend on managing the disease effectively, and without access to the necessary tools and strategies, Canadians living with diabetes will not be able to achieve optimal results.

All levels of government should commit to a strategy that ensures that the personal cost of managing diabetes and its complications will not be a barrier to the effective management of this chronic disease. More than ever, Canada needs to shift to an evidence-based model of managing diabetes. With healthcare sustainability remaining at the top of the Canadian political agenda, all levels of government require justification for healthcare expenditures, and evidence-based guidelines can be used to make funding decisions that improve cost and efficiency in healthcare delivery.

RESEARCH

Canada continues to be a world leader in diabetes research. This research is essential for continued improvement in the lives of people with diabetes. Regulatory agencies should not apply these guidelines in a rigid way with regards to clinical research in diabetes. There are already many safeguards in place to protect clinical trial subjects, including ethics review boards and the integrity of Canadian researchers. It is suggested that study protocols can include guideline recommendations, but individual decisions belong in the domain of the patient-physician relationship. The merits of each research study must be assessed individually so as not to block or restrict the pursuit of new information. The Canadian Diabetes Association welcomes the opportunity to work with regulatory agencies to enhance research in Canada and ultimately improve the care of people with diabetes.

DISSEMINATION AND IMPLEMENTATION

The challenges of effective dissemination and implementation of the 2 previous clinical practice guidelines were assessed prior to the launch of the 2008 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. In response, strategies were developed to increase practitioner implementation and to improve patient care and health outcomes. The Expert Committee established a Dissemination & Implementation Committee with the mandate to develop a strategic plan to be implemented at the launch of the guidelines. More than 80 volunteers from across Canada were involved in creating a 3-year plan to translate the evidence compiled in the guidelines into community practice. The guidelines will continue to be available on the web, and summary articles will be placed in journals and newsletters. In addition, key messages and tools supporting specific themes from the guidelines will be highlighted in focused awareness campaigns over the next 3 years. Primary care physicians, healthcare providers, government officials, Canadians living with diabetes and the general public continue to be the audiences for these campaigns.

CONCLUSION

Diabetes is a complex and complicated disease. The burgeoning evidence on new technologies and therapeutic treatments is rapidly expanding our knowledge and ability to manage diabetes and its complications; at the same time, however, it is challenging physicians and other healthcare professionals who care for people with diabetes.

These 2008 clinical practice guidelines are evidence-based recommendations that provide a useful reference tool to help healthcare professionals translate the best available evidence into practice. A cost-benefit analysis of the 2008 recommendations is not included. The most effective therapies may not be the most cost-effective ones. The hope is that these guidelines will provide government officials with the evidence they need when rationalizing access to healthcare so that the potentially beneficial health outcomes are maximized for people living with diabetes. Moreover, the issue of evidence-based versus cost-effective healthcare is an ethical debate that should involve all citizens, because the outcome of this debate ultimately impacts every Canadian.

Physicians, other healthcare professionals and general readers are encouraged to judge independently the value of the diagnostic, prognostic and therapeutic recommendations published in the 2008 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. By doing so, they will remain current in this ever-changing field.

REFERENCES

1. McCormack JP, Loewen P. Adding "value" to clinical practice guidelines. *Can Fam Physician*. 2007;53:1326-1327.

2. Clinical Guidelines Task Force. *Guide for Guidelines: A Guide for Clinical Guideline Development*. Brussels, Belgium: International Diabetes Federation; 2003. Available at: http://www.idf.org/webdata/docs/Guide%20for%20Guidelines.pdf. Accessed September 1, 2008.

3. *United for Diabetes Campaign: Key Messages*. Brussels, Belgium: International Diabetes Federation; 2007. Available at: http://www.unitefordiabetes.org/assets/files/UNR_key_messages_20060828.pdf. Accessed September 1, 2008.

4. *National Diabetes Fact Sheet; Canada 2007*. Public Health Agency of Canada website. Available at: http://www.phac-aspc.gc.ca/ccdpc-cpcmc/diabetes-diabete/english/pubs/ndfs-fnrd07-eng.html. Accessed September 1, 2008.

5. Ohinmaa A, Jacobs P, Simpson S, et al. The projection of prevalence and cost of diabetes in Canada: 2000 to 2016. *Can J Diabetes*. 2004;28:116-123.

6. Egede LE. Effect of depression on work loss and disability bed days in individuals with diabetes. *Diabetes Care*. 2004;27:1751-1753.

7. Brown LC, Svenson LW, Beck CA. Diabetes and mental health disorders in Alberta. In: *Alberta Diabetes Atlas 2007*. Edmonton,

AB: Institute for Health Economics; 2007:113-126.

8. *Why Health Care Reform Matters.* Ottawa, ON: Health Council of Canada; 2007.

9. *Highlights 2006–2007: Inpatient Hospitalizations and Emergency Department Visits.* Ottawa, ON: Canadian Institute for Health Information; 2007.

10. Hux JE, Booth GL, Slaughter PM, et al, eds. *Diabetes in Ontario. An ICES Practice Atlas.* Toronto, ON: Institute for Clinical Evaluative Sciences; 2003.

11. Dawson KG, Gomes D, Gerstein H, et al. The economic cost of diabetes in Canada, 1998. *Diabetes Care.* 2002;25:1303-1307.

12. O'Brien JA, Caro I, Getsios D, et al. Diabetes in Canada: direct medical costs of major macrovascular complications. *Value Health.* 2001;4:258-265.

13. Pagano E, Brunetti M, Tediosi F, et al. Costs of diabetes. A methodological analysis of the literature. *Pharmacoeconomics.* 1999;15:583-595.

14. Ray JA, Valentine WJ, Secnik K, et al. Review of the cost of diabetes complications in Australia, Canada, France, Germany, Italy and Spain. *Curr Med Res Opin.* 2005;21:1617-1629.

15. Simpson SH, Corabian P, Jacobs P, et al. The cost of major comorbidity in people with diabetes mellitus. *CMAJ.* 2003; 168:1661-1667.

16. *2008 Report on Ontario's Health System.* Toronto, ON: Ontario Health Quality Council; 2008.

17. Shields M, Tjepkema M. *Nutrition: Findings from the Canadian Community Health Survey*. Ottawa, ON: Statistics Canada; 2005.

18. The Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New Engl Med J.* 2002;346:393-403.

Methods

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee
The initial draft of this chapter was prepared by Gillian Booth MD MSc FRCPC, Sarah Capes MD MSc FRCPC and Vincent Woo MD FRCPC

PROCESS

Following the process used to develop previous Canadian Diabetes Association clinical practice guidelines (1,2), an Executive Committee, Steering Committee and Expert Committee with broad expertise and geographic representation were assembled. In total, 99 volunteer physicians and allied health professionals (including endocrinologists, family doctors, pediatricians, nephrologists, cardiologists, ophthalmologists, neurologists, urologists, diabetes nurse educators, dietitians, pharmacists, podiatrists, psychologists and other professionals, as well as researchers in a variety of disciplines) participated in the guideline development process.

The following basic principles were adopted to ensure that the values and empirical basis underlying each recommendation were explicitly identified, and to facilitate the critical scrutiny and analysis of each recommendation by other organizations and individuals.

- Each recommendation had to address a clinically important question related to 1 or more of the following: detection, prognosis, prevention or management of diabetes and its sequelae. Health benefits, risks and side effects of interventions were considered in formulating the recommendations.
- Whenever possible, each recommendation had to be justified by the strongest clinically relevant, empirical evidence that could be identified; the citation(s) reporting this evidence had to be noted adjacent to the relevant guideline.
- The strength of this evidence, based on prespecified criteria from the epidemiologic literature and other guidelines processes, had to be noted (3-8).
- This evidence had to be incorporated into a recommendation that was assigned a grade based on the available evidence, its methodological strength and its applicability to the Canadian population.
- Each recommendation had to be approved by the Steering Committee and Executive Committee, with 100% consensus.
- Guidelines based on biological or mechanistic reasoning, expert opinion or consensus had to be explicitly identified and graded as such.

IDENTIFYING AND APPRAISING THE EVIDENCE

At the outset of the process, and in order to ensure a consistent approach to the development of recommendations, committee members from each section of the guidelines attended a workshop on evidence-based methodology. Committee members identified clinically important questions related to diagnosis, prognosis, prevention and treatment of diabetes and its complications.

Authors were to explicitly define a) the population to which a guideline would apply; b) the test, risk factor or intervention being addressed; c) the "gold standard" test or relevant intervention to which the test or intervention in question was compared; and d) clinically relevant outcomes being targeted. This information was used to develop specific, clinically relevant questions that were the focus of literature searching. For each question, individual strategies were developed combining diabetes terms with methodological terms. A librarian with expertise in literature reviews performed a comprehensive search of the relevant English-language, published, peer-reviewed literature using validated search strategies (http://hiru.mcmaster.ca/hedges/indexHIRU.htm) of electronic databases (MEDLINE, EMBASE, CINAHL, the Cochrane Central Register of Trials and PsycINFO [where appropriate]). This was complemented by authors' own manual and electronic searches. For topics that were covered in the 2003 guidelines, the literature searches focused on new evidence published since those guidelines. For new topics, the search time frame included the literature published since 1990, or earlier where relevant.

Key citations retrieved from the literature searches were then reviewed. Each citation that was used to formulate or revise a recommendation was assigned a level of evidence according to the prespecified criteria in Table 1, reflecting the methodological quality of the paper. When evaluating papers, authors were required to use standardized checklists that highlighted the most important elements of a well-conducted study. The level of evidence was then determined by the cited paper's objectives, methodological rigour, susceptibility to bias and generalizability (Table 1). Because they could not be critically appraised, meeting abstracts, narrative review articles, news reports and other sources could not be used to support recommendations. Papers evaluating the cost-effectiveness of therapies or diagnostic tests were not included.

A number of considerations were made when evaluating the evidence within a given area. For example, people with diabetes are at high risk for several sequelae that are not exclusive to diabetes (e.g. cardiovascular diseases, renal failure and erectile dysfunction). As such, some evidence relating to these problems was identified that either excluded, did not report on, or did not focus on people with diabetes. Whenever such evidence was identified, a level was assigned using the approach described above. Higher levels were assigned if a) people with diabetes comprised a predefined subgroup; b) the results in the diabetes subgroup were unlikely to have occurred by chance; and c) the evidence was generated in response to questions that were formulated prior to the analysis of the results.

Table 1. Criteria for assigning levels of evidence to the published studies	
Level	*Criteria*
Studies of diagnosis	
Level 1	a) Independent interpretation of test results (without knowledge of the result of the diagnostic or gold standard) b) Independent interpretation of the diagnostic standard (without knowledge of the test result) c) Selection of people suspected (but not known) to have the disorder d) Reproducible description of both the test and diagnostic standard e) At least 50 patients with and 50 patients without the disorder
Level 2	Meets 4 of the Level 1 criteria
Level 3	Meets 3 of the Level 1 criteria
Level 4	Meets 1 or 2 of the Level 1 criteria
Studies of treatment and prevention	
Level 1A	Systematic overview or meta-analysis of high-quality RCTs a) Comprehensive search for evidence b) Authors avoided bias in selecting articles for inclusion c) Authors assessed each article for validity d) Reports clear conclusions that are supported by the data and appropriate analyses OR Appropriately designed RCT with adequate power to answer the question posed by the investigators a) Patients were randomly allocated to treatment groups b) Follow-up at least 80% complete c) Patients and investigators were blinded to the treatment* d) Patients were analyzed in the treatment groups to which they were assigned e) The sample size was large enough to detect the outcome of interest
Level 1B	Nonrandomized clinical trial or cohort study with indisputable results
Level 2	RCT or systematic overview that does not meet Level 1 criteria
Level 3	Nonrandomized clinical trial or cohort study
Level 4	Other
Studies of prognosis	
Level 1	a) Inception cohort of patients with the condition of interest, but free of the outcome of interest b) Reproducible inclusion/exclusion criteria c) Follow-up of at least 80% of subjects d) Statistical adjustment for extraneous prognostic factors (confounders) e) Reproducible description of outcome measures
Level 2	Meets criterion a) above, plus 3 of the other 4 criteria
Level 3	Meets criterion a) above, plus 2 of the other criteria
Level 4	Meets criterion a) above, plus 1 of the other criteria

*In cases where such blinding was not possible or was impractical (e.g. intensive vs. conventional insulin therapy), the blinding of individuals who assessed and adjudicated study outcomes was felt to be sufficient

RCT = randomized controlled trial

GUIDELINE DEVELOPMENT

Expert Committee members evaluated the relevant literature, and guidelines were developed and initially reviewed by the Expert Committee. In the absence of new evidence since the publication of the 2003 clinical practice guidelines, recommendations from the 2003 document were not changed.

The studies used to develop and support each recommendation are cited beside the level of evidence. In some cases, each of the citations that supported a recommendation were not assigned the same level of evidence, but rather were of varying levels of evidence. In those circumstances, all relevant studies were cited, regardless of the grading assigned to the recommendation. The final grading depended on the overall evidence available, including the relative strengths of the studies from a methodological perspective and the studies' findings. Further details on the grading process are described below.

Finally, several treatment recommendations were based on evidence generated from the use of 1 therapeutic agent from a given class (e.g. 1 of the "statins"). Whenever evidence relating to 1 or more agents from a recognized class of agents was available, the recommendation was written so as to be relevant to the class, but specifically studied therapeutic agents were identified within the recommendation and/or cited reference(s). Only medications with Health Canada Notice of Compliance granted by February 18, 2008, were included in the recommendations.

GRADING THE RECOMMENDATIONS

After formulating new recommendations or modifying existing ones based on new evidence, each recommendation was assigned a grade from A through D (Table 2). The highest possible grade that a recommendation could have was based on the level of evidence. However, the assigned grading was lowered in some cases; for example, if the evidence was found not to be applicable to the Canadian population, or if based on the consensus of the Steering and Executive Committees, there were additional concerns regarding the recommendation. In some situations, the grading was also lowered for sub-

Table 2. Criteria for assigning grades of recommendations for clinical practice	
Grade	*Criteria*
Grade A	The best evidence was at Level 1
Grade B	The best evidence was at Level 2
Grade C	The best evidence was at Level 3
Grade D	The best evidence was at Level 4 or consensus

groups that were not well represented in the study, or in whom the beneficial effect of an intervention was less clear. Thus, a recommendation based on Level 1 evidence, deemed to be very applicable to Canadians and supported by strong consensus, was assigned a grade of A. A recommendation not deemed to be applicable to Canadians, or judged to require further supporting evidence, was assigned a lower grade. Where available, the number of patients that would need to be treated in order to prevent 1 clinical event (number needed to treat [NNT]) or to cause an adverse event (number needed to harm [NNH]) was considered in assessing the impact of a particular intervention. The degree to which evidence derived from other populations was felt to be relevant to diabetes was also reflected in the wording and grading of the recommendation. Finally, in the absence of Level 1, 2 or 3 supporting evidence, or if the recommendation was based on the consensus of the Steering and Executive Committees, the highest grade that could be assigned was D.

INTERPRETING THE ASSIGNED GRADE OF A RECOMMENDATION

The grade assigned to each recommendation is closely linked to the methodological rigour and robustness of the relevant clinical research. Therefore, as noted above, a high grade reflects a high degree of confidence that following the recommendation will lead to the desired outcome. Similarly, a lower grade reflects weaker evidence, and a greater possibility that the recommendation will change when more evidence is generated in the future. Of note, the assigned grade contains no subjective information regarding the importance of the recommendation or how strongly members of the committee felt about it; it contains information regarding only the evidence upon which the recommendation is based. Thus, many Grade D recommendations were deemed to be very important to the contemporary management of diabetes, based on clinical experience, case series, physiological evidence and current concepts of disease pathophysiology. However, the paucity of clinical evidence addressing the areas of therapy, prevention, diagnosis or prognosis precluded the assignment of a higher grade.

Clearly, clinicians need to base clinical decisions on the best available relevant evidence that addresses clinical situations. However, they are also frequently faced with having to act in the absence of clinical evidence, and there are many situations where good clinical evidence may be impossible, impractical or too expensive to generate (which implies that it would be impossible to develop Grade A recommendations). For example, it took the United Kingdom Prospective Diabetes Study (UKPDS) Group >20 years to collect and publish Level 1 evidence leading to a Grade A recommendation in support of the role of tight glycemic control to reduce microvascular disease in people with type 2 diabetes. Prior to the publication of the UKPDS results, the recommendation for glycemic control to prevent microvascular consequences

was a Grade B recommendation (1).

Varying grades of recommendations, therefore, reflect varying degrees of certainty regarding the strength of inference that can be drawn from the evidence in support of the recommendation. Therefore, these evidence-based guidelines and their graded recommendations are designed to satisfy 2 important needs: 1) the explicit identification of the best research upon which the recommendation is based, and an assessment of its scientific relevance and quality (captured by the assignment of a level of evidence to each citation); and 2) the explicit assignment of strength of the recommendation based on this evidence (captured by the grade). In this way, they provide a convenient summary of the evidence to facilitate clinicians' task of "weighting" and incorporating ever-increasing evidence into their daily clinical decision-making. They also facilitate the ability of clinicians, healthcare planners, healthcare providers and society in general to critically examine any recommendation and arrive at their own conclusions regarding its appropriateness. Thus, these guidelines facilitate their own scrutiny by others according to the same principles that they use to scrutinize the literature.

It is important to note that the system chosen for grading recommendations differs from the approach used in some other guideline documents, such as the one pertaining to the periodic health examination in Canada, in which harmful practices were assigned a grade of D (8). In this Canadian Diabetes Association guidelines document, recommendation to avoid any harmful practices would be graded in the same manner as all other recommendations. However, it should be noted that the authors of these guidelines focused on clinical practices that were thought to be potentially beneficial, and did not seek out evidence regarding the harmfulness of interventions.

EXTERNAL PEER REVIEW AND INDEPENDENT METHODOLOGICAL REVIEW

In July 2007, a draft document was circulated nationally and internationally for review by numerous stakeholders and experts in relevant fields. This input was then considered by the Executive and Steering Committees and revisions were made accordingly. Subsequently, a panel of 6 methodologists, who were not directly involved with the initial review and assessment of the evidence, independently reviewed each recommendation, its assigned grade and supportive citations. Based on this review, the wording, assigned level of evidence and grade of each recommendation were reassessed and modified as necessary. Revised recommendations were reviewed and approved by the Executive and Steering Committees. Selected recommendations were presented at a public forum at the Canadian Diabetes Association/Canadian Society of Endocrinology and Metabolism Professional Conference and Annual Meetings in Vancouver, British Columbia, in October 2007.

GUIDELINE UPDATES

A process to update the full guidelines will commence within 5 years. Updates to individual chapters may be published sooner in the event of significant changes in evidence supporting the recommendations.

OTHER RELEVANT GUIDELINES

Introduction, p. S1.

METHODS

Zubin Punthakee MD MSc FRCPS ABIM
Assistant Professor, Department of Medicine and Department of Pediatrics, Division of Endocrinology and Metabolism, McMaster University, Hamilton, Ontario

Joel Ray MD MSc FRCPC
Assistant Professor, Department of Medicine, Divisions of General Internal Medicine and Endocrinology Metabolism, the Department of Obstetrics and Gynecology, and the Department of Health Policy Management and Evaluation, St. Michael's Hospital, Toronto, Ontario

REFERENCES

1. Meltzer S, Leiter L, Daneman D, et al. 1998 clinical practice guidelines for the management of diabetes in Canada. *CMAJ.* 1998;159(suppl 8):S1-S29.

2. Canadian Diabetes Association Clinical Practice Guideline Expert Committee. Canadian Diabetes Association 2003 clinical practice guidelines for the prevention and management of diabetes in Canada. *Can J Diabetes.* 2003;27(suppl 2):S1-S152.

3. Straus SE, McAlister FA. What is the prognosis? In: Gerstein HC, Haynes RB, eds. *Evidence-based Diabetes Care*. Hamilton, ON: BC Decker Inc.;2001:6-12.

4. American Medical Association. *Users' Guides to the Medical Literature: Essentials of Evidence-based Clinical Practice*. Chicago, IL: American Medical Association; 2001.

5. Jaeschke R, Guyatt GH. How should diagnostic tests be chosen and used? In: Gerstein HC, Haynes RB, eds. *Evidence-based Diabetes Care.* Hamilton, ON: BC Decker Inc.; 2001:13-23.

6. Holbrook AM, Clarke J-A, Raymond C, et al. How should a particular problem be managed? Incorporating evidence about therapies into practice. In: Gerstein HC, Haynes RB, eds. *Evidence-based Diabetes Care*. Hamilton, ON: BC Decker Inc.; 2001:24-47.

7. Harris SB, Webster-Bogaert SM. Evidence-based clinical practice guidelines. In: Gerstein HC, Haynes RB, eds. *Evidence-based Diabetes Care.* Hamilton, ON: BC Decker Inc.; 2001:48-61.

8. Goldbloom R, Battista RN. The periodic health examination: 1. Introduction. *CMAJ.* 1986;134:721-723.

Definition, Classification and Diagnosis of Diabetes and Other Dysglycemic Categories

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee
The initial draft of this chapter was prepared by Ehud Ur MB FRCP

KEY MESSAGES

- The chronic hyperglycemia of diabetes is associated with significant long-term sequelae, particularly damage, dysfunction and failure of various organs.

- A fasting plasma glucose (FPG) level of 7.0 mmol/L correlates most closely with a 2-hour plasma glucose value of ≥11.1 mmol/L in a 75-g oral glucose tolerance test and best predicts the development of microvascular disease. This permits the diagnosis of diabetes to be made on the basis of the commonly available FPG test.

- The term "prediabetes" is a practical and convenient term for impaired fasting glucose and impaired glucose tolerance, conditions that place individuals at risk of developing diabetes and its complications.

DEFINITION OF DIABETES AND DYSGLYCEMIA

Diabetes mellitus is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action or both. The chronic hyperglycemia of diabetes is associated with significant long-term sequelae, particularly damage, dysfunction and failure of various organs – especially the kidneys, eyes, nerves, heart and blood vessels.

Dysglycemia is a qualitative term used to describe blood glucose (BG) that is abnormal without defining a threshold. The adoption of this term reflects uncertainty about optimal BG ranges and the current understanding that cardiovascular (CV) risk and mortality risk exist in people with even slightly elevated BG levels.

CLASSIFICATION OF DIABETES

The classification of type 1 diabetes, type 2 diabetes and gestational diabetes mellitus (GDM) is summarized in Table 1. Appendix 1 addresses ideologic classification of diabetes.

DIAGNOSTIC CRITERIA

The diagnostic criteria for diabetes and the plasma glucose thresholds for other diagnostic categories are summarized in Tables 2 and 3 (1). These criteria are based on venous samples and laboratory methods.

Table 1. Classification of diabetes (1)

- **Type 1 diabetes*** encompasses diabetes that is primarily a result of pancreatic beta cell destruction and is prone to ketoacidosis. This form includes cases due to an autoimmune process and those for which the etiology of beta cell destruction is unknown.

- **Type 2 diabetes** may range from predominant insulin resistance with relative insulin deficiency to a predominant secretory defect with insulin resistance.

- **Gestational diabetes mellitus** refers to glucose intolerance with onset or first recognition during pregnancy.

- **Other specific types** include a wide variety of relatively uncommon conditions, primarily specific genetically defined forms of diabetes or diabetes associated with other diseases or drug use (Appendix 1).

*Includes latent autoimmune diabetes in adults (LADA), the term used to describe the small number of people with apparent type 2 diabetes who appear to have immune-mediated loss of pancreatic beta cells (2)

Table 2. Diagnosis of diabetes

FPG ≥7.0 mmol/L
Fasting = no caloric intake for at least 8 hours
or
Casual PG ≥11.1 mmol/L + symptoms of diabetes
Casual = any time of the day, without regard to the interval since the last meal
Classic symptoms of diabetes = polyuria, polydipsia and unexplained weight loss
or
2hPG in a 75-g OGTT ≥11.1 mmol/L

A confirmatory laboratory glucose test (an FPG, a casual PG or a 2hPG in a 75-g OGTT) must be done in all cases on another day in the absence of unequivocal hyperglycemia accompanied by acute metabolic decompensation. However, in individuals in whom type 1 diabetes is a possibility (younger individuals and lean, older individuals), to avoid rapid deterioration, confirmatory testing should not delay initiation of treatment.

2hPG = 2-hour plasma glucose
FPG = fasting plasma glucose
OGTT = oral glucose tolerance test
PG = plasma glucose

Diabetes

A fasting plasma glucose (FPG) level of 7.0 mmol/L correlates most closely with a 2-hour plasma glucose (2hPG) value of ≥11.1 mmol/L in a 75-g oral glucose tolerance test (OGTT) and best predicts the development of microvascular disease (1). This permits the diagnosis of diabetes to be made on the basis of the commonly available FPG test. Although the frequency distributions of glycated hemoglobin (A1C) levels in some studies have characteristics similar to those obtained from FPG and 2hPG tests, the lack of standardization of the A1C test precludes its use in the diagnosis of diabetes.

Prediabetes

Elevated BG levels below the threshold for diabetes also have clinical consequences. The term "prediabetes" is a practical and convenient term for impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) (Table 3), conditions that place individuals at risk of developing diabetes and its complications. It is important to stress that not all individuals with prediabetes will necessarily progress to diabetes. Indeed, a significant proportion of people who are diagnosed with IFG or IGT will revert to normoglycemia. People with prediabetes, particularly in the context of the metabolic syndrome (see below), would benefit from CV risk factor modification.

While people with IFG or IGT do not have the diabetes-associated risk for microvascular disease, they are at higher risk for the development of diabetes and CVD (3). IGT is more strongly associated with CVD outcomes. However, individuals identified as having both IFG and IGT are at higher risk for diabetes as well as CVD. Lifestyle interventions have been shown to be highly effective in delaying or preventing the onset of diabetes in people with IGT (4,5). Studies have not yet been done to examine CVD and total mortality.

There is no worldwide consensus on the definition of IFG (6,7). While the Canadian Diabetes Association continues to define IFG as an FPG value of 6.1 to 6.9 mmol/L (7), a number of limitations have been identified with regards to the existing lower limit of 6.1 mmol/L. These include suboptimal sensitivity for undiagnosed diabetes and IGT, and potential instability on retesting (due to the narrowness of the diagnostic range). For those individuals with an FPG value between 5.6 and 6.0 mmol/L and ≥1 risk factors for diabetes, consideration should be given to performing a 75-g OGTT (6-10).

Metabolic syndrome

Dysglycemia and type 2 diabetes are often manifestations of a much broader underlying disorder (11,12), including the metabolic syndrome – a highly prevalent, multifaceted condition characterized by a distinctive constellation of abnormalities that include abdominal obesity, hypertension, dyslipidemia, insulin resistance and dysglycemia. Individuals with the metabolic syndrome are at significant risk of developing diabetes and CVD. Evidence now exists to support an aggressive approach to identifying people with the metabolic syndrome and treating not only the hyperglycemia but also the associated CV risk factors, such as hypertension, dyslipidemia and abdominal obesity, in the hope of significantly reducing CV morbidity and mortality.

A lack of consensus exists regarding the operational definitions of the metabolic syndrome. In 1998, the World Health Organization (13) proposed a unifying definition that includes identification of the presence of insulin resistance. The United States (US) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) provided an operational definition based on ≥3 criteria that does not require a measure of insulin resistance (14,15). In the International Diabetes Federation (IDF) definition, the presence of abdominal obesity is a requisite risk factor. The IDF definition also provides ethnic-specific values for waist circumference (16). Table 4 presents the definitions of metabolic syndrome proposed by these 3 organizations. Data from the Third National Health and Nutrition Survey, which employed the 2001 ATP III criteria (15), showed that the overall prevalence of the metabolic syndrome in the US was approximately 20 to 25% (17).

Table 3. PG levels for diagnosis of IFG, IGT and diabetes			
	FPG (mmol/L)		*2hPG in the 75-g OGTT (mmol/L)*
IFG	6.1–6.9		NA
IFG (isolated)	6.1–6.9	and	<7.8
IGT (isolated)	<6.1	and	7.8–11.0
IFG and IGT	6.1–6.9	and	7.8–11.0
Diabetes	≥7.0	or	≥11.1

2hPG = 2-hour plasma glucose
FPG = fasting plasma glucose
IFG = impaired fasting glucose
IGT = impaired glucose tolerance
OGTT = oral glucose tolerance test
NA = not applicable
PG = plasma glucose

Table 4. Definitions of the metabolic syndrome

	WHO (13)	NCEP ATP III 2001 (14)	NCEP ATP III 2004 (15)	IDF (16)
Diagnostic criteria	Diabetes, IFG, IGT or insulin resistance (assessed by clamp studies) plus ≥2 other risk determinants are present	≥3 risk determinants are present		Central obesity (using ethnic-specific values) plus ≥2 other risk determinants are present (if BMI is >30 kg/m^2, central obesity can be assumed and WC does not need to be measured)
BG	Diabetes, IFG, IGT or insulin resistance	FPG ≥6.1 mmol/L	FPG ≥5.6 mmol/L	FPG ≥5.6 mmol/L (or previously diagnosed type 2 diabetes)
BP	≥140/90 mm Hg	≥130/85 mm Hg		≥130/85 mm Hg (or receiving treatment for previously diagnosed hypertension)
TG	≥1.7 mmol/L	≥1.7 mmol/L		≥1.7 mmol/L (or receiving treatment)
HDL-C	<0.9 mmol/L (men) <1.0 mmol/L (women)	<1.0 mmol/L (men) <1.3 mmol/L (women)		<1.0 mmol/L (men) <1.3 mmol/L (women) (or receiving treatment)
Abdominal obesity	Waist-to-hip ratio: >0.90 (men) >0.85 (women)	WC: >102 cm (men) >88 cm (women)		Europids / Sub-Saharan Africans / Eastern Mediterranean and Middle East (Arab) populations: WC ≥94 cm (men) WC ≥80 cm (women) South Asian / Malaysian / Asian / Indian / Chinese / Japanese / Ethnic South and Central American populations: WC ≥90 cm (men) WC ≥80 cm (women)
Kidney function	Urinary albumin excretion rate >20 µg/min or ACR ≥30 mg/g	NA		NA

ACR = albumin to creatinine ratio
BG = blood glucose
BMI = body mass index
BP = blood pressure
FPG = fasting plasma glucose
HDL-C = high-density lipoprotein cholesterol
IDF = International Diabetes Federation
IFG = impaired fasting glucose
IGT = impaired glucose tolerance

NA = not applicable
NCEP ATP III = National Cholesterol Education
  Program Adult Treatment Panel III
TG = triglycerides
WC = waist circumference
WHO = World Health Organization

OTHER RELEVANT GUIDELINES

RELEVANT APPENDIX

Appendix 1. Etiologic Classification of Diabetes Mellitus

REFERENCES

1. American Diabetes Association. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care.* 2008;31(suppl 1):S55-S60.

2. Turner R, Stratton I, Horton V, et al. UKPDS 25: autoantibodies to islet-cell cytoplasm and glutamic acid decarboxylase for prediction of insulin requirement in type 2 diabetes. UK Prospective Diabetes Study Group. *Lancet.* 1997;350:1288-1293.

3. Coutinho M, Gerstein HC, Wang Y, et al. The relationship between

glucose and incident cardiovascular events. A meta-regression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care.* 1999;22:233-240.

4. Tuomilehto J, Lindström J, Eriksson JG, et al; Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med.* 2001;344:1343-1350.

5. Knowler WC, Barrett-Connor E, Fowler SE, et al; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med.* 2002;346:393-403.

6. Shaw JE, Zimmet PZ, Alberti KG. Point: Impaired fasting glucose: the case for the new American Diabetes Association criterion. *Diabetes Care.* 2006;29:1170-1172.

7. Forouhi NG, Balkau B, Borch-Johnsen K, et al; EDEG. The threshold for diagnosing impaired fasting glucose: a position statement by the European Diabetes Epidemiology Group. *Diabetologia.* 2006;49:822-827.

8. Shaw JE, Zimmet PZ, Hodge AM, et al. Impaired fasting glucose: how low should it go? *Diabetes Care.* 2000;23:34-39.

9. Ko GT, Chan JC, Yeung VT, et al. Combined use of a fasting plasma glucose concentration and HbA1C or fructosamine predicts the likelihood of having diabetes in high-risk subjects. *Diabetes Care.* 1998;21:1221-1225.

10. Tirosh A, Shai I, Tekes-Manova D, et al; Israeli Diabetes Research Group. Normal fasting plasma glucose levels and type 2 diabetes in young men. *N Engl J Med.* 2005;353:1454-1462.

11. Zimmet PZ. Diabetes epidemiology as a tool to trigger diabetes research and care. *Diabetologia.* 1999;42:499-518.

12. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes.* 1988;37:1595-1607.

13. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med.* 1998;15:539-553.

14. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA.* 2001;285:2486-2497.

15. Grundy SM, Cleeman JI, Daniels SR, et al; American Heart Association; National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation.* 2005;112:2735-2752.

16. International Diabetes Federation. *The IDF Consensus Worldwide Definition of the Metabolic Syndrome.* Brussels: IDF Communications; 2006. Available at: http://www.idf.org/web data/docs/IDF_Meta_def_final.pdf. Accessed September 1, 2008.

17. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third national Health and Nutrition Examination Survey. *JAMA.* 2002;287:356-359.

Screening for Type 1 and Type 2 Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Ehud Ur MB FRCP, Jean-Louis Chiasson MD, Tom Ransom MD MSc FRCPC and Richard Rowe MBBS MAEd FRCPC

KEY MESSAGES

- In the absence of evidence for interventions to prevent or delay type 1 diabetes, screening for type 1 diabetes is not recommended.

- Screening for type 2 diabetes using a fasting plasma glucose (FPG) should be performed every 3 years in individuals ≥40 years of age.

- While the FPG is the recommended screening test, a 2-hour plasma glucose in a 75-g oral glucose tolerance test is indicated when the FPG is 6.1 to 6.9 mmol/L and may be indicated when FPG is 5.6 to 6.0 mmol/L and suspicion of type 2 diabetes or impaired glucose tolerance is high (e.g. for individuals with risk factors).

SCREENING FOR TYPE 1 DIABETES

Type 1 diabetes mellitus is primarily a result of pancreatic beta cell destruction due to an immune-mediated process that is likely incited by environmental factors in genetically predisposed individuals. An individual's risk of developing type 1 diabetes can be estimated by considering family history of type 1 diabetes with attention to age of onset and sex of the affected family members (1) and profiling immunity and genetic markers (2). The loss of pancreatic beta cells in the development of type 1 diabetes passes through a subclinical prodrome that can be detected reliably in first- and second-degree relatives of persons with type 1 diabetes by the presence of pancreatic islet autoantibodies in their sera (3). Given that the various serologic markers are not universally available, and in the absence of evidence for interventions to prevent or delay type 1 diabetes, no recommendations for screening for type 1 diabetes can be made.

SCREENING FOR TYPE 2 DIABETES

Adults

Undiagnosed type 2 diabetes may occur in >2.8% of the general adult population (4), with the number increasing to >10% in some populations (5,6). Tests for hyperglycemia can identify these individuals, many of whom will have or will be at risk for preventable diabetes complications (5,6). Although the relatively low prevalence of diabetes in the general population makes it unlikely that mass screening will be cost-effective, testing for diabetes in people with risk factors for type 2 diabetes or with diabetes-associated conditions is likely to

result in more benefit than harm and will lead to overall cost savings (7,8). Routine testing for type 2 diabetes is, therefore, justifiable in some but not all settings (9). Screening individuals as early as age 40 in family physicians' offices has proved to be useful in detecting unrecognized diabetes (10).

While fasting plasma glucose (FPG) is the recommended screening test, a 2-hour plasma glucose (2hPG) in a 75-g oral glucose tolerance test (OGTT) is indicated when the FPG is 6.1 to 6.9 mmol/L (11) and may be indicated when the FPG is 5.6 to 6.0 mmol/L and suspicion of type 2 diabetes or impaired glucose tolerance (IGT) is high (e.g. for individuals with risk factors listed in Table 1); see Figure 1.

As people with impaired fasting glucose (IFG) or IGT are at increased risk of developing type 2 diabetes and have an increased risk of macrovascular complications, the diagnosis of IGT, particularly in apparently healthy people, has impor-

Table 1. Risk factors for type 2 diabetes

- Age ≥40 years
- First-degree relative with type 2 diabetes
- Member of high-risk population (e.g. people of Aboriginal, Hispanic, South Asian, Asian or African descent)
- History of IGT or IFG*
- Presence of complications associated with diabetes
- Vascular disease (coronary, cerebrovascular or peripheral)*
- History of gestational diabetes mellitus
- History of delivery of a macrosomic infant
- Hypertension*
- Dyslipidemia*
- Overweight*
- Abdominal obesity*
- Polycystic ovary syndrome*
- Acanthosis nigricans*
- Schizophrenia[†]
- Other (see Appendix 1)

*Associated with insulin resistance

[†] The incidence of type 2 diabetes is at least 3 times higher in people with schizophrenia than in the general population (12,13). Using data collected in 1991, the prevalence of diabetes was assessed in >20 000 individuals diagnosed with schizophrenia. The rate of diagnosed diabetes was 9 to 14%, exceeding rates for the general population prior to the widespread use of new antipsychotic drugs (14)

IFG = impaired fasting glucose
IGT = impaired glucose tolerance

tant prognostic implications (15). Classifying individuals with IFG and/or IGT, particularly in the context of the metabolic syndrome, identifies people who would benefit from cardiovascular risk factor reduction.

Risk scores

A number of risk scores based on clinical characteristics have been developed to identify individuals at high risk of having undiagnosed diabetes. However, the impact of known risk

Figure 1. Screening for type 2 diabetes in adults

SCREENING FOR TYPE 1 AND TYPE 2
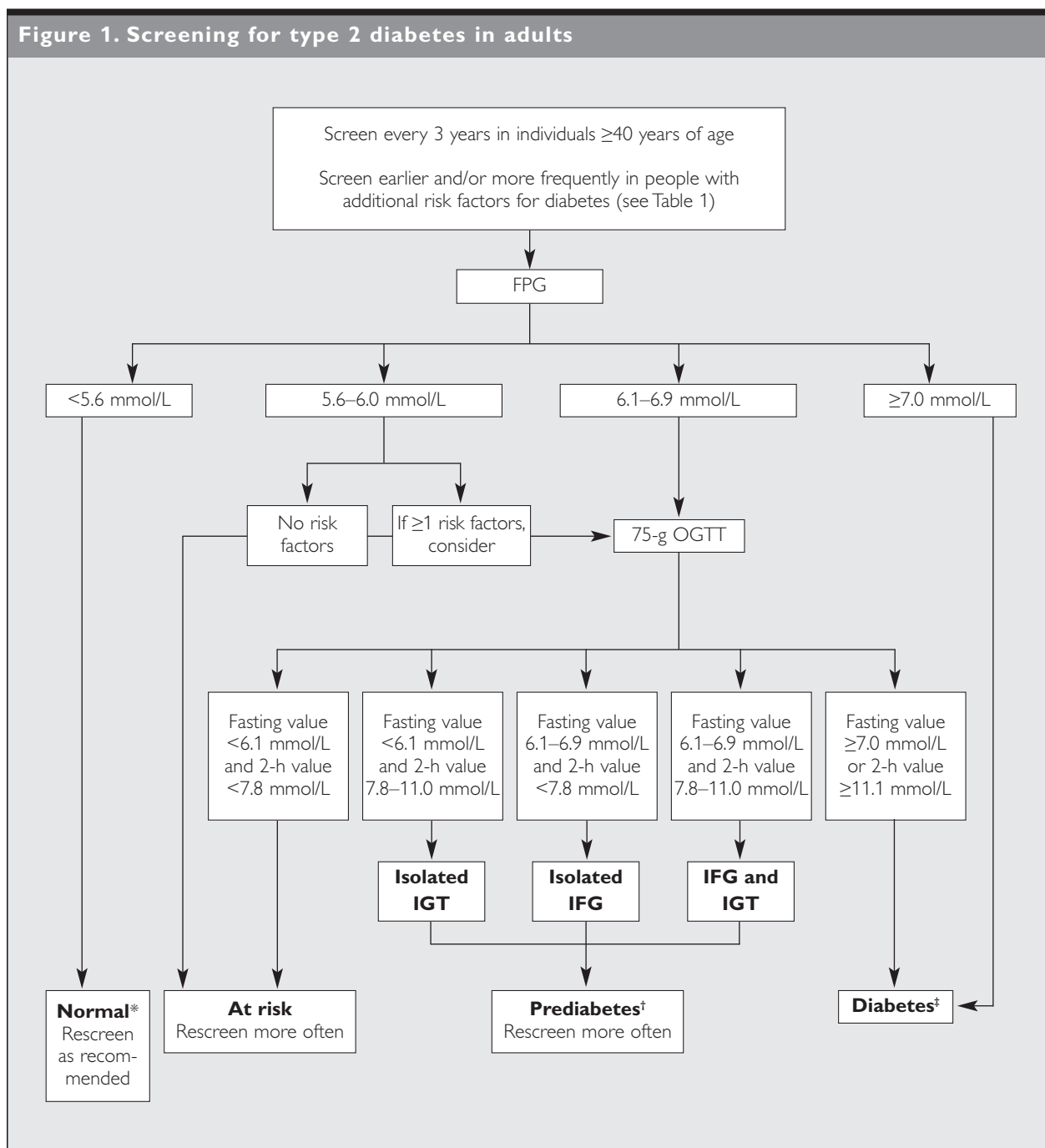
*If, despite a normal fasting value, an OGTT is subsequently performed and the 2hPG value is 7.8–11.0 mmol/L, a diagnosis of isolated IGT is made

†Prediabetes = isolated IFG, isolated IGT, IFG and IGT (see Table 3 in "Definition, Classification and Diagnosis of Diabetes and Other Dysglycemic Categories," p. S10)

‡A confirmatory laboratory glucose test (either an FPG, a casual PG or a 2hPG in a 75-g OGTT) must be done on another day in all cases in the absence of unequivocal hyperglycemia accompanied by acute metabolic decompensation

2hPG = 2-hour plasma glucose   IGT = impaired glucose tolerance
FPG = fasting plasma glucose   OGTT = oral glucose tolerance test
IFG = impaired fasting glucose   PG = plasma glucose

factors on having undiagnosed type 2 diabetes differs between populations of different ethnic origins, and risk scores developed in Caucasian populations cannot be applied to populations of other ethnic groups (16).

RECOMMENDATIONS

1. All individuals should be evaluated annually for type 2 diabetes risk on the basis of demographic and clinical criteria *[Grade D, Consensus]*.

2. Screening for diabetes using an FPG should be performed every 3 years in individuals ≥40 years of age *[Grade D, Consensus]*. More frequent and/or earlier testing with either an FPG or a 2hPG in a 75-g OGTT should be considered in people with additional risk factors for diabetes *[Grade D, Consensus]*. These risk factors include:
   - First-degree relative with type 2 diabetes
   - Member of high-risk population (e.g. people of Aboriginal, Hispanic, Asian, South Asian or African descent)
   - History of IGT or IFG
   - Presence of complications associated with diabetes
   - Vascular disease (coronary, cerebrovascular or peripheral)
   - History of gestational diabetes mellitus
   - History of delivery of a macrosomic infant
   - Hypertension
   - Dyslipidemia
   - Overweight
   - Abdominal obesity
   - Polycystic ovary syndrome
   - Acanthosis nigricans
   - Schizophrenia
   - Other risk factors (see Appendix 1)

3. Testing with a 2hPG in a 75-g OGTT should be undertaken in individuals with an FPG of 6.1 to 6.9 mmol/L in order to identify individuals with IGT or diabetes *[Grade D, Consensus]*.

4. Testing with a 2hPG in a 75-g OGTT may be undertaken in individuals with an FPG of 5.6 to 6.0 mmol/L and ≥1 risk factors in order to identify individuals with IGT or diabetes *[Grade D, Consensus]*.

OTHER RELEVANT GUIDELINES

Definition, Classification and Diagnosis of Diabetes
  and Other Dysglycemic Categories, p. S10
Prevention of Diabetes, p. S17
Type 1 Diabetes in Children and Adolescents, p. S150
Type 2 Diabetes in Children and Adolescents, p. S162

RELEVANT APPENDIX

Appendix 1. Etiologic Classification of Diabetes Mellitus

REFERENCES

1. Harjutsalo V, Reunanen A, Tuomilehto J. Differential transmission of type 1 diabetes from diabetic fathers and mothers to their offspring. *Diabetes*. 2006;55:1517-1524.

2. Decochez K, Truyen I, van der Auwera B, et al; Belgian Diabetes Registry. Combined positivity for HLA DQ2/DQ8 and IA-2 antibodies defines population at high risk of developing type 1 diabetes. *Diabetologia*. 2005;48:687-694.

3. Bingley PJ. Interactions of age, islet cell antibodies, insulin autoantibodies, and first-phase insulin response in predicting risk of progression to IDDM in ICA+ relatives: the ICARUS data set. *Islet Cell Antibody Register Users Study Diabetes*. 1996; 45:1720-1728.

4. Cowie CC, Rust KF, Byrd-Holt DD, et al. Prevalence of diabetes and impaired fasting glucose in adults in the U.S. population: National Health And Nutrition Examination Survey 1999-2002. *Diabetes Care*. 2006;29:1263-1268.

5. Rolka DB, Narayan KM, Thompson TJ, et al. Performance of recommended screening tests for undiagnosed diabetes and dysglycemia. *Diabetes Care*. 2001;24:1899-1903.

6. Rathmann W, Haastert B, Icks A, et al. High prevalence of undiagnosed diabetes mellitus in Southern Germany: target populations for efficient screening. The KORA survey 2000. *Diabetologia*. 2003;46:182-189.

7. Raikou M, McGuire A. The economics of screening and treatment in type 2 diabetes mellitus. *Pharmacoeconomics*. 2003;21: 543-564.

8. The cost-effectiveness of screening for type 2 diabetes. CDC Diabetes Cost-Effectiveness Study Group, Centers for Disease Control and Prevention. *JAMA*. 1998;280:1757-1763.

9. Knowler WC. Screening for NIDDM. Opportunities for detection, treatment, and prevention. *Diabetes Care*. 1994;17: 445-450.

10. Leiter LA, Barr A, Bélanger A, et al; Diabetes Screening in Canada (DIASCAN) Study. Diabetes Screening in Canada (DIASCAN) Study: prevalence of undiagnosed diabetes and glucose intolerance in family physician offices. *Diabetes Care*. 2001;24:1038-1043.

11. Saydah SH, Byrd-Holt D, Harris MI. Projected impact of implementing the results of the Diabetes Prevention Program in the U.S. population. *Diabetes Care*. 2002;25:1940-1945.

12. McKee HA, D'Arcy PF, Wilson PJ. Diabetes and schizophrenia — a preliminary study. *J Clin Hosp Pharm*. 1986;11:297-299.

13. Mukherjee S, Decina P, Bocola V, et al. Diabetes mellitus in schizophrenic patients. *Compr Psychiatry*. 1996;37:68-73.

14. Dixon L, Weiden P, Delahanty J, et al. Prevalence and correlates of diabetes in national schizophrenia samples. *Schizophr Bull*. 2000;26:903-912.

15. Hu G, Qiao Q, Tuomilehto J, et al; DECODE Study Group. Prevalence of the metabolic syndrome and its relation to all-cause and cardiovascular mortality in nondiabetic European men and women. *Arch Intern Med*. 2004;164:1066-1076.

16. Glumer C, Vistisen D, Borch-Johnsen K, et al for the Detect 2 Collaboration. Risk scores for type 2 diabetes can be applied in some populations but not all. *Diabetes Care*. 2006;29:410-414.

Prevention of Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Ehud Ur MB FRCP, Jean-Louis Chiasson MD, Tom Ransom MD MSc FRCPC and Richard Rowe MBBS MAEd FRCPC

KEY MESSAGES

- As safe and effective preventive therapies for type 1 diabetes have not yet been identified, any attempts to prevent type 1 diabetes should be undertaken only within the confines of formal research protocols.

- Intensive and structured lifestyle modification that results in loss of approximately 5% of initial body weight can reduce the risk of progression from impaired glucose tolerance to type 2 diabetes by almost 60%.

- Progression from prediabetes to type 2 diabetes can also be reduced by pharmacologic therapy with metformin (~30% reduction), acarbose (~30% reduction) and thiazolidinedione (~60% reduction).

PREVENTION OF TYPE 1 DIABETES

Two major trials of interventions to prevent or delay the onset of type 1 diabetes have recently been completed. The European Nicotinamide Diabetes Intervention Trial (ENDIT), a randomized, double-blind, placebo-controlled trial of high-dose nicotinamide therapy, recruited first-degree relatives of people who were >20 years old when diagnosed with type 1 diabetes, islet cell antibody-positive, >40 years of age and had a normal oral glucose tolerance test (OGTT) result. Although nicotinamide had proved protective in animal studies, no effect was observed in the ENDIT study during the 5-year trial period (1).

The Diabetes Prevention Trial–Type 1 (DPT-1) studied the efficacy of low-dose insulin injections in high-risk (>50%) first-degree relatives of subjects with type 1 diabetes. Overall, the insulin treatments had no effect (2), but in a subset of participants with high levels of insulin autoantibodies, a delay, and perhaps a reduction, in the incidence of type 1 diabetes was observed (3).

As safe and effective preventive therapies for type 1 diabetes have not yet been identified, any attempts to prevent type 1 diabetes should be undertaken only within the confines of formal research protocols.

PREVENTION OF TYPE 2 DIABETES

Preventing type 2 diabetes would result in significant public health benefits, including lower rates of cardiovascular disease (CVD), renal failure, blindness and premature mortality. An epidemiologic analysis projected that if all diabetes could be avoided in white American males through effective primary prevention, the risk of all-cause and cardiovascular mortality in the entire population could be reduced by up to 6.2 and 9.0%, respectively (4). Recent data from the US indicate that 28% of cardiovascular expenditures are attributable to diabetes (5).

Primary approaches to preventing diabetes in a population include the following: 1) programs targeting high-risk individuals in the community (such as those with impaired glucose tolerance [IGT] or obesity); 2) programs targeting high-risk subgroups of the population, such as high-risk ethnic groups; and 3) programs for the general population, such as those designed to promote physical activity and healthy eating in adults or children (6-8).

Prospective cohort studies have identified historical, physical and biochemical variables associated with the subsequent development of type 2 diabetes. These include older age, certain ethnic backgrounds, obesity (especially abdominal obesity), physical inactivity, history of gestational diabetes mellitus, overt coronary artery disease, high fasting insulin levels and IGT (9-11).

Results of large, well-designed studies assessing lifestyle and pharmacologic interventions in adults to prevent the progression from IGT to diabetes have been published.

Changes in lifestyle were assessed in the Finnish Diabetes Prevention Study (DPS) (12) and the Diabetes Prevention Program (DPP) (13). Dietary modification that targeted a low-calorie, low-fat, low-saturated fat, high-fibre diet and moderate-intensity physical activity of at least 150 minutes per week resulted in loss of approximately 5% of initial body weight. In both studies, the risk reduction for diabetes was 58% at 4 years. These studies included comprehensive, sustained programs to achieve these outcomes.

In another lifestyle intervention trial (14), 458 Japanese males with IGT were randomly assigned in a 4:1 ratio to a standard intervention (n=356) or an intensive intervention (n=102) and followed for 4 years. Intensive treatment was associated with a 67.4% reduction in risk of diabetes (p<0.001). IGT and diabetes were diagnosed using a 100-g OGTT and the following diagnostic criteria: IGT = 2-hour plasma glucose (2hPG) 8.8–13.1 mmol/L; diabetes = 2hPG ≥13.2 mmol/L. These levels have been shown to correspond to the WHO diagnostic criteria using a 75-g OGTT (15,16).

Metformin was used in a second arm of the DPP (13).

A dosage of 850 mg BID for an average of 2.8 years significantly decreased progression to diabetes by 31%. In the DPP population, metformin did not have any significant effect in the older age group (≥60 years) and in less obese (body mass index [BMI] <35 kg/m²) subjects. To determine whether the observed benefit was a transient pharmacologic effect or more sustained, a repeat OGTT was undertaken after a short washout period. The results of this study suggested that 26% of the diabetes prevention effect could be accounted for by the pharmacologic action of metformin (which did not persist when the drug was stopped). After the washout, the incidence of diabetes was still reduced by 25% (17). The DPP Research Group recently published the results from the troglitazone arm, which was part of the original protocol (18). The drug was discontinued after a mean follow-up of 0.9 year due to liver toxicity. Troglitazone 400 mg OD resulted in a relative risk reduction of 75% (p=0.02) during the short period of time. This effect was not sustained after discontinuation of troglitazone.

The Study to Prevent Non Insulin Dependent Diabetes (STOP-NIDDM) used acarbose at a dosage of 100 mg TID in a 5-year study with a mean follow-up of 3.3 years (19). Overall, there was a 25% reduction in the risk of progression to diabetes when the diagnosis was based on 1 OGGT and a 36% reduction in the risk of progression to diabetes when the diagnosis was based on 2 consecutive OGTTs. This beneficial effect was not affected by age or BMI. However, when the drug was discontinued, the effect of acarbose did not persist (19). In this IGT population, acarbose treatment was also associated with a 49% reduction in CV events (p=0.032) and a 50% reduction in the progression of carotid intima-media thickness (20,21).

The Xenical in the Prevention of Diabetes in Obese Subjects (XENDOS) study (22) examined the effect of orlistat in combination with an intensive lifestyle modification program (diet and exercise) on the prevention of diabetes in 3305 obese individuals. Subjects were randomized to orlistat 120 mg or placebo TID with meals for 4 years. Weight loss was observed in both groups, but the orlistat group lost significantly more (5.8 vs. 3 kg, p<0.001). Compared to placebo, orlistat treatment was associated with a further 37% reduction in the incidence of diabetes. However, 2 important methodological limitations affect the interpretation of these results. First, there was a very high dropout rate – 48% in the orlistat group and 66% in the placebo group. Second, the last observation carried forward was used for analysis, which is generally not favoured for prevention or survival studies. Nonetheless, the significant weight loss would be expected to decrease the risk of diabetes as already shown in the DPS and the DPP.

Most recently the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial (23,24) randomized 5269 subjects with IGT and/or impaired fasting glucose (IFG), in a 2x2 factorial fashion, to ramipril (15 mg/day) and/or rosiglitazone (8 mg/day) vs. placebo. Eligible subjects were ≥30 years old and not known to have CVD. The primary outcome of DREAM was a composite of development of diabetes or death. The conclusion of the DREAM investigators was that the "results suggest an effect of ramipril on glucose metabolism, a finding that is consistent with other reports. For now, the routine use of ramipril for the express purpose of preventing diabetes is not indicated." Treatment with rosiglitazone resulted in a 60% reduction in the primary composite outcome of diabetes or death (HR 0.40, 95% CI, 0.35–0.46), primarily due to a 62% relative reduction in the risk of progression to diabetes (HR 0.38, 95% CI, 0.33–0.44). Although the trial was not powered to provide a definitive estimate of the effect of rosiglitazone on CV outcomes, there was a trend toward an increase in risk of the CV composite outcome with rosiglitazone (HR 1.37, 95% CI, 0.97–1.94) driven primarily by a significant increase in nonfatal congestive heart failure (HR 7.03, 95% CI, 1.60–30.9, p=0.01). The final conclusion of the DREAM investigators was that "further work is needed to determine whether the beneficial effects seen with rosiglitazone will lead to a reduction in cardiovascular, renal, retinal, or other serious health consequences."

RECOMMENDATIONS

1. A structured program of lifestyle modification that includes moderate weight loss and regular physical activity should be implemented to reduce the risk of type 2 diabetes in individuals with IGT *[Grade A, Level 1A (12,13)]* and IFG *[Grade D, Consensus]*.

2. In individuals with IGT, pharmacologic therapy with a biguanide (metformin) *[Grade A, Level 1A (13)]* or an alpha-glucosidase inhibitor *[Grade A, Level 1A (19)]* should be considered to reduce the risk of type 2 diabetes. In individuals with IGT and/or IFG and no known cardiovascular disease, treatment with a thiazolidinedione could be considered to reduce the risk of type 2 diabetes *[Grade A, Level 1A (23)]*.

REFERENCES

1. Gale EA, Bingley PJ, Emmett CL, et al; European Nicotinamide Diabetes Intervention Trial (ENDIT) Group. European Nicotinamide Diabetes Intervention Trial (ENDIT): a randomized controlled trial of intervention before the onset of type 1 diabetes. *Lancet*. 2004;363:925-931.

2. Diabetes Prevention Trial — Type 1 Diabetes Study Group. Effects of insulin in relatives of patients with type 1 diabetes mellitus. *N Engl J Med*. 2002;346:1685-1691.

3. Skyler JS, Krischer JP, Wolfsdorf J, et al. Effects of oral insulin in relatives of patients with type 1 diabetes: the Diabetes Prevention Trial–Type 1. *Diabetes Care*. 2005;28:1068-1076.

4. Narayan KM, Thompson TJ, Boyle JP, et al. The use of population attributable risk to estimate the impact of prevention and

early detection of type 2 diabetes on population-wide mortality risk in US males. *Health Care Manag Sci*. 1999;2:223-227.

5. American Diabetes Association. Economic costs of diabetes in the US in 2007. *Diabetes Care*. 2008;31:596-615.

6. Micucci S, Thomas H, Vohra J. The effectiveness of school-based strategies for the primary prevention of obesity and for promoting physical activity and/or nutrition, the major modifiable risk factors for type 2 diabetes: a review of reviews. Hamilton, ON: Public Health Research, Education and Development Program, Ministry of Health and Long-Term Care; 2002. Available at: http://old.hamilton.ca/phcs/ephpp/Research/Full-Reviews/Diabetes-Review.pdf. Accessed September 1, 2008.

7. Daniel M, Green LW, Marion SA, et al. Effectiveness of community-directed diabetes prevention and control in a rural Aboriginal population in British Columbia, Canada. *Soc Sci Med*. 1999;48:815-832.

8. Simmons D, Voyle J, Swinburn B, et al. Community-based approaches for the primary prevention of non-insulin-dependent diabetes mellitus. *Diabet Med*. 1997;14:519-526.

9. Charles MA, Fontbonne A, Thibult N, et al. Risk factors for NIDDM in white population. Paris prospective study. *Diabetes*. 1991;40:796-799.

10. Eastman RC, Cowie CC, Harris MI. Undiagnosed diabetes or impaired glucose tolerance and cardiovascular risk. *Diabetes Care*. 1997;20:127-128.

11. Tuomilehto J, Knowler WC, Zimmet P. Primary prevention of non-insulin-dependent diabetes mellitus. *Diabetes Metab Rev*. 1992;8:339-353.

12. Tuomilehto J, Lindström J, Eriksson JG, et al; Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med*. 2001;344:1343-1350.

13. Knowler WC, Barrett-Connor E, Fowler SE, et al; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393-403.

14. Kosaka K, Noda M, Kuzuya T. Prevention of type 2 diabetes by lifestyle intervention: a Japanese trial in IGT males. *Diabetes Res Clin Pract*. 2005;67:152-162.

15. Kosaka K. Diagnostic criteria for diabetes mellitus in Japan — from a report of the Japan Diabetes Society (JDS) Committee on the Diagnosis of Diabetes Mellitus, 1982. *Diabetes Res Clin Pract*. 1994;24(suppl):S59-S62.

16. WHO Expert Committee on Diabetes Mellitus. 2nd report. *WHO Technical Report Series No. 646*. SFr 5. Geneva, Switzerland: World Health Organization;1980.

17. Diabetes Prevention Program Research Group. Effects of withdrawal from metformin on the development of diabetes in the Diabetes Prevention Program. *Diabetes Care*. 2003;26:977-980.

18. Knowler WC, Hamman RF, Edelstein SL, et al; Diabetes Prevention Program Research Group. Prevention of type 2 diabetes with troglitazone in the Diabetes Prevention Program. *Diabetes*. 2005;54:1150-1156.

19. Chiasson JL, Josse RG, Gomis R, et al; STOP-NIDDM Trial Research Group. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet*. 2002;359:2072-2077.

20. Chiasson JL, Josse RG, Gomis R, et al; STOP-NIDDM Trial Research Group. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM Trial. *JAMA*. 2003;290:486-494.

21. Hanefeld M, Chiasson JL, Koehler C, et al. Acarbose slows progression of intima-media thickness of the carotid arteries in subjects with impaired glucose tolerance. *Stroke*. 2004;35:1073-1078.

22. Torgerson JS, Hauptman J, Boldrin MN, et al. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care*. 2004;27:155-161.

23. DREAM (Diabetes Reduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators, Gerstein HC, Yusuf S, Bosch J, et al. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomized controlled trial. *Lancet*. 2006;368:1096-1105.

24. DREAM Trial Investigators, Bosch J, Yusuf S, Gerstein HC. Effect of ramipril on the incidence of diabetes. *N Engl J Med*. 2006;355:1551-1562.

PREVENTION OF DIABETES

Organization of Diabetes Care

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Sora Ludwig MD FRCPC, Maureen Clement MD CCFP, Peggy Dunbar MEd PDt CDE and Jeffrey A. Johnson PhD

KEY MESSAGES

- Diabetes care depends upon the daily commitment of the person with diabetes to self-management practices with the support of an integrated diabetes healthcare (DHC) team.

- The DHC team should be multi- and interdisciplinary, and should establish and sustain a communication network among the health and community systems needed in the long-term care of the person with diabetes.

- Diabetes care should be systematic and, when possible, should incorporate organizational interventions such as electronic databases, automatic reminders for the patient and DHC team, to enable timely feedback.

INTRODUCTION

Diabetes care depends upon the daily commitment of the person with diabetes to self-management practices with the support of an integrated diabetes healthcare (DHC) team (1-3). Multifaceted interventions by a wide array of healthcare providers within the DHC team are needed to improve management, and should be supported by organizational interventions that promote regular diabetes monitoring and recall (4). Diabetes care should be founded on evidence-based clinical practice guidelines and be continuous, planned and equitable in terms of access. Diabetes programs and services should be community-based, culturally and socially appropriate, and respectful of age, gender and socioeconomic conditions.

DHC TEAM

The DHC team should be multi- and interdisciplinary. It should establish and sustain a communication network among the health and community systems needed in the long-term care of the person with diabetes (1-3,5-7). The person with diabetes and his or her family are central members of the DHC team. Family support has been shown to benefit the person with diabetes (8).

The core DHC team includes the family physician and/or specialist, and the diabetes educators (nurse and dietitian) (3,5-7). The membership of the team is extensive and includes numerous disciplines. A variety of individual and community healthcare supports, in particular psychological support, can improve glycemic control when part of usual diabetes care (9). Flexibility in the operation of the DHC team is important. Changes in the core team, such as adding a team member, active participation by >1 discipline, and role expansion, have been shown to be associated with improved clinical outcomes (10,11).

The DHC team provides comprehensive, shared care that is collaborative in nature. This approach has been shown to increase the commitment and participation of the person with diabetes, and recognizes and enhances the role and practices of all members of the team (12-15).

The family physician's role is unique as the first, and at times, the principal medical contact for the person with diabetes. Family physicians can provide continuity of care for the person with diabetes, and provide care in the context of the family unit (16). This unique provider relationship can also provide opportunities to assist other family members who may be at risk for developing type 2 diabetes.

In some circumstances, this role may be shared with or assumed by a diabetes specialist (4,17,18). Studies suggest that diabetes-related outcomes are improved if medical care provided by the family physician is influenced by a diabetes specialist (18). This influence can vary from indirect input by the specialist as an opinion leader to direct involvement as part of a collaborative care model (4,19). Other effective interventions include the opportunity for input into quality-improvement working groups and direct feedback on processes and outcomes (20).

SELF-MANAGEMENT

Diabetes self-management is most effective when ongoing diabetes education and comprehensive care occur together (21-23). Effective diabetes self-management programs have been demonstrated to improve glycated hemoglobin (A1C) values (23-25).

Diabetes education must support self-management through approaches that promote informed, independent decisions relating to the individual's diabetes management. These approaches have been shown to improve patient adherence to treatment recommendations (26). Self-management education should include problem-solving, goal-setting and active participation in decision-making. This includes supporting the learner in interpreting and acting on the results of self-monitoring of blood glucose; making informed management decisions about insulin,

medication, nutrition, physical activity and other lifestyle issues; and including daily preventive practices such as good foot care.

The timing of referrals for self-management education should be based on the severity of presenting symptoms, the degree of metabolic control and the individual's understanding of immediate survival and safety skills and long-term management practices. Regular reinforcement through diabetes self-management education should be integrated into standard diabetes care (21,23).

Didactic programs alone should not be supported (27-28). In type 2 diabetes, group education has been shown to be as effective as individual education and promotes efficiency in delivery of diabetes self-management education programs (10,29,30). Ongoing rather than time-limited diabetes education sessions are beneficial in the long-term management of all forms of diabetes (31).

ORGANIZATIONAL INTERVENTIONS

A number of organizational interventions have been shown to improve the efficiency and effectiveness of the DHC team.

The DHC team should work within a structure that provides reminders and recall for diabetes metabolic control and complications risk assessment (3,32-35). Several studies have shown that the establishment of centralized computerized systems to monitor and remind both the person and the DHC team about appointments, investigations and interventions (including management changes and/or referrals) improves the diabetes care (35-37). Technological interventions including telemedicine are successful when the systems are designed to initiate timely actions (e.g. medication dosage changes in response to metabolic control markers) (38,39). Telephone feedback can be successful when the advice is individualized and specific (40). Internet-based programs, even with supports, have had mixed results (41).

Management systems with a population approach have been shown to have a positive impact on evidence-based care (42). Population-level clinical registries take an overview perspective to help deliver and monitor patient care, and allow an individual team member or the entire DHC team to assess key elements of care for a large group of patients. This approach can lead to both efficiencies in the use of existing resources and improvements in the overall level of care for a given patient population (42,43).

Case management or care coordination across a number of disciplines (primarily nursing, but also pharmacy and others) has been shown to improve the delivery of care. The role of diabetes case managers is most effective when integrated as part of a collaborative team (i.e. DHC team) and where the role of the team members is enhanced by focusing on the specific expertise of the discipline involved (e.g. a pharmacist's advice on medication adverse effects or interactions; a nurse educator's recommendations on medication selection and/or dosage adjustments) (44,45). Case management may also improve clinical outcomes through the additional use of treatment algorithms and information systems (11,22,25,44-54). Case management is particularly successful when medication changes can be made in a timely fashion without the delay of waiting for physician approval (11).

DIABETES SYSTEMS ORGANIZATION

Diabetes has often been identified as the model for chronic disease management. Successful management of chronic disease requires more than the implementation of evidence-based clinical practice guidelines. It requires reframing existing community and healthcare systems. Unlike the approaches used to manage acute episodic illness, approaches to chronic disease require significant investment to create and support patients who are informed and engaged in their care and motivated practice teams (55-57). Innovative healthcare policy and delivery system redesign are required to fully support chronic disease management.

The United Kingdom, Australia and New Zealand have taken the lead in adopting models of chronic care (58-60). In Canada, British Columbia and Ontario have embraced an expanded chronic-care model that includes health promotion and prevention (49,61,62). Other provinces and territories are in various stages of discussion or adoption of chronic care models as a springboard for continued work within the primary-care and acute-care sectors.

Chronic disease management is usually framed within the context of the Chronic Care Model (CCM) (63-65). Adaptations of this model are reflected in the World Health Organization (WHO) Innovative Care for Chronic Conditions Framework and the Continuous Chronic Care Model (66). The CCM is a multifaceted, interdependent framework to improve healthcare delivery (55-57). It recognizes that the conventional acute healthcare delivery model must change to meet the needs of those with chronic illness within a system that is more inclusive and addresses healthcare from prevention to advanced management. The CCM identifies 6 interrelated components that are key to improving care (55): community resources and policy; health system organization of healthcare; self-management support; delivery-system design; decision support; and clinical information systems.

The CCM should be used as framework for continuous quality improvement. The effectiveness of the implementation of the CCM in primary-care settings in a multilevel, cluster-design randomized controlled trial (67) showed a mean decline in A1C of 0.6% (p=0.008). Other studies have examined the application of the CCM approach from local community health centres to a broader application in healthcare organizations and governmental jurisdictions. These studies support the broad application of the principles of the CCM, as well as implementation of specific aspects such as the use of self-management support and delivery system redesign (59,68,69).

RECOMMENDATIONS

1. Diabetes care should be organized around the person with diabetes using a multi- and interdisciplinary DHC team approach centred on self-care management [Grade B, Level 2 (3,11,23,24)].

2. Diabetes care should be systematic and incorporate organizational interventions such as electronic databases and clinical flow charts with automatic reminders for the patient and DHC team, to enable timely feedback for management changes [Grade B, Level 2 (3,11,35,36)].

3. The DHC team should facilitate the transfer of information among all members of the team as appropriate to ensure continuity of care and knowledge transfer [Grade B, Level 2 (11,70,71)].

4. Members of the DHC team should receive support and education, which can vary from indirect input to direct involvement from a diabetes specialist as part of a collaborative care model [Grade C, Level 3 (4,11,17-19)].

5. The role of DHC team members, including nurse educators [Grade B, Level 2 (11,44,51)], pharmacists [Grade B, Level 2 (11,44)] and dietitians [Grade B, Level 2 (51)], should be enhanced in cooperation with the physician to improve coordination of care. The DHC team should facilitate and/or implement timely diabetes management changes without unnecessary delay [Grade B, Level 2 (3)].

6. Case management or care coordination by health professionals with specialized training in diabetes should be considered for those individuals with difficult-to-manage diabetes [Grade B, Level 2 (11,50)].

OTHER RELEVANT GUIDELINES

Self-management Education, p. S25
Type 1 Diabetes in Children and Adolescents, p. S150
Type 2 Diabetes in Children and Adolescents, p. S162
Diabetes and Pregnancy, p. S168

REFERENCES

1. Brown SA. Effects of educational interventions in diabetes care: a meta-analysis of findings. *Nurs Res.* 1988;37:223-230.

2. Brown SA. Meta-analysis of diabetes patient education research: variations in intervention effects across studies. *Res Nurs Health.* 1992;15:409-419.

3. Renders CM, Valk GD, Griffin SJ, et al. Interventions to improve the management of diabetes in primary care, outpatient, and community settings: a systemic review. *Diabetes Care.* 2001;24:1821-1833.

4. Renders CM, Valk GD, de Sonnaville JJ, et al. Quality of care for patients with type 2 diabetes mellitus: a long-term comparison of two quality improvement programmes in the Netherlands. *Diabet Med.* 2003;20:846-852.

5. Funnell MM. Integrated approaches to the management of NIDDM patients. *Diabetes Spectrum.* 1996;9:55-59.

6. Dunn SM, Hoskins PL, Constantino M, et al. Diabetic management: the role of the diabetes center. *Diabetes Rev.* 1994;2:389-402.

7. Clement S. Diabetes self-management education. *Diabetes Care.* 1995;18:1204-1214.

8. Armour TA, Norris SL, Jack Jr L, et al. The effectiveness of family interventions in people with diabetes mellitus: a systematic review. *Diabet Med.* 2005;22:1295-1305.

9. Ismail K, Winkley K, Rabe-Hesketh S. Systemic review and meta-analysis of randomized controlled trial of psychological interventions to improve glycaemic control in patients with type 2 diabetes. *Lancet.* 2004;363:1589-1597.

10. Van Dam HA, van der Horst F, van den Borne B, et al. Provider-patient interaction in diabetes care: effects on patient self-care and outcomes. A systematic review. *Patient Educ Couns.* 2003;51:17-28.

11. Shojania KG, Ranjii SR, McDonald KM, et al. Effects of quality improvement strategies for type 2 diabetes on glycemic control: a meta-regression analysis. *JAMA.* 2006;296:427-440.

12. Greenhalgh PM. Shared care for diabetes. A systemic review. *Occas Pap R Coll Gen Pract.* 1994;67:1-35.

13. Hoskins PL, Fowler PM, Constantino M, et al. Sharing the care of diabetic patients between hospital and general practitioners: does it work? *Diabet Med.* 1993;10:81-86.

14. Hurwirz B, Goodman C, Yudkin J. Prompting the clinical care of non-insulin dependent (type II) diabetic patients in an inner city area: one model of community care. *BMJ.* 1993;306:624-630.

15. Griffin S. Diabetes care in general practice: a meta-analysis of randomized control trials. *BMJ.* 1998;317:390-396.

16. Cabana MD, Jee SH. Does continuity of care improve patient outcomes? *J Fam Pract.* 2004;53:974-980.

17. Zgibor JC, Songer TJ, Kelsey SF, et al. Influence of health care providers on the development of diabetes complications: long term follow-up from the Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetes Care.* 2003;25:1584-1590.

18. Shah BR, Hux JE, Laupacis A, et al. Diabetic patients with a prior specialist care have better glycaemic control than those with prior primary care. *J Evaluation Clin Prac.* 2005;11:568-575.

19. Abrahamian H, Schueller A, Mauler H, et al. Transfer of knowledge from the specialist to the generalist by videoconferencing: effect on diabetes care. *J Telemed Telecare.* 2002;8:350-355.

20. Ziemer DC, Doyle JP, Barnes CS, et al. An intervention to overcome clinical inertia and improve diabetes mellitus control in a primary care setting. Improving primary care of African Americans with diabetes (IPCAAD) 8. *Arch Intern Med.* 2006;166:507-513.

21. Goudswaard AN, Stolk RP, Zuithoff NP, et al. Long-term effects of self-management education for patients with Type 2 diabetes taking maximal oral hypoglycemic therapy: a randomized trial in primary care. *Diabet Med.* 2004;21:491-496.

22. Loveman E, Cave C, Green C, et al. The clinical and cost-effectiveness of patient education models for diabetes: a systematic

review and economic evaluation. *Health Technol Assess.* 2003; 7:1-190.

23. Norris SL, Lau J, Smith J, et al. Self-management education for adults with type 2 diabetes: a meta-analysis of the effect on glycemic control. *Diabetes Care.* 2002;25:1159-1171.

24. Chodosh J, Morton SC, Mojica W, et al. Meta-analysis: chronic disease self-management programs for older adults. *Ann Intern Med.* 2005;143:427-438.

25. Gary T, Genkinger J, Guallar E, et al. Meta-analysis of randomized educational and behavioral interventions in type 2 diabetes. *Diabetes Educ.* 2003;29:488-501.

26. Vermeire E, Wens J, VanRoyen P, et al. Interventions for improving adherence to treatment recommendations with people with type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2005;(2):CD003638.

27. Williams GC, McGregor H, Zeldman A, et al. Promoting glycemic control through diabetes self-management: evaluating a patient activation intervention. *Patient Educ Couns.* 2005;56:28-34.

28. Steed L, Lankester J, Barnard M, et al. Evaluation of the UCL diabetes self-management programme (UCL-DSMP): a randomized controlled trial. *J Health Psychol.* 2005;10;261-276.

29. Sarkadi A, Rosenqvist U. Experience-based group education in type 2 diabetes: a randomized trial. *Patient Educ Couns.* 2004; 53:291-298.

30. Rickheim R, Weaver T, Flader JL, et al. Assessment of group verus individual diabetes education: a randomized study. *Diabetes Care.* 2002;25:269-274.

31. Brown SA, Garcia AA, Winchell M. Reaching underserved populations and cultural competence in diabetes education. *Curr Diab Rep.* 2002;2:166-176.

32. Brown JB, Nichols GA, Glauber HS. Case-control study of 10 years of comprehensive diabetes care. *West J Med.* 2000;172: 85-90.

33. Wagner EH, Grotahus LC, Sandhu, N et al. Chronic care clinics for diabetes in primary care: a system-wide randomized trial. *Diabetes Care.* 2001;24:695-700.

34. Balas EA, Krishna S, Kretschmer RA, et al. Computerized knowledge management in diabetes care. *Med Care.* 2004;42: 610-621.

35. Stroebel RJ, Scheitel SM, Fitz JS, et al. A randomized trial of three diabetes registry implementation strategies in a community internal medicine practice. *Jt Comm J Qual Improv.* 2002; 28:441-450.

36. Sequist TD, Gandhi TK, Karson AS, et al. A randomized trial of electronic clinical reminders to improve quality of care for diabetes and coronary artery disease. *J Am Med Inform Assoc.* 2005; 12:431.

37. Bellazzi R, Arcelloni M, Bensa G, et al. Design, methods and evaluation directions of a multi-access service for the management of diabetes mellitus patients. *Diabetes Technol Ther.* 2003; 5:621-629.

38. Izquierdo RE, Knudson PE, Meyer S, et al. A comparison of diabetes education administered through telemedicine versus in person. *Diabetes Care.* 2003:26:1002-2007.

39. Farmer A, Gibson OJ, Tarassenko L, et al. A systematic review of telemedicine interventions to support blood glucose self-monitoring in diabetes. *Diabet Med.* 2005;22:1372-1378.

40. Bergenstal RM, Andersons RL, Bina DM, et al. Impact of modem-transferred blood glucose data on clinician work efficiency and patient glycemic control. *Diabetes Technol Ther.* 2005;7:241-247.

41. Glasgow RE, Boles SM, McKay HG, et al. The D-Net diabetes self-management program: long-term implementation, outcomes, and generalization results. *Prev Med.* 2003;36:410-419.

42. Grant RW, Hamrick HE, Sullivan CM, et al. Impact of population management with direct physician feedback on care of patients with type 2 diabetes. *Diabetes Care.* 2003;26:2275-2280.

43. Grant RW, Cagliero E, Sullivan CM, et al. A controlled trial of population management: diabetes mellitus: putting evidence into practice (DM-PEP). *Diabetes Care.* 2004;27:2299-2305.

44. Choe HM, Mitrovich S, Dubay D, et al. Proactive case management of high-risk patients with type 2 diabetes by a clinical pharmacist: a randomized trial. *Am J Manag Care.* 2005;11:253-260.

45. Blenkinsopp A, Hassey A. Effectiveness and acceptability of community pharmacy-based interventions in type 2 diabetes: a critical review of intervention design, pharmacist and patient perspectives. *Int J Pharmacy Pract.* 2005;13:231-240.

46. Taylor CB, Miller NH, Reilly KR, et al. Evaluation of a nurse-care management system to improve outcomes in patients with complicated diabetes. *Diabetes Care.* 2003;26:1058-1063.

47. Herrin J, Nicewander DA, Hollander PA, et al. Effectiveness of diabetes resource nurse case management and physician profiling in a fee-for-service setting: a cluster randomized trial. *Proc (Bayl Univ Med Cent).* 2006;19:95-102.

48. Davidson MB. Effect of nurse-directed diabetes care in a minority population. *Diabetes Care.* 2003;26:2281-2287.

49. Wong J, Gilber J, Kilburn L. *Seeking Program Sustainability in Chronic Disease Management: The Ontario Experience.* Toronto, Ontario: The Change Foundation; 2004. Available at: http://www.change foundation.com. Accessed September 1, 2008.

50. Rothman RL, Malone R, Bryant B, et al. A randomized trial of a primary care-based disease management program to improve cardiovascular risk factors and glycated hemoglobin levels in patients with diabetes. *Am J Med.* 2005;188:276-284.

51. Wolf AM, Conaway MR, Crowther JQ, et al. Translating lifestyle intervention to practice in obese patients with type 2 diabetes Improving Control with Activity and Nutrition (ICAN) study. *Diabetes Care.* 2004;27:1570-1576.

52. Gabbay RA, Lendel I, Saleem TM, et al. Nurse case management improves blood pressure, emotional distress and diabetes complication screening. *Diabetes Res Clin Pract.* 2006;71:28-35.

53. Maljanian R, Grey N, Staff I, et al. Improved diabetes control through a provider-based disease management program. *Dis Manag Health Outcomes.* 2002;10:1-8.

54. Fanning MF, Oakes DW. A tool for quantifying organizational

support for evidence-based practice change. *J Nurs Care Qual*. 2006;21:110-113.

55. Bodenheimer T, Wagner EH, Grumbach K. Improving primary care for patients with chronic illness. *JAMA*. 2002;288:1775-1779.

56. Bodenheimer T, Wagner EH, Grumbach K. Improving primary care for patients with chronic illness: the chronic care model, part 2. *JAMA*. 2002;288:1909-1914.

57. Bodenheimer T, Wang MC, Rundall TG, et al. What are the facilitators and barriers in physician organizations' use of care management process? *Jt Comm J Qual Saf*. 2004;30:505-514.

58. Battersby M. Health reform through coordinated care: SA HealthPlus. *BMJ*. 2005;330:662-665.

59. Singh D, Surrey and Sussex Primary Care Trust Alliance. Transforming chronic care: a systematic review of the evidence. *Evid Based Cardiovasc Med*. 2005;8:91-94.

60. Wellingham J, Tracey J, Rea H, et al. The development and implementation of the Chronic Care Management Program in Counties Manukau. *N Z Med J*. 2003;116:U327.

61. Government of British Columbia, Ministry of Health website. Available at: http://www.healthservices.gov.bc.ca/cdm. Accessed September 1, 2008.

62. Barr VJ, Robinson S, Marin-Link B, et al. The expanded Chronic Care Model: an integration of concepts and strategies from population health promotion and the chronic care model. *Hosp Q*. 2003;7:73-82.

63. Wagner EH, Austin BT, Von Korff M. Organizing care for patients with chronic illness. *Milbank Q*. 1996;74:511-544.

64. Groves T, Wagner EH. High quality care for people with chronic diseases. *BMJ*. 2005;330:609-610.

65. Baquet CR, Carter-Pokras O, Bengen-Seltzer B. Healthcare disparities and models for change. *Am J Manag Care*. 2004;10: SP5-SP11.

66. World Health Organization. *Innovative Care for Chronic Conditions: Building Blocks for Action. Global Report*. Geneva, Switzerland: World Health Organization; 2002. Available at: http://www.who.int/diabetesactiononline/about/icccglobal report.pdf. Accessed September 1, 2008.

67. Piatt GA, Orchard TJ, Emerson S, et al. Translating the chronic care model into the community. *Diabetes Care*. 2006;29:811-817.

68. Tsai AC, Morton SC, Mangione CM, et al. A meta-analysis of interventions to improve care for chronic illnesses. *Am J Manag Care*. 2005;11:478-488.

69. Ansari Z, Ackland MJ, Carson NJ, et al. Small area analysis of diabetes complications: opportunities for targeting public health and health services interventions. *Aust J Primary Health*. 2005;11:72-78.

70. Smith S, Bury G, O'Leary M, et al. The North Dublin randomized controlled trial of structured diabetes shared care. *Fam Pract*. 2004;21:39-45.

71. Diabetes Integrated Care Evaluation Team. Integrated care for diabetes: clinical, psychological, and economic evaluation. *BMJ*. 1994;308:1208-1212.

Self-management Education

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Helen Jones RN MSN CDE, Lori D. Berard RN CDE and Heather Nichol RN MScN CDE

KEY MESSAGES

- Self-management education (SME) that incorporates knowledge and skills development, as well as cognitive-behavioural interventions, should be implemented for all individuals with diabetes.

- The content of SME programs must be individualized according to the individual's type of diabetes, current state of metabolic stability, treatment recommendations, readiness for change, learning style, ability, resources and motivation.

- SME is a fundamental component of diabetes care and is most effective when ongoing diabetes education and comprehensive healthcare occur together.

INTRODUCTION

The objectives of diabetes self-management education (SME) are to increase the individual's involvement in, confidence with and motivation for control of their diabetes, its treatment and its effect on their lives (1). The term "SME," rather than "diabetes education," emphasizes the importance of including a variety of client-centred strategies and interventions that address the physical, psychological and social management of living with a chronic illness.

SME goes beyond a focus on adherence to guidelines and treatment prescriptions; it incorporates didactic and non-didactic (e.g. active, participatory) education, as well as social, behavioural and psychological interventions (2).

ELEMENTS OF SME

SME, which includes skills training, coping strategies, problem-solving and case management, has been demonstrated to improve the individual's ability to engage in effective self-care, lower glycated hemoglobin (A1C) levels and enhance quality of life (3-6). The essential components of SME are hypothesized to include: education tailored to individual needs and circumstances; a group setting with others who share the same condition; feedback following an intervention; psychological emphasis in the intervention; and involvement of medical providers in providing the intervention (4). Long-term education with scheduled follow-up has also been shown to enhance the effect of education on glycemic control (7). Didactic programs alone are not advocated (3). Motivational interviewing, added to a behaviour-change program, may have greater impact (1,8).

The content and skill training components of SME programs must be individualized according to the type of diabetes, current state of metabolic stability, treatment recommendations, learning ability, ability to change, resources and motivation. Education should be offered in a timely and needs-based manner (5,9,10). Interventions that include face-to-face delivery, a cognitive-reframing teaching method and practical application content are more likely to improve glycemic control (9). The following basic knowledge areas are generally accepted as essential to an SME program (11,12), and each topic should include a problem-solving component; monitoring of relevant health parameters; healthy eating; physical activity; pharmacotherapy; hypo- and hyperglycemia prevention and management; and prevention and surveillance of complications and comorbid conditions. Suggested learning objectives for each topic area have been developed at basic, intermediate and advanced levels (Table 1) (11).

Skill training during SME should include self-monitoring of blood glucose (SMBG), making dietary choices, incorporating an exercise regimen, using medications as recommended and possible medication adjustment (5,9,10). For example, individuals with diabetes should be taught to interpret their own blood glucose (BG) meter results and make appropriate changes (5,13). Additional information regarding dietary choices, physical activity and BG levels before and after meals is frequently required to guide treatment decisions (13).

Table 1. Levels of learning (11)	
Survival/ basic level	• The knowledge, skills and motivation required for self-care to prevent, identify and treat the acute short-term complications of hyperglycemia or severe hypoglycemia • The person may or may not wish and/or need or be able to progress beyond this level
Intermediate level	• The knowledge, skills and motivation required for self-care to achieve recommended metabolic control, reduce the risk of long-term complications and facilitate the adjustment to living with diabetes
Advanced level	• The knowledge, skills and motivation required for self-care to support intensive diabetes management for optimal metabolic control, and full integration of care into the individual's life activities and goals

Interventions should focus on medications (including regimen changes and adherence), SMBG and physical activity to reduce A1C (10). For individuals with type 1 diabetes, education offered as part of intensified treatment interventions can result in long-lasting improvement in metabolic control and reduction in complications (14). Education for flexible insulin management and dietary freedom has been shown to improve quality of life as well as glycemic control (15,16).

EMPOWERMENT

Empowerment is an essential psychological component of SME (17). To implement interventions using an empowerment approach and ensure informed decision making, the educator should engage in the following behaviours: demonstrate acceptance (respect) for the individual's perspectives; explore the affective or emotional aspect of an issue; work in an alliance or partnership with the individual; and facilitate active participation of all parties in the education process (18).

Approaches that increase an individual's participation and collaboration in decision making regarding care and education have been shown to be more effective than a didactic approach in enhancing psychological adjustment to diabetes and potentially preventing psychological distress (5,18-20).

SUPPORT SYSTEMS

Evidence suggests that including family members (parents, spouses, significant others) in educational interventions is beneficial for both children and adults in improving diabetes-related knowledge and glycemic control (20). Interventions that target families' ability to cope with stress or diabetes-related conflict are effective (20). Peer programs geared toward developing self-efficacy (i.e. self-confidence in one's ability to carry out a behaviour), sometimes referred to as "self-management" programs within the Chronic Disease Model, have demonstrated small improvements in psychological outcomes (21).

Figure 1. Process of teaching people to manage their diabetes (adapted from 28)

Self-management education
Incorporate didactic, cognitive, behavioural and social interventions that include:
• Goal-setting
• Problem-solving
• Other motivational strategies

• Knowledge
• Psychomotor skills

Psychosocial mediators
• Motivation (beliefs, attitudes)
• Coping skills

Healthy self-management behaviours
• Diet
• SMBG
• Medications
• Physical activity
• Smoking cessation

Short-term outcomes
• Glycemic, BP and lipid control
• Weight
• Quality of life
• Attendance at healthcare provider appointments

Long-term outcomes
• Morbidity
• Mortality
• Quality of life

BP = blood pressure
SMBG = self-monitoring of blood glucose

EDUCATIONAL SETTINGS

SME conducted in community gathering places and group education settings has been shown to be effective in improving glycemic control in type 2 diabetes and promoting efficiencies in delivery of diabetes self-management programs (22,23). SME in home settings is also effective for adolescents with type 1 diabetes (9).

METHODS OF DELIVERY

Disease-specific chronic disease management models have demonstrated positive outcomes (4). Improved outcomes are also associated with integrated care, which includes case management (24,25). Diabetes self-management is most effective when ongoing diabetes education and comprehensive healthcare occur together (5,14). Interactive health communications (computer-based information packages combined with either social, decision or behaviour-change support) have a largely positive effect on users and support improved behaviour and clinical outcomes (26,27).

CONCLUSION

While further study is required to define its most effective elements, SME is widely accepted as being essential in enhancing knowledge, skills and subsequent behavioural change. It has been shown to result in improved ability to handle the physical and emotional demands of self-care and in improved short- and long-term clinical outcomes (1-6,28). The key elements of effective SME are summarized in Figure 1.

RECOMMENDATIONS

1. People with diabetes should be offered timely diabetes education that is tailored to enhance self-care practices and behaviours [Grade A, Level 1A (5,9)].

2. All people with diabetes who are able should be taught how to self-manage their diabetes, including SMBG [Grade A, Level 1A (5)].

3. Self-management education that incorporates cognitive behavioural interventions such as problem-solving, goal-setting and self-monitoring of health parameters should be implemented in addition to didactic education programming for all individuals with diabetes [Grade B, Level 2 (3,9)].

4. Interventions that increase patients' participation and collaboration in healthcare decision-making should be used by providers [Grade B, Level 2 (5)].

5. SME interventions should be offered in small group and/or one-on-one settings, as both are effective for people with type 2 diabetes [Grade A, Level 1A (22,23)].

6. Interventions that target families' ability to cope with stress or diabetes-related conflict should be considered in education interventions when indicated [Grade B, Level 2 (20)].

OTHER RELEVANT GUIDELINES

Organization of Diabetes Care, p. S20
Monitoring Glycemic Control, p. S32
Psychological Aspects of Diabetes, p. S82
Type 1 Diabetes in Children and Adolescents, p. S150

REFERENCES

1. Newman S, Steed L, Mulligan K. Self-management interventions for chronic illness. *Lancet*. 2004;364:1523-1537.

2. Ismail K, Winkley K, Rae-Hesketh S. Systematic review and meta-analysis of randomized controlled trials of psychological interventions to improve glycaemic control in patients with type 2 diabetes. *Lancet*. 2004;363:1589-1597.

3. Steed L, Cooke D, Newman S. A systematic review of psychosocial outcomes following education, self-management and psychological interventions in diabetes mellitus. *Patient Educ Couns*. 2003;51:5-15.

4. Chodosh J, Morton SC, Mojica W, et al. Meta-analysis: chronic diseases self-management programs for older adults. *Ann Intern Med*. 2005;143:427-458.

5. Norris SL, Engelgau MM, Narayan KMV. Effectiveness of self-management training in type 2 diabetes: a systematic review of randomized controlled trials. *Diabetes Care*. 2001;24:561-587.

6. Norris SL, Lau J, Smith CH, et al. Self-management education for adults with type 2 diabetes: a meta-analysis of the effect on glycemic control. *Diabetes Care*. 2002;25:1159-1171.

7. Brown S, Blozis S, Kouzekanani K, et al. Dosage effects of self-management education for Mexican-Americans. *Diabetes Care*. 2005;28:527-532.

8. Channon SJ, Huws-Thomas MV, Rollnick S, et al. A multicenter randomized controlled trial of motivational interviewing in teenagers with diabetes. *Diabetes Care*. 2007;30:1390-1395.

9. Ellis S, Speroff T, Dittus R, et al. Diabetes patient education: a meta analysis and meta-regression. *Patient Educ Couns*. 2004;52 97-105.

10. Gary T, Genkinger J, Guallar E, et al. Meta-analysis of randomized educational and behavioral interventions in type 2 diabetes. *Diabetes Educ*. 2003;29:488-501.

11. Canadian Diabetes Association. Jones H, ed. *Building Competency in Diabetes Education: The Essentials*. Toronto, ON: Canadian Diabetes Association; 2004.

12. American Association of Diabetes Educators. Standards for outcome measures of diabetes self-management. *Diabetes Educ*. 2003;29:804-816.

13. Bergenstal R, Gavin JR 3rd, on behalf of the Global Consensus Conference on Glucose Monitoring Panel. The role of self-monitoring of blood glucose in the care of people with diabetes: report of a global consensus conference. *Am J Med*. 2005;118(suppl 9A):1S-6S.

14. Loveman E, Cave C, Green C, et al. The clinical and cost-effectiveness of patient education models for diabetes: a systematic review and economic evaluation. *Health Technol Assess*. 2003; 7:1-190.

15. Funnell M, Nwankwo R, Gillard ML, et al. Implementing an

empowerment-based diabetes self-management education program. *Diabetes Educ.* 2005;31:53-56.

16. DAFNE Study Group. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomized controlled trial. *BMJ.* 2002;325:746.

17. Skinner TC, Cradock S. Empowerment: what about the evidence? *Practical Diabetes Int.* 2000;17:91-95.

18. Greenfield S, Kaplan SH, Ware JE Jr, et al. Patients' participation in medical care: effects on blood sugar control and quality of life in diabetes. *J Gen Intern Med.* 1988;3:448-457.

19. Gage H, Hampson S, Skinner TC, et al. Educational and psychosocial programmes for adolescents with diabetes: approaches, outcomes and cost-effectiveness. *Patient Educ Couns.* 2004;53:333-346.

20. Armour TA, Norris SL, Jack L Jr, et al. The effectiveness of family interventions in people with diabetes mellitus: a systematic review. *Diabet Med.* 2005;22:1295-1305.

21. Lorig KR, Sobel DS, Stewart AL, et al. Evidence suggesting that a chronic disease self-management program can improve health status while reducing hospitalization: a randomized trial. *Med Care.* 1999;37:5-14.

22. Rickheim PL, Weaver TW, Flader JL, et al. Assessment of group versus individual diabetes education: a randomized study. *Diabetes Care.* 2002;25:269-274.

23. Deakin T, McShane CE, Cade JE, et al. Group based training for self-management strategies in people with type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2005;(2):CD003417.

24. Shojania KG, Ranjii SR, McDonald KM, et al. Effects of quality improvement strategies for type 2 diabetes on glycemic control; a meta-regression analysis. *JAMA.* 2006;296:427-440.

25. Rothman RL, Malone R, Bryant B, et al. A randomized trial of a primary care-based disease management program to improve cardiovascular risk factors and glycated hemoglobin levels in patients with diabetes. *Am J Med.* 2005;118:276-284.

26. Murray E, Burns J, See TS, et al. Interactive health communication applications for people with chronic disease. *Cochrane Database Syst Rev.* 2005;(4):CD004274.

27. Jones H, Edwards L, Vallis TM, et al. Changes in diabetes self-care behaviors make a difference in glycemic control: the Diabetes Stages of Change (DiSC) study. *Diabetes Care.* 2003; 26:732-737.

28. Norris SL, Nichols PJ, Caspersen CJ, et al. Increasing diabetes self-management education in community settings: a systematic review. *Am J Prev Med.* 2002;22:39-66.

Targets for Glycemic Control

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by S. Ali Imran MBBS FRCP(Edin) FRCPC and Stuart A. Ross MB ChB FRCPC FRACP

KEY MESSAGES

- Optimal glycemic control is fundamental to the management of diabetes.

- Both fasting and postprandial plasma glucose levels correlate with the risk of complications and contribute to the measured glycated hemoglobin value.

- When setting treatment goals and strategies, consideration must be given to individual risk factors such as age, prognosis, presence of diabetes complications or comorbidities, and their risk for and ability to perceive hypoglycemia.

RELATIONSHIP BETWEEN BLOOD GLUCOSE LEVELS AND COMPLICATIONS OF DIABETES

Optimal glycemic control is fundamental to the management of diabetes. There is compelling evidence that improved glycemic control reduces risks of microvascular complications in both type 1 and type 2 diabetes (1-4). There is also evidence in patients with type 1 diabetes that improved glycemic control reduces the risk of cardiovascular disease (CVD) (5). However, similar benefit of improved glycemic control on macrovascular complications in people with type 2 diabetes has not been demonstrated through randomized controlled trials (4,6). In epidemiologic analyses, glycated hemoglobin (A1C) levels >7.0% are associated with a significantly increased risk of both microvascular and macrovascular complications, regardless of underlying treatment (3,7-9). The data from the Diabetes Control and Complications Trial (DCCT) (7) and the United Kingdom Prospective Diabetes Study (UKPDS) (8) demonstrated a continuous relationship between A1C and diabetes complications, with no apparent threshold of benefit. In the DCCT, a 10% reduction in A1C (e.g. from 8.0 to 7.2%) was associated with a 40 to 50% lower risk of retinopathy progression, although the absolute reduction in risk was substantially less at lower A1C levels (7). In the subsequent prospective follow-up of the DCCT cohort over 11 years, the risk of CVD and death from CV causes was reduced by 42 to 57% in the intensive insulin therapy group (5). In the UKPDS, this relationship was directly linear, with each 1.0% (absolute) reduction in mean A1C associated with a 37% decline in the risk of microvascular complications, a 14% lower rate of myocardial infarction

(MI) and fewer deaths from diabetes or any cause (8).

Both fasting plasma glucose (FPG) and postprandial PG levels correlate with the risk of complications. The analyses from the DCCT indicated that mean capillary glucose levels (based on both pre- and postprandial measurements) are also directly correlated to the risk of complications (10). FPG is directly related to CV events, with the increase in risk apparent even at PG levels that are within the normal range for people without diabetes (11). In a meta-analysis of 38 prospective studies, an FPG of >5.5 mmol/L was associated with an increased risk of CV events (12).

Postprandial hyperglycemia is a powerful predictor of adverse outcomes. The Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study found the 2-hour postchallenge PG to be a better predictor of CVD and all-cause mortality than FPG (13). This association between CV disease and 2-hour postprandial PG appears to be linear without a threshold (12,13). In another study, a 2-hour postprandial PG level >7.8 mmol/L was associated with an increase in all-cause mortality (14). The data from the Study to Prevent Non-Insulin Dependent Diabetes Mellitus (STOP-NIDDM) also suggest that targeting postprandial PG with acarbose may reduce the risk of CV outcomes (15). There is also a strong association between postprandial hyperglycemia and microvascular complications. In a prospective observational study, postprandial hyperglycemia was found to be a better predictor of diabetic retinopathy than A1C (16). Similarly, in the Kumamoto study, the risk of microvascular complications increased with 2-hour postprandial PG levels >10.0 mmol/L (2). Additionally, the Diabetes Intervention Study found that in patients with type 2 diabetes, a 1-hour postprandial PG level ≤8.0 mmol/L conferred the lowest risk of MI or death, while levels >10.0 mmol/L were associated with the highest risk (17).

Despite the association between PG and CVD, 2 large, randomized, controlled, multicentre trials, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (5) and the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial (4) have shown that intensive glucose lowering in type 2 diabetes does not reduce major CV events.

The ACCORD trial recruited individuals with type 2 diabetes who were between the ages of 40 and 79 years and had CVD, or were between the ages of 55 and 79 years and had evidence

of significant atherosclerosis, albuminuria, left ventricular hypertrophy or at least 2 additional risk factors for CVD (obesity, hypertension, dyslipidemia or current status as a smoker). At baseline, mean age was 62.2 years, median duration of diabetes was 10 years and mean A1C was 8.3%. One of the major arms of the trial was to determine whether an intensive PG-lowering approach aimed at achieving A1C levels <6.0% would reduce CV events compared to a more conventional approach, aiming at achieving an A1C between 7.0 and 7.9%. After a mean 3.5 years of follow-up, the intensive treatment arm was halted because of safety concerns. The incidence of death was 11 per 1000 per year in the conventional treatment group (median achieved A1C of 7.5%) vs. 14 per 1000 per year in the intensive treatment group (median achieved A1C of 6.4%). Furthermore, intensive treatment was also associated with a significantly higher risk of severe hypoglycemia requiring medical assistance (3.1% in the intensive treatment group vs. 1.4% in the conventional treatment group) and weight gain. At the same time, there was evidence of a nonsignificant 10% reduction in the primary composite endpoint of nonfatal MI, stroke or CV death. The ADVANCE trial is a similar trial that enrolled individuals with type 2 diabetes who were at least 55 years of age and had a history of major macrovascular or microvascular disease or at least 1 other risk factor for vascular disease. At baseline, mean age was 66 years, mean duration of diabetes was 8 years and mean A1C was 7.48%. Intensive control with gliclazide (modified release) based therapy (median achieved A1C of 6.5%) vs. the conventional treatment (which did not use gliclazide-based treatment) (median achieved A1C of 7.3%) decreased nephropathy by 21% but did not decrease CV events. Similar to the ACCORD study, weight gain and severe hypoglycemia occurred more frequently in the intensive treatment group. The risk of hypoglycemia was 2.7% in the intensive treatment group, compared to 1.5% in the standard group. However, there was no increased risk of death in the intensively controlled group in the ADVANCE trial.

These trials suggest that in patients with type 2 diabetes and a CV risk profile similar to the ACCORD population, a strategy to target a normal A1C (i.e. <6.0%) may increase mortality. However, this risk must be balanced against the decrease in the incidence of nephropathy shown in the ADVANCE study, in which a similar population was treated with a strategy to target an A1C <6.5%.

Both FPG and postprandial PG values contribute to the A1C value. When the A1C values are higher (>8.5%), the major contribution is from the FPG levels, but as the A1C value approaches the target value of ≤7.0%, there is a greater contribution from the postprandial PG values (18,19). A recent study by Monnier and colleagues in 130 patients with type 2 diabetes using continuous glucose monitoring demonstrated that a 2-hour postprandial PG of <8.0 mmol/L correlates best with an A1C of <7.0% (20). In view of this, if A1C targets cannot be achieved with a postprandial target of

5.0 to 10.0 mmol/L, further postprandial BG lowering to 5.0 to 8.0 mmol/L can be considered (20).

RISK OF HYPOGLYCEMIA

While epidemiologic data suggest that the lowest risk of complications will occur in those with normoglycemia, the absolute benefit of lowering A1C levels from 7.0 to 6.5% is expected to be small and must be weighed against the risk of hypoglycemia. The hypoglycemia data from the DCCT showed that the risk of severe hypoglycemia was 3 times higher among participants receiving intensive therapy (1). Similarly, intensive therapy in type 2 diabetes increases the risk of severe hypoglycemia by 2-to-3 fold, particularly among those using insulin(3,4,6).

GLYCEMIC TARGETS

The glycemic targets recommended for most patients with type 1 and type 2 diabetes are listed in Table 1. However, clinical judgment is required to determine which people can reasonably and safely achieve these targets. Treatment goals and strategies must be tailored to the patient, with consideration given to individual risk factors (e.g. the patient's age, prognosis, level of glycemic control, duration of diabetes, the presence of diabetes complications or comorbidities, and their risk for and ability to perceive hypoglycemia). To make the guidelines easier to incorporate into clinical practice, a single A1C target is provided, and PG targets have been rounded to whole numbers.

Table 1. Recommended targets for glycemic control			
	A1C* **(%)**	**FPG or preprandial PG (mmol/L)**	**2-hour postprandial PG (mmol/L)**
Type 1 and type 2 diabetes	≤7.0	4.0–7.0	5.0–10.0 (5.0–8.0 if A1C targets not being met)

*Treatment goals and strategies must be tailored to the individual with diabetes, with consideration given to individual risk factors. Glycemic targets for children ≤12 years of age and pregnant women differ from these targets. See relevant guidelines for further details. An A1C of 7.0% corresponds to a laboratory value of 0.070. Where possible, Canadian laboratories should standardize their A1C values to Diabetes Control and Complications Trial levels (reference range: 0.040 to 0.060). However, as many laboratories continue to use a different reference range, the target A1C value should be adjusted based on the specific reference range used by the laboratory that performed the test. As a useful guide, an A1C target of 7.0% refers to a threshold that is approximately 15% above the upper limit of normal.

A1C = glycated hemoglobin
FPG = fasting plasma glucose
PG = plasma glucose

RECOMMENDATIONS

1. Glycemic targets must be individualized; however, therapy in most individuals with type 1 or type 2 diabetes should be targeted to achieve an A1C ≤7.0% in order to reduce the risk of microvascular *[Grade A, Level 1A (1-4)]* and, in individuals with type 1 diabetes, macrovascular complications *[Grade C, Level 3 (5)]*.

2. A target A1C of ≤6.5% may be considered in some patients with type 2 diabetes to further lower the risk of nephropathy *[Grade A Level 1A (4)]*, but this must be balanced against the risk of hypoglycemia *[Grade A Level 1A (4,5)]* and increased mortality in patients who are at significantly elevated risk of cardiovascular disease *[Grade A Level 1A (4)]*.

3. In order to achieve A1C of ≤7.0%, people with diabetes should aim for:
   • An FPG or preprandial PG target of 4.0 to 7.0 mmol/L *[Grade B, Level 2 (1), for type 1; Grade B, Level 2 (2,3), for type 2 diabetes]*; and
   • A 2-hour postprandial PG target of 5.0 to 10.0 mmol/L *[Grade B, Level 2 (1), for type 1 diabetes; Grade B, Level 2 (2,3), for type 2 diabetes]*. If A1C targets cannot be achieved with a postprandial target of 5.0 to 10.0 mmol/L, further postprandial BG lowering to 5.0 to 8.0 mmol/L can be considered *[Grade D, Consensus, for type 1 diabetes; Grade D, Level 4 (18,19), for type 2 diabetes]*.

OTHER RELEVANT GUIDELINES

Monitoring Glycemic Control, p. S32
Hypoglycemia, p. S62
Type 1 Diabetes in Children and Adolescents, p. S150
Type 2 Diabetes in Children and Adolescents, p. S162
Diabetes and Pregnancy, p. S168
Diabetes in the Elderly, p. S181

REFERENCES

1. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329:977-986.

2. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract*. 1995;28:103-117.

3. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352:837-853.

4. The ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *New Engl J Med*. 2008;358:2560-2572.

5. Nathan DM, Cleary PA, Backlund JY, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Eng J Med*. 2005;353:2643-2653.

6. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *New Engl J Med*. 2008;358:2545-2559.

7. The Diabetes Control and Complications Trial Research Group. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the Diabetes Control and Complications Trial. *Diabetes*. 1995;44:968-983.

8. Stratton IM, Adler AI, Neil HAW, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;321:405-412.

9. Standl E, Balletshofer B, Dahl B, et al. Predictors of 10-year macrovascular and overall mortality in patients with NIDDM: the Munich General Practitioner Project. *Diabetologia*. 1996; 39:1540-1545.

10. Service FJ, O'Brien PC. The relation of glycaemia to the risk of development and progression of retinopathy in the Diabetic [sic] Control and Complications Trial. *Diabetologia*. 2001;44:1215-1220.

11. Coutinho M, Gerstein HC, Wang Y, et al. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care*. 1999;22:233-240.

12. Levitan EB, Song Y, Ford ES, et al. Is nondiabetic hyperglycemia a risk factor for cardiovascular disease? *Arch Intern Med*. 2004;164:2147-2155.

13. DECODE Study Group, European Diabetes Epidemiology Group. Is current definition for diabetes relevant to mortality risk from all causes and cardiovascular and noncardiovascular causes? *Diabetes Care*. 2003;26:688-696.

14. Sorkin JD, Muller DC, Fleg JL, et al. The relation of fasting and 2-h postchallenge plasma glucose to mortality: data from the Baltimore Longitudinal Study of Aging with a critical review of the literature. *Diabetes Care*. 2005;28:2626-2632.

15. Chaisson JL, Josse RG, Gomis R, et al. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM Trial. *JAMA*. 2003;290:486-494.

16. Shiraiwa T, Kaneto H, Miyatsuka T, et al. Post prandial hyperglycemia is an important predictor of the incidence of diabetic microangiopathy in Japanese type 2 diabetic patients. *Biochem Biophys Res Commun*. 2005;336:339-345.

17. Hanefeld M, Fischer S, Julius U, et al. Risk factors for myocardial infarction and death in newly detected NIDDM: the Diabetes Intervention Study, 11-year follow-up. *Diabetologia*. 1996;39:1577-1583.

18. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients. *Diabetes Care*. 2003;26:881-885.

19. Woerle HHJ, Neumann C, Zschau S, et al. Impact of fasting and postprandial glycemia on overall glycemic control in type 2 diabetes. Importance of postprandial glycemia to achieve target HbA1c levels. *Diab Res Clin Pract*. 2007;77:280-285.

20. Monnier L, Colette C, Dunseath GJ, et al. The loss of postprandial glycemic control precedes stepwise deterioration of fasting with worsening diabetes. *Diabetes Care*. 2007;30:263-269.

Monitoring Glycemic Control

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee
This initial draft of this chapter was prepared by Sharon Brez RN BScN MA(Ed) CDE, Lori Berard RN CDE and Ian Blumer MD FRCPC

KEY MESSAGES

- Glycated hemoglobin (A1C) is a valuable indicator of treatment effectiveness, and should be measured every 3 months when glycemic targets are not being met and when diabetes therapy is being adjusted.

- Awareness of all measures of glycemia, including self-monitoring of blood glucose (SMBG) results and A1C, provide the best information to assess glycemic control.

- The frequency of SMBG should be determined individually, based on the type of diabetes, the treatment prescribed, the need for information about BG levels and the individual's capacity to use the information from testing to modify behaviours or adjust medications.

GLYCATED HEMOGLOBIN TESTING

The Diabetes Control and Complications Trial (DCCT) (1) and the United Kingdom Prospective Diabetes Study (UKPDS) (2) demonstrated that glycated hemoglobin (A1C) and the development of long-term complications are correlated in both type 1 and type 2 diabetes, respectively. A1C is a reliable estimate of mean plasma glucose (PG) levels over the previous 3 to 4 months for most individuals (3). In uncommon circumstances where the rate of red blood cell turnover is significantly shortened or extended, or the structure of hemoglobin is altered, A1C may not accurately reflect glycemic status. A1C is a valuable indicator of treatment effectiveness and should be measured every 3 months when glycemic targets are not being met and when diabetes therapy is being adjusted. Testing at 6-month intervals may be considered in situations when glycemic targets are consistently achieved (4).

Currently, A1C is the preferred standard for assessing glycated hemoglobin, and laboratories are encouraged to use assay methods for this test that are standardized to the DCCT reference (4,5). A strong mathematical relationship between mean blood glucose (BG) values and A1C levels has been identified (6). In the future, A1C may be reported as "average blood glucose" in order to assist people to better understand the meaning of the results of this test (7).

SELF-MONITORING OF BLOOD GLUCOSE

Awareness of all measures of glycemia, including self-monitoring of blood glucose (SMBG) results and A1C, provide

the best information to assess glycemic control (4). Most people with diabetes can benefit from SMBG (8,9). Potential benefits, which may include improvement in A1C, avoidance and identification of hypoglycemia and increased lifestyle flexibility, are enhanced when individuals receive self-management education that enables them to adjust their dietary choices, physical activity and medication(s) in response to SMBG values (8,10-14). Effective education and implementation of strategies that employ patient empowerment and behaviour change theory may be most effective in supporting the incorporation of SMBG into the diabetes management routine (10,15-18).

Frequency of SMBG

The frequency of SMBG should be determined individually, based on the type of diabetes, the treatment prescribed, the need for information about BG levels and the individual's capacity to use the information from testing to modify behaviours or adjust medication.

For people with type 1 diabetes, SMBG is an essential component of daily diabetes management. In a large cohort study, performance of ≥3 self-tests per day was associated with a statistically and clinically significant 1.0% reduction in A1C levels (8). The results of multiple tests each day provide information that is better correlated to A1C than fasting results alone. BG measurements taken after lunch, after supper and at bedtime have demonstrated the highest correlation to A1C (6). More frequent testing is often required to provide the information needed to reduce hypoglycemia risk, adjust treatment and make appropriate lifestyle choices.

The benefits and optimal frequency of SMBG in type 2 diabetes are less clear than for type 1 (8,9,12,19-26). Current evidence is at times contradictory, and methodological and conceptual limitations exist in the literature. SMBG in those who are recently diagnosed, regardless of treatment, has been demonstrated to be of benefit (24). A large cohort study found that for people with type 2 diabetes treated with oral antihyperglycemic agents, testing at least once daily was associated with a 0.6% lower A1C than less frequent monitoring (8). A more recent randomized controlled trial (RCT) of SMBG with or without instruction on how to use results for diabetes self-management failed to demonstrate improvement in glycemic control (26). However, other adequately powered RCTs, large cohort studies and consensus state-

ments have identified benefits of more frequent testing on glycemic control, especially when this information is used to make appropriate and timely treatment and lifestyle adjustments (8,15,21,22,27,28). Given current uncertainties regarding the benefits of SMBG for individuals with type 2 diabetes not taking insulin, a well-designed RCT is needed to adequately answer this important but complex question.

For those with type 2 diabetes using insulin, frequent testing is also an integral component of care. In a large, nonrandomized study of individuals with stable type 2 diabetes using insulin, testing at least 3 times a day was associated with improved glycemic control (28).

In people with type 2 diabetes, timing of testing should take into account the potential for hypoglycemia associated with oral insulin secretagogues, and the fact that postprandial hyperglycemia is associated with increased cardiovascular risk (29). Postprandial PG results are generally better correlated to A1C than tests taken at other times of the day (30,31). In people with very poor glycemic control, however, fasting plasma glucose (FPG) may more strongly reflect overall glycemia (31).

Individuals who are intensively managed with multiple daily insulin injections or continuous subcutaneous insulin infusion (CSII), with the goal of near normalization of BG levels, can use information obtained from preprandial and bedtime testing, as well as intermittent postprandial and nocturnal tests, to adjust insulin, dietary choices and activity levels. Testing before and after meals is associated with improved glycemic control compared to preprandial testing alone (32). Since nocturnal hypoglycemia may be more frequent in intensively managed individuals, periodic overnight testing at a time corresponding to peak insulin action should be undertaken (1,33-37).

Verification of accuracy of SMBG performance and results

Variability exists between BG results obtained using self-monitoring devices and laboratory testing of PG. At BG levels >4.2 mmol/L, a difference of <20% between fingertip sampling of capillary BG and simultaneous venous FPG levels is considered acceptable (5). Less variation is recommended for BG readings ≤4.2 mmol/L (5). In order to ensure accuracy of meter readings, meter results should be compared with laboratory measurement of PG at least annually and when indicators of glycemic control do not match meter readings. In addition, as errors in testing techniques are commonly observed, periodic re-education on correct monitoring technique may improve the accuracy of SMBG results (10,38). In rare situations, therapeutic interventions may interfere with the accuracy of some BG meter results. For example, icodextrin-containing peritoneal dialysis solutions may cause false high readings in some meters utilizing glucose dehydrogenase methods. To avoid unsafe treatment decisions, care should be taken to select an appropriate meter in these situations.

Alternate site testing

Meters are available that allow SMBG using blood samples from sites other than the fingertip, such as the forearm, palm of the hand or thigh. Accuracy of results over a wide range of BG levels and during periods of rapid change in BG levels is variable across sites. During periods of rapid change in BG levels (e.g. after meals, after exercise and during hypoglycemia), fingertip testing has been shown to more accurately reflect glycemic status than forearm or thigh testing (39,40). In comparison, blood samples taken from the palm near the base of the thumb (thenar area), demonstrate a closer correlation to fingertip samples at all times of day, and during periods of rapid change in BG levels (41,42).

KETONE TESTING

Ketone testing is recommended for all individuals with type 1 diabetes during periods of acute illness accompanied by elevated BG, when preprandial BG levels remain elevated (>14.0 mmol/L) or when symptoms of diabetic ketoacidosis (DKA) such as nausea, vomiting or abdominal pain are present (4). If all of these conditions are present in type 2 diabetes, ketone testing should be considered, as DKA can also occur in these individuals.

During DKA, the equilibrium that is usually present between ketone bodies shifts toward formation of beta-hydroxybutyric acid (beta-OHB). As a result, testing methods that measure blood beta-OHB levels may provide more clinically useful information than those that measure urine acetoacetate or acetone levels. Assays that measure acetoacetate through urine testing may not identify the onset and resolution of ketosis as quickly as those that quantify beta-OHB levels in blood, since acetoacetate or acetone can increase as beta-OHB decreases with effective treatment (4,5). Meters that quantify beta-OHB from capillary sampling may be preferred for self-monitoring of ketones, as they have been associated with earlier detection of ketosis (4,43-45) and may provide information required to prevent progression to DKA. This may be especially useful for individuals with type 1 diabetes using CSII, as interruption of insulin delivery can result in rapid onset of DKA (46).

CONTINUOUS GLUCOSE MONITORING SYSTEMS

Continuous glucose monitoring systems (CGMS) measure glucose concentrations in the interstitial fluid. Two types of devices are available – newer systems that display "real time" glucose results directly on the monitoring system, and earlier "non-real time" (i.e. retrospective) devices that do not have this result display capability.

Real-time CGMS has been associated with positive outcomes, including improved A1C (47) and significantly reduced duration of hypoglycemia (48), hyperglycemia (48) and nocturnal hypoglycemia (48) in insulin-treated patients. Real-time CGMS results have been found to be closely correlated to BG

RECOMMENDATIONS

1. For most individuals with diabetes, A1C should be measured every 3 months to ensure that glycemic goals are being met or maintained. Testing at least every 6 months may be considered in adults during periods of treatment and lifestyle stability when glycemic targets have been consistently achieved *[Grade D, Consensus]*.

2. For individuals using insulin, SMBG should be recommended as an essential part of diabetes self-management *[Grade A, Level 1 (33), for type 1 diabetes; Grade C, Level 3 (8), for type 2 diabetes]* and should be undertaken at least 3 times per day *[Grade C, Level 3 (8,28)]* and include both pre- and postprandial measurements *[Grade C, Level 3 (6,28,32)]*. In those with type 2 diabetes on once-daily insulin in addition to oral antihyperglycemic agents, testing at least once a day at variable times is recommended *[Grade D, Consensus]*.

3. For individuals treated with oral antihyperglycemic agents or lifestyle alone, the frequency of SMBG should be individualized depending on glycemic control and type of therapy and should include both pre- and postprandial measurements *[Grade D, Consensus]*.

4. In many situations, for all individuals with diabetes, more frequent testing should be undertaken to provide information needed to make behavioural or treatment adjustments required to achieve desired glycemic targets and avoid risk of hypoglycemia *[Grade D, Consensus]*.

5. In order to ensure accuracy of BG meter readings, meter results should be compared with laboratory measurement of simultaneous venous FPG at least annually, and when indicators of glycemic control do not match meter readings *[Grade D, Consensus]*.

6. Individuals with type 1 diabetes should be instructed to perform ketone testing during periods of acute illness accompanied by elevated BG, when preprandial BG levels remain >14.0 mmol/L or in the presence of symptoms of DKA *[Grade D, Consensus]*. Blood ketone testing methods may be preferred over urine ketone testing, as they have been associated with earlier detection of ketosis and response to treatment *[Grade B, Level 2 (44)]*.

values, although some discordance with BG levels during periods of hypoglycemia and significant hyperglycemia have been observed (48,49). Given the precision of current systems and the lag between changes in BG and interstitial glucose, particularly when BG levels are rapidly fluctuating (such as in the few hours after eating), CGMS readings may not reflect simultaneous BG values (50,51). As a result, CGMS technologies do not eliminate the need for capillary BG testing. Capillary tests must be performed both for the purposes of calibrating the device and for therapeutic decision-making.

With non-real time (i.e. retrospective) CGMS, glucose readings for intermittent time periods (usually 72 hours) are captured, but results are available only for retrospective viewing and analysis when data are downloaded to a computer. Non-real time (i.e. retrospective) CGMS has been associated with detection of unrecognized hypoglycemia in patients with either type 1 or type 2 diabetes (52,53), detection of unexpected hyperglycemia in women with gestational diabetes mellitus (54), reduction in the duration of hypoglycemia in insulin-treated patients (55) and less frequent hypoglycemia in a pediatric, insulin-treated population (53). It is not yet clear if use of non-real time technology reduces A1C values (49,53,55,56). Discrepancies in non-real time CGMS accuracy have been identified (46,57-60), especially during hypoglycemia (57,58) and nocturnally (59,60).

The scarcity of data (including accuracy data) presently available precludes making definitive recommendations regarding the role of real-time CGMS in diabetes management. However, given its rapidly increasing use, it is incumbent upon healthcare providers involved in the management of people with diabetes (particularly type 1 diabetes) to be aware of this technology.

OTHER RELEVANT GUIDELINES

Self-management Education, p. S25
Targets for Glycemic Control, p. S29
Physical Activity and Diabetes, p. S37
Insulin Therapy in Type 1 Diabetes, p. S46
Hypoglycemia, p. S62
Hyperglycemic Emergencies in Adults, p. S65
Type 1 Diabetes in Children and Adolescents, p. S150
Type 2 Diabetes in Children and Adolescents, p. S162
Diabetes and Pregnancy, p. S168

REFERENCES

1. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329: 977-986.

2. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352: 837-853.

3. McCarter RJ, Hempe JM, Chalew SA. Mean blood glucose and biological variation have greater influence on HbA1c levels than glucose instability: an analysis of data from the Diabetes Control and Complications Trial. *Diabetes Care*. 2006; 29:352-355.

4. American Diabetes Association. Standards of medical care in diabetes – 2007. *Diabetes Care*. 2007;30(suppl 1):S4-S41.

5. Sacks DB, Bruns DE, Goldstein DE, et al. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. *Clin Chem*. 2002;48:436-472.

6. Rohlfing CL, Wiedmeyer HM, Little RR, et al. Defining the relationship between plasma glucose and HbA(1c): analysis of glucose profiles and HbA(1c) in the Diabetes Control and Complications Trial. *Diabetes Care*. 2002;25:275-278.

7. Consensus statement on the worldwide standardisation of the HbA1c measurement. American Diabetes Association, European Association for the Study of Diabetes, International Federation of Clinical Chemistry and Laboratory Medicine, and the International Diabetes Federation. *Diabetologia*. 2007; 50:2042-2043.

8. Karter AJ, Ackerson LM, Darbinian JA, et al. Self-monitoring of blood glucose levels and glycemic control: the Northern California Kaiser Permanente Diabetes Registry. *Am J Med*. 2001;111:1-9.

9. Karter AJ, Parker MM, Moffet HH, et al. Longitudinal study of new and prevalent use of self-monitoring of blood glucose. *Diabetes Care*. 2006;29:1757-1763.

10. Norris SL, Engelgau MM, Narayan KM. Effectiveness of self-management training in type 2 diabetes: a systematic review of randomized controlled trials. *Diabetes Care*. 2001;24:561-587.

11. Franciosi M, Pellegrini F, De Berardis G, et al; QuED Study Group. The impact of blood glucose self-monitoring on metabolic control and quality of life in type 2 diabetic patients: an urgent need for better educational strategies. *Diabetes Care*. 2001;24:1870-1877.

12. Faas A, Schellevis FG, van Eijk JT. The efficacy of self-monitoring of blood glucose in NIDDM subjects. A criteria-based literature review. *Diabetes Care*. 1997;20:1482-1486.

13. Norris SL, Lau J, Smith SJ, et al. Self-management education for adults with type 2 diabetes: a meta-analysis of the effect on glycemic control. *Diabetes Care*. 2002;25:1159-1171.

14. Polonsky WH, Earles J, Smith S, et al. Integrating medical management with diabetes self-management training: a randomized control trial of the Diabetes Outpatient Intensive Treatment program. *Diabetes Care*. 2003;26:3048-3053.

15. Jones H, Edwards L, Vallis TM, et al; Diabetes Stages of Change (DiSC) Study. Changes in diabetes self-care behaviors make a difference in glycemic control: the Diabetes Stages of Change (DiSC) study. *Diabetes Care*. 2003;26:732-737.

16. Davidson J. Strategies for improving glycemic control: effective use of glucose monitoring. *Am J Med*. 2005;118(suppl 9A):27S-32S.

17. Blonde L, Karter AJ. Current evidence regarding the value of self-monitored blood glucose testing. *Am J Med*. 2005;118 (suppl 9A):20S-26S.

18. Schiel R, Voigt U, Ross IS, et al. Structured diabetes therapy and education improves the outcome of patients with insulin treated diabetes mellitus. The 10 year follow-up of a prospective, population-based survey on the quality of diabetes care (the JEVIN Trial). *Exp Clin Endocrinol Diabetes*. 2006;114:18-27.

19. Harris MI; National Health and Nutrition Examination Survey (NHANES III). Frequency of blood glucose monitoring in relation to glycemic control in patients with type 2 diabetes. *Diabetes Care*. 2001;24:979-982.

20. Coster S, Gulliford MC, Seed PT, et al. Self-monitoring in type 2 diabetes mellitus: a meta-analysis. *Diabet Med*. 2000;17:755-761.

21. Welschen LM, Bloemendal E, Nijpels G, et al. Self-monitoring of blood glucose in patients with type 2 diabetes who are not using insulin: a systematic review. *Diabetes Care*. 2005;28: 1510-1517.

22. Welschen LM, Bloemendal E, Nijpels G, et al. Self-monitoring of blood glucose in patients with type 2 diabetes who are not using insulin. *Cochrane Database Syst Rev*. 2005;(2):CD005060.

23. Davidson MB, Castellanos M, Kain D, et al. The effect of self monitoring of blood glucose concentrations on glycated hemoglobin levels in diabetic patients not taking insulin: a blinded, randomized trial. *Am J Med*. 2005;118:422-425.

24. Davis WA, Bruce DG, Davis TM. Is self-monitoring of blood glucose appropriate for all type 2 diabetic patients? The Fremantle Diabetes Study. *Diabetes Care*. 2006;29:1764-1770.

25. Davis WA, Bruce DG, Davis TM. Does self-monitoring of blood glucose improve outcome in type 2 diabetes? The Fremantle Diabetes Study. *Diabetologia*. 2007;50:510-515.

26. Farmer A, Wade A, Goyder E, et al. Impact of self monitoring of blood glucose in the management of patients with non-insulin treated diabetes: open parallel group randomised trial. *BMJ*. 2007;335:132.

27. Bergenstal RM, Gavin JR 3rd; Global Consensus Conference on Glucose Monitoring Panel. The role of self-monitoring of blood glucose in the care of people with diabetes: report of a global consensus conference. *Am J Med*. 2005;118(suppl 9A): 1S-6S.

28. Sheppard P, Bending JJ, Huber JW. Pre- and post-prandial capillary glucose self-monitoring achieves better glycaemic control than pre-prandial only monitoring. A study in insulin treated diabetic patients. *Practical Diabetes Int*. 2005;22:15-22.

29. Leiter LA, Ceriello A, Davidson JA, et al; International Prandial Glucose Regulation Study Group. Postprandial glucose regulation: new data and new implications. *Clin Ther*. 2005;27(suppl B):S42-S56.

30. Avignon A, Radauceanu A, Monnier L. Nonfasting plasma glucose is a better marker of diabetic control than fasting plasma glucose in type 2 diabetes. *Diabetes Care*. 1997;20:1822-1826.

31. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA(1c). *Diabetes Care*. 2003;26:881-885.

32. Murata GH, Shah JH, Hoffman RM, et al; Diabetes Outcomes in Veterans Study (DOVES). Intensified blood glucose monitoring improves glycemic control in stable, insulin-treated veterans with type 2 diabetes: the Diabetes Outcomes in Veterans Study (DOVES). *Diabetes Care*. 2003;26:1759-1763.

33. Epidemiology of severe hypoglycemia in the Diabetes Control and Complications Trial. The DCCT Research Group. *Am J Med*. 1991;90:450-459.

34. Gale EAM, Tattersall RB. Unrecognised nocturnal hypogly-

caemia in insulin-treated diabetics. *Lancet*. 1979;1:1049-1052.

35. Beregszàszi M, Tubiana-Rufi N, Benali K, et al. Nocturnal hypoglycemia in children and adolescents with insulin-dependent diabetes mellitus: prevalence and risk factors. *J Pediatr*. 1997;131:27-33.

36. Vervoort G, Goldschmidt HM, van Doorn LG. Nocturnal blood glucose profiles in patients with type 1 diabetes mellitus on multiple (> or = 4) daily insulin injection regimens. *Diabet Med*. 1996;13:794-799.

37. Jones TW, Porter P, Sherwin RS, et al. Decreased epinephrine responses to hypoglycemia during sleep. *N Engl J Med*. 1998; 338:1657-1662.

38. Bergenstal R, Pearson J, Cembrowski GS, et al. Identifying variables associated with inaccurate self-monitoring of blood glucose: proposed guidelines to improve accuracy. *Diabetes Educ*. 2000;26:981-989.

39. Jungheim K, Koschinsky T. Glucose monitoring at the arm: risky delays of hypoglycemia and hyperglycemia detection. *Diabetes Care*. 2002;25:956-960.

40. Ellison JM, Stegmann JM, Colner SL, et al. Rapid changes in postprandial blood glucose produce concentration differences at finger, forearm, and thigh sampling sites. *Diabetes Care*. 2002; 25:961-964.

41. Bina DM, Anderson RL, Johnson ML, et al. Clinical impact of prandial state, exercise, and site preparation on the equivalence of alternative-site blood glucose testing. *Diabetes Care*. 2003;26:981-985.

42. Jungheim K, Koschinsky T. Glucose monitoring at the thenar: evaluation of upper dermal blood glucose kinetics during rapid systemic blood glucose changes. *Horm Metab Res*. 2002;34:325-329.

43. Guerci B, Benichou M, Floriot M, et al. Accuracy of an electrochemical sensor for measuring capillary blood ketones by fingerstick samples during metabolic deterioration after continuous subcutaneous insulin infusion interruption in type 1 diabetic patients. *Diabetes Care*. 2003;26:1137-1141.

44. Bektas F, Eray O, Sari R, et al. Point of care blood ketone testing of diabetic patients in the emergency department. *Endocr Res*. 2004;30:395-402.

45. Khan AS, Talbot JA, Tieszen KL, et al. Evaluation of a bedside blood ketone sensor: the effects of acidosis, hyperglycaemia and acetoacetate on sensor performance. *Diabet Med*. 2004; 21:782-785.

46. Guerci B, Floriot M, Böhme P, et al. Clinical performance of CGMS in type 1 diabetic patients treated by continuous subcutaneous insulin infusion using insulin analogs. *Diabetes Care*. 2003;26:582-589.

47. Deiss D, Bolinder J, Riveline JP, et al. Improved glycemic control in poorly controlled patients with type 1 diabetes using real-time continuous glucose monitoring. *Diabetes Care*. 2006; 29:2730-2732.

48. Garg S, Zisser H, Schwartz S, et al. Improvement in glycemic excursions with a transcutaneous, real-time continuous glucose sensor: a randomized controlled trial. *Diabetes Care*. 2006;29:44-50.

49. Chase HP, Roberts MD, Wightman C, et al. Use of the GlucoWatch biographer in children with type 1 diabetes. *Pediatrics*. 2003;111:790-794.

50. Rebrin K, Steil GM, van Antwerp WP, et al. Subcutaneous glucose predicts plasma glucose independent of insulin: implications for continuous monitoring. *Am J Physiol*. 1999;277: E561-E571.

51. Steil GM, Rebrin K, Mastrototaro J, et al. Determination of plasma glucose during rapid glucose excursions with a subcutaneous glucose sensor. *Diabetes Technol Ther*. 2003;5:27-31.

52. Chico A, Vidal-Ríos P, Subirà M, et al. The continuous glucose monitoring system is useful for detecting unrecognized hypoglycemias in patients with type 1 and type 2 diabetes but is not better than frequent capillary glucose measurements for improving metabolic control. *Diabetes Care*. 2003;26:1153-1157.

53. Chase HP, Kim LM, Owen SL, et al. Continuous subcutaneous glucose monitoring in children with type 1 diabetes. *Pediatrics*. 2001;107:222-226.

54. Bühling KJ, Kurzidim B, Wolf C, et al. Introductory experience with the continuous glucose monitoring system (CGMS; Medtronic Minimed) in detecting hyperglycemia by comparing the self-monitoring of blood glucose (SMBG) in non-pregnant women and in pregnant women with impaired glucose tolerance and gestational diabetes. *Exp Clin Endocrinol Diabetes*. 2004;112:556-560.

55. Tanenberg R, Bode B, Lane W, et al. Use of the Continuous Glucose Monitoring System to guide therapy in patients with insulin-treated diabetes: a randomized controlled trial. *Mayo Clin Proc*. 2004;79:1521-1526.

56. Ludvigsson J, Hanas R. Continuous subcutaneous glucose monitoring improved metabolic control in pediatric patients with type 1 diabetes: a controlled crossover study. *Pediatrics*. 2003;111:933-938.

57. Diabetes Research in Children Network (DirecNet) Study Group. Accuracy of the GlucoWatch G2 Biographer and the continuous glucose monitoring system during hypoglycemia: experience of the Diabetes Research in Children Network. *Diabetes Care*. 2004;27:722-726.

58. Diabetes Research in Children Network (DirecNet) Study Group. The accuracy of the CGMS in children with type 1 diabetes: results of the Diabetes Research in Children Network (DirecNet) accuracy study. *Diabetes Technol Ther*. 2003;5:781-789.

59. McGowan K, Thomas W, Moran A. Spurious reporting of nocturnal hypoglycemia by CGMS in patients with tightly controlled type 1 diabetes. *Diabetes Care*. 2002;25:1499-1503.

60. Nybäck-Nakell A, von Heijne M, Adamson U, et al. Accuracy of continuous nocturnal glucose screening after 48 and 72 hours in type 2 diabetes patients on combined oral and insulin therapy. *Diabetes Metab*. 2004;30:517-521.

Physical Activity and Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Ronald Sigal MD MPH FRCPC, Glen Kenny PhD, Paul Oh MD MSc FRCPC, Bruce A. Perkins MD MPH FRCPC, Ronald C. Plotnikoff PhD, Denis Prud'homme MD MSc and Michael C. Riddell PhD

KEY MESSAGES

- Moderate to high levels of physical activity and cardio-respiratory fitness are associated with substantial reductions in morbidity and mortality in both men and women and in both type 1 and type 2 diabetes.

- Before beginning a program of physical activity more vigorous than walking, people with diabetes should be assessed for conditions that might be contraindications to certain types of exercise, predispose to injury or be associated with increased likelihood of cardiovascular disease.

- Structured physical activity counselling by a physician or skilled healthcare personnel or case managers has been very effective in increasing physical activity, improving glycemic control, reducing the need for antihyperglycemic agents and insulin, and producing modest but sustained weight loss.

BENEFITS OF PHYSICAL ACTIVITY

Physical activity can help people with diabetes achieve a variety of goals, including increased cardiorespiratory fitness, increased vigour, improved glycemic control, decreased insulin resistance, improved lipid profile and maintenance of weight loss (1,2). The terms "physical activity" and "exercise" are used interchangeably in this chapter.

A systematic review and meta-analysis found that supervised programs involving aerobic or resistance exercise improved glycemic control in adults with type 2 diabetes (3). In contrast, most clinical trials evaluating exercise interventions in people with type 1 diabetes have not demonstrated a beneficial effect of exercise on glycemic control (4).

Moderate to high levels of physical activity and cardiorespiratory fitness are associated with substantial reductions in morbidity and mortality in both men and women and in both type 1 and type 2 diabetes. Large cohort studies have demonstrated that in people with type 2 diabetes, regular physical activity (5-7) and/or moderate to high cardiorespiratory fitness (8) are associated with reductions in cardiovascular and overall mortality of 39 to 70% over 15 to 20 years of follow-up. A cohort study in people with type 1 diabetes found that 7-year mortality was 50% lower in those reporting ≥2000 kcal of weekly exercise (equivalent to ≥7 hours per week of brisk walking) compared to those reporting <1000 kcal of physical activity per week (9). Aerobic exercise increases cardiorespiratory fitness in both type 1 and type 2 diabetes (10), and has recently been shown to limit the development of peripheral neuropathy (11).

EXERCISE CONSIDERATIONS IN PEOPLE WITH DIABETES

People with diabetes should be informed that regular exercise is a key part of their treatment plan. Before beginning a program of physical activity more vigorous than walking, people with diabetes should be assessed for conditions that might be contraindications to certain types of exercise, predispose to injury or be associated with increased likelihood of cardiovascular disease (CVD). Examples of such conditions would include severe autonomic neuropathy, severe peripheral neuropathy, and preproliferative or proliferative retinopathy, all of which require treatment prior to commencement of vigorous exercise. An exercise electrocardiogram (ECG) stress test should be considered for previously sedentary individuals with diabetes at high risk for CVD who wish to undertake exercise more vigorous than brisk walking. Previously sedentary individuals may have to gradually build up their amount of exercise, starting with as little as 5 to 10 minutes per day. Multiple, shorter exercise sessions (each lasting at least 10 minutes) in the course of a day should be considered, as this regimen is probably as useful as a single longer session of equivalent length and intensity (12,13).

Studies have demonstrated a role for both aerobic and resistance exercise in suitable people with diabetes (Table 1, Table 2). Walking is the most popular and most feasible type of aerobic exercise in most overweight middle-aged and elderly people with diabetes. For most middle-aged individuals, moderately brisk walking on level ground would be an example of moderate aerobic exercise, while brisk walking up an incline or jogging would be vigorous aerobic exercise. Resistance exercise performed 2 or 3 times per week may provide benefits that complement those of aerobic training (e.g. increased strength and vigour, reduced body fat and increased resting metabolic rate) (3,14). The studies reporting the greatest impact of resistance exercise on glycated hemoglobin (A1C) have had subjects progress to 3 sets (with approximately 8 repetitions per set) of resistance-type exercises at relatively high intensity (i.e. the maximum weight that

Table 1. Aerobic exercise		
Definition and recommended frequency	**Intensity**	**Examples**
Rhythmic, repeated and continuous movements of the same large muscle groups for at least 10 minutes at a time Recommended for a minimum of 150 minutes per week (moderate intensity)	Moderate: 50–70% of person's maximum heart rate	• Biking • Brisk walking • Continuous swimming • Dancing • Raking leaves • Water aerobics
	Vigorous: >70% of person's maximum heart rate	• Brisk walking up an incline • Jogging • Aerobics • Hockey • Basketball • Fast swimming • Fast dancing

Table 2. Resistance exercise		
Definition	**Recommended frequency**	**Examples**
Activities that use muscular strength to move a weight or work against a resistant load*	**3 times per week** • Start with 1 set of 10–15 repetitions at moderate weight • Progress to 2 sets of 10–15 repetitions • Progress to 3 sets of 8 repetitions at heavier weight	• Exercise with weight machines • Weight lifting

*Initial instruction and periodic supervision are recommended

can be lifted 8 times), 3 times per week (15,16) or more (17). The effects of resistance exercise and aerobic exercise are additive (18). Individuals who wish to begin resistance exercise should receive initial instruction and periodic supervision by a qualified exercise specialist.

During and after all but the most intense exercise, blood glucose tends to decline due to increased glucose disposal and insulin sensitivity (19). However, during and especially after brief, very intense exercise (e.g. competitive track and field, hockey, basketball, intense resistance training), blood glucose will rise as a result of increases in glucose production that exceed increases in glucose disposal (20). Exercise late in the day can be associated with increased risk of overnight hypoglycemia in people with type 1 diabetes (21). In type 1 diabetes, small studies have explored 3 types of strategies for the prevention of hypoglycemia using protocols that generally involve postprandial exercise. These strategies include the consumption of extra carbohydrates for exercise (22), limiting preprandial bolus insulin doses (23) or altering basal insulin for insulin pump users (24). These strategies can be used alone or in combination (25).

Despite a strong body of evidence supporting the health benefits of lifestyle modification in people with type 2 diabetes, application in medical care settings remains a challenge (26). Healthcare professionals can heighten awareness of the importance of physical activity by promoting regular exercise as a key component of therapy and identifying resources in the community (27). Structured physical activity counselling by a physician (28) or skilled healthcare personnel or case managers (29,30) has been very effective in increasing physical activity, improving glycemic control (29), reducing the need for oral antihyperglycemic agents and insulin (30), and producing modest but sustained weight loss (31).

RECOMMENDATIONS

1. People with diabetes should accumulate a minimum of 150 minutes of moderate- to vigorous-intensity aerobic exercise each week, spread over at least 3 days of the week, with no more than 2 consecutive days without exercise [Grade B, Level 2, for type 2 diabetes (3); Grade C, Level 3, for type 1 diabetes (9)].

2. People with diabetes (including elderly people) should also be encouraged to perform resistance exercise 3 times per week [Grade B, Level 2 (15,16)] in addition to aerobic exercise [Grade B, Level 2 (18)]. Initial instruction and periodic supervision by an exercise specialist are recommended [Grade D, Consensus].

3. An exercise ECG stress test should be considered for previously sedentary individuals with diabetes at high risk for CVD who wish to undertake exercise more vigorous than brisk walking [Grade D, Consensus].

OTHER RELEVANT GUIDELINES

Monitoring Glycemic Control, p. S32
Insulin Therapy in Type 1 Diabetes, p. S46
Hypoglycemia, p. S62
Identification of Individuals at High Risk of Coronary Events, p. S95
Screening for the Presence of Coronary Artery Disease, p. S99
Vascular Protection in People With Diabetes, p. S102

REFERENCES

1. Sigal RJ, Kenny GP, Wasserman DH, et al. Physical activity/exercise and type 2 diabetes: a consensus statement from the American Diabetes Association. *Diabetes Care*. 2006;29:1433-1438.

2. Wing RR, Goldstein MG, Acton KJ, et al. Behavioral science research in diabetes: lifestyle changes related to obesity, eating behavior, and physical activity. *Diabetes Care*. 2001;24:117-123.

3. Snowling NJ, Hopkins WG. Effects of different modes of exercise training on glucose control and risk factors for complications in type 2 diabetic patients: a meta-analysis. *Diabetes Care*. 2006;29:2518-2527.

4. Laaksonen DE, Atalay M, Niskanen LK, et al. Aerobic exercise and the lipid profile in type 1 diabetic men: a randomized controlled trial. *Med Sci Sports Exerc.* 2000;32:1541-1548.

5. Hu G, Jousilahti P, Barengo NC, et al. Physical activity, cardiovascular risk factors, and mortality among Finnish adults with diabetes. *Diabetes Care.* 2005;28:799-805.

6. Hu FB, Stampfer MJ, Solomon C, et al. Physical activity and risk for cardiovascular events in diabetic women. *Ann Intern Med.* 2001;134:96-105.

7. Gregg EW, Gerzoff RB, Caspersen CJ, et al. Relationship of walking to mortality among US adults with diabetes. *Arch Intern Med.* 2003;163:1440-1447.

8. Church TS, LaMonte MJ, Barlow CE, et al. Cardiorespiratory fitness and body mass index as predictors of cardiovascular disease mortality among men with diabetes. *Arch Intern Med.* 2005;165:2114-2120.

9. Moy CS, Songer TJ, LaPorte RE, et al. Insulin-dependent diabetes mellitus, physical activity, and death. *Am J Epidemiol.* 1993; 137:74-81.

10. Nielsen PJ, Hafdahl AR, Conn VS, et al. Meta-analysis of the effect of exercise interventions on fitness outcomes among adults with type 1 and type 2 diabetes. *Diabetes Res Clin Pract.* 2006;74:111-120.

11. Balducci S, Iacobellis G, Parisi L, et al. Exercise training can modify the natural history of diabetic peripheral neuropathy. *J Diabetes Complications.* 2006;20:216-223.

12. Jakicic JM, Winters C, Lang W, et al. Effects of intermittent exercise and use of home exercise equipment on adherence, weight loss, and fitness in overweight women: a randomized trial. *JAMA.* 1999;282:1554-1560.

13. Murphy MH, Hardman AE. Training effects of short and long bouts of brisk walking in sedentary women. *Med Sci Sports Exerc.* 1998;30:152-157.

14. Eves ND, Plotnikoff RC. Resistance training and type 2 diabetes: considerations for implementation at the population level. *Diabetes Care.* 2006;29:1933-1941.

15. Castaneda C, Layne JE, Munoz-Orians L, et al. A randomized controlled trial of resistance exercise training to improve glycemic control in older adults with type 2 diabetes. *Diabetes Care.* 2002;25:2335-2341.

16. Dunstan DW, Daly RM, Owen N, et al. High-intensity resistance training improves glycemic control in older patients with type 2 diabetes. *Diabetes Care.* 2002;25:1729-1736.

17. Durak EP, Jovanovic-Peterson L, Peterson CM. Randomized crossover study of effect of resistance training on glycemic control, muscular strength, and cholesterol in type 1 diabetic men. *Diabetes Care.* 1990;13:1039-1043.

18. Sigal RJ, Kenny GP, Boulé NG, et al. Effects of aerobic exercise training, resistance exercise, or both on glycemic control in type 2 diabetes: a randomized trial. *Ann Intern Med.* 2007; 147:357-369.

19. Riddell MC, Perkins BA. Type 1 diabetes and vigorous exercise: applications of exercise physiology to patient management. *Can J Diabetes.* 2006;30:63-71.

20. Sigal RJ, Purdon C, Fisher SJ, et al. Hyperinsulinemia prevents prolonged hyperglycemia after intense exercise in insulin-dependent diabetic subjects. *J Clin Endocrinol Metab.* 1994;79: 1049-1057.

21. Tsalikian E, Mauras N, Beck RW, et al. Impact of exercise on overnight glycemic control in children with type 1 diabetes mellitus. *J Pediatr.* 2005;147:528-534.

22. Dubé MC, Weisnagel SJ, Prud'homme D, et al. Exercise and newer insulins: how much glucose supplement to avoid hypoglycemia? *Med Sci Sports Exerc.* 2005;37:1276-1282.

23. Rabasa-Lhoret R, Bourque J, Ducros F, et al. Guidelines for premeal insulin dose reduction for postprandial exercise of different intensities and durations in type 1 diabetic subjects treated intensively with a basal-bolus insulin regimen (ultralente-lispro). *Diabetes Care.* 2001;24:625-630.

24. Sonnenberg GE, Kemmer FW, Berger. M. Exercise in type 1 (insulin-dependent) diabetic patients treated with continuous subcutaneous insulin infusion: prevention of exercise-induced hypoglycaemia. *Diabetologia.* 1990;33:696-703.

25. Perkins BA, Riddell MC. Type 1 diabetes and exercise: using the insulin pump to maximum advantage. *Can J Diabetes.* 2006; 30:72-79.

26. Harris SB, Petrella RJ, Leadbetter W. Lifestyle interventions for type 2 diabetes. Relevance for clinical practice. *Can Fam Physician.* 2003;49:1618-1625.

27. Eden KB, Orleans CT, Mulrow CD, et al. Does counseling by clinicians improve physical activity? A summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2002;137:208-215.

28. Petrella RJ, Koval JJ, Cunningham DA, et al. Can primary care doctors prescribe exercise to improve fitness? The Step Test Exercise Prescription (STEP) project. *Am J Prev Med.* 2003; 24:316-322.

29. Kirk A, Mutrie N, MacIntyre P, et al. Effects of a 12-month physical activity counselling intervention on glycaemic control and on the status of cardiovascular risk factors in people with Type 2 diabetes. *Diabetologia.* 2004;47:821-832.

30. Wolf AM, Conaway MR, Crowther JQ, et al. Translating lifestyle intervention to practice in obese patients with type 2 diabetes: Improving Control with Activity and Nutrition (ICAN) study. *Diabetes Care.* 2004;27:1570-1576.

31. Norris SL, Zhang X, Avenell A, et al. Long-term non-pharmacologic weight loss interventions for adults with type 2 diabetes. *Cochrane Database Syst Rev.* 2005(2):CD004095.

Nutrition Therapy

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Réjeanne Gougeon PhD, Nicole Aylward RD CDE, Heather Nichol RN MScN CDE, Karie Quinn RD CDE and Dana Whitham MSc RD CDE

KEY MESSAGES

- Nutrition therapy can reduce glycated hemoglobin by 1.0 to 2.0% and, when used with other components of diabetes care, can further improve clinical and metabolic outcomes.

- Consistency in carbohydrate intake, and spacing and regularity in meal consumption may help control blood glucose and weight.

- Replacing high-glycemic index carbohydrates with low-glycemic index carbohydrates in mixed meals has a clinically significant effect on glycemic control in people with type 1 or type 2 diabetes.

INTRODUCTION

Nutrition therapy is an integral part of the treatment and self-management of diabetes. The goals of nutrition therapy are to maintain or improve quality of life and nutritional and physiological health, and to prevent and treat acute and long-term complications of diabetes, associated comorbid conditions and concomitant disorders.

It is well documented that nutrition therapy can improve glycemic control (1) by reducing glycated hemoglobin (A1C) by 1.0 to 2.0% (2-4) and, when used with other components of diabetes care, can further improve clinical and metabolic outcomes (2-4). Counselling provided by a registered dietitian with expertise in diabetes management (5,6), either delivered in a small group and/or individual setting (7-9), has demonstrated benefits for those with, or at risk for, diabetes. Nutrition therapy should be based on individual needs, be regularly evaluated and reinforced in an intensive manner (10-12), and be part of self-management education programs (13).

As evidence is limited for the rigid adherence to any single dietary prescription (14,15), nutrition therapy and meal planning should be individualized to accommodate the person's preferences, age, needs, culture, lifestyle, economic status (16), activity level and readiness to change. In general, people with diabetes should follow the healthy diet recommended for the general population in *Eating Well with Canada's Food Guide* (17). This involves consuming a variety of foods from the 4 food groups (vegetables and fruits; grain products; milk and alternatives; meat and alternatives). Foods should be low in energy density to optimize satiety and discourage overconsumption, help attain and maintain a healthy body weight, and ensure an adequate intake of carbohydrate, fibre, protein, essential fatty acids, vitamins and minerals.

Consistency in carbohydrate intake (18), and spacing and regularity in meal consumption may help control blood glucose (BG) levels (13,18,19). Inclusion of snacks as part of a person's meal plan should be individualized based on meal spacing, metabolic control, treatment regimen and risk of hypoglycemia, and should be balanced against the potential risk of weight gain (20,21).

CARBOHYDRATE

Individuals using insulin therapy should adjust their insulin based on the carbohydrate content of their meals. Intensive insulin therapy regimens that include multiple injections of rapid-acting insulin matched to carbohydrate allow for flexibility in meal size and frequency (22,23). Improvements in BG and quality of life can be achieved when individuals with type 1 diabetes receive education on matching insulin to carbohydrate content (e.g. carbohydrate counting) (24,25). In doing so, dietary fibre should be subtracted from total carbohydrate. The acceptable macronutrient distribution range, or percentage of total daily energy associated with reduced risk of chronic disease for adults, is as follows: carbohydrate intake of no less than 45% (in part to prevent high intakes of fat); and fat intake of a maximum of 35% (26). Diets that provide >60% of total daily energy from low-glycemic-index and high-fibre carbohydrates improve glycemic and lipid control in adults with type 2 diabetes (27).

Replacing high-glycemic-index carbohydrates with low-glycemic-index carbohydrates in mixed meals has a clinically significant effect on glycemic control in people with type 1 or type 2 diabetes (28-32). Dietary advice aimed at increasing the use of low-glycemic-index foods can help improve glycemic control in people with type 1 diabetes by reducing A1C and the number of hypoglycemic episodes (29,33). Choosing low-glycemic-index foods within the same category of food may help improve glycemic control in insulin-resistant individuals with type 2 diabetes (29). The decision to teach a person to use the glycemic index should be based on the individual's interest and ability.

Evidence suggests that the addition of soluble dietary fibre (e.g. eggplant, okra, oat products, beans, psyllium and barley) slows gastric emptying and delays the absorption of

glucose in the small intestine, thereby improving post-prandial BG control (34). In addition, cohort studies demonstrate that diets high in dietary fibre, especially cereal fibre, are associated with a decreased risk of cardiovascular disease (CVD) (35). Due to the recognized beneficial effects of dietary fibre intake in people with diabetes, higher intakes than those recommended for the general population are recommended for adults with diabetes (25 to 50 g/day) (36).

Sucrose
Sucrose intake of up to 10% of total daily energy (e.g. 50 to 65 g/day in a 2000 to 2600 kcal/day diet) is acceptable, as there is no evidence that sucrose intake up to this level has any deleterious effect on glycemic control or lipid profile in people with type 1 or type 2 diabetes (37-39). Intake of sucrose >10% of total daily energy may increase BG and triglycerides (TG) levels in some individuals (40,41).

Fructose
Consumption of up to 60 g of added fructose (e.g. fructose-sweetened beverages or foods) per day in place of an equal amount of sucrose is unlikely to have any harmful effect in most people with diabetes (42). Fructose has been shown to improve the capacity of hyperglycemia to suppress hepatic glucose production in type 2 diabetes (43). However, fructose has no definite advantage over sucrose in long-term use. Consumption of >60 g of added fructose per day by people with diabetes is not recommended, as it may increase circulating TG levels (44).

Sugar alcohols
Sugar alcohols (maltitol, mannitol, sorbitol, lactitol, isomalt and xylitol) vary in the degree to which they are absorbed. The conversion rate is slow, variable, usually minimal and may have no significant effect on BG. Matching rapid-acting insulin to the intake of sugar alcohols is not recommended (45). Consumption of >10 g/day may produce adverse gastrointestinal symptoms in some individuals (46). Although there are no long-term studies of consumption of sugar alcohols by people with diabetes, consumption of up to 10 g/day by people with diabetes does not appear to result in adverse effects (47).

Sweeteners
Acesulfame potassium, aspartame, cyclamates, saccharin and sucralose have been approved by Health Canada, and all have been shown to be safe when used by people with diabetes (Table 1) (47). While the safety of sweeteners in pregnancy has not been rigorously studied, based on their history of use and lack of reported adverse effects during pregnancy and lactation (48), acesulfame potassium, aspartame and sucralose may be consumed within the acceptable daily intake limits. Saccharin and cyclamates are not recommended during pregnancy and lactation because of a lack of evidence for their safety (47,48).

Table 1. Acceptable daily intake* of sweeteners (47)	
Sweetener	**Acceptable daily intake (mg/kg body weight)**
Acesulfame potassium	15
Aspartame	40
Cyclamate	11
Saccharin	5
Sucralose	9

*Defined as the amount of sweetener that can be safely consumed on a daily basis over a person's lifetime without any adverse effects

PROTEIN
There is no evidence to suggest that the usual recommended protein intake (15 to 20% of total daily energy) needs to be modified for people with diabetes. Essential amino acids are toxic in excess (49), when intake is at a rate that exceeds the body's capacity to eliminate the end products of their metabolism.

FAT
Current recommendations for the general population to limit fat intake to <35% of energy (26) apply equally to people with diabetes and prediabetes. As the risk of coronary artery disease (CAD) in people with diabetes is 2 to 3 times that of those without diabetes, saturated fats should be restricted to <7% of total energy daily intake (50) and trans fatty acids should be kept to a minimum. Polyunsaturated fats should be limited to <10% of total energy intake (51). Meal plans should favour monounsaturated fats, when possible, and include foods rich in polyunsaturated omega-3 fatty acids (e.g. fatty fish) and plant oils (e.g. canola, walnut, flax). In secondary prevention trials, omega-3 fatty acids from both plant (alpha-linolenic acid) and marine (eicosapentaenoic acid and docosahexaenoic acid) sources have demonstrated significant cardioprotective effects (52). In a prospective cohort study of women with type 2 diabetes, higher consumption (1 to 3 servings per month) of omega-3 fatty acids from fish was associated with a 40% reduction in CAD compared to those with a low intake (<1 serving per month) (53). Those who consumed fatty fish >5 times per week had a 64% reduction in CAD compared with those in the low-intake category (53). Flexibility regarding total fat intake may be appropriate. For example, if an individual's fat intake is primarily composed of mono- and polyunsaturated fats and is low in trans fatty acids arising from industrial hydrogenation, a higher fat intake (i.e. 35% of total daily energy) may be justified (54-57).

VITAMIN AND MINERAL SUPPLEMENTS

People with diabetes should be encouraged to meet their nutritional needs by consuming a well-balanced diet. Routine vitamin and mineral supplementation is generally not recommended. Antioxidant supplements (vitamin E, vitamin C or beta-carotene) have not demonstrated benefits in CVD outcomes or glycemic control (58-60). As there is evidence that long-term beta-carotene supplementation may be harmful in smokers, antioxidant supplementation should be discussed with patients who smoke (59,61). Supplementation with 10 μg (400 IU) vitamin D is recommended in people >50 years of age. Supplementation with folic acid (400 μg) is recommended in women who could become pregnant (17). There is no evidence that dietary supplements such as meal replacements, specialty bars or formulas designed for diabetes are needed for glycemic control. No studies have identified which foods they displace from the diet.

ALCOHOL

The same recommendations regarding alcohol consumption in the general population apply to people with diabetes (i.e. ≤2 standard drinks per day and ≤14 standard drinks per week for men, and ≤9 per week for women) (62,63). Moderate amounts of alcohol (1 to 2 standard drinks) consumed with food do not cause acute hyperglycemia or hypoglycemia, and do not require subtracting food from the usual meal plan (Table 2).

Table 2. Examples of standard alcoholic drinks		
Drink	*Ethanol content (%)*	*Quantity (mL)*
Beer	5	341 (12 oz)
Table wine	12	142 (5 oz)
Spirits	40	43 (1.5 oz)
Fortified wine (e.g. sherry, port)	18	85 (3 oz)

Caution must be exercised to prevent hypoglycemia secondary to alcohol consumption in people with type 2 diabetes, particularly the fasted elderly who are using insulin and/or insulin secretagogues (64). For people with type 1 diabetes, moderate consumption of alcohol with, or 2 or 3 hours after, the previous evening meal may result in hypoglycemia the next morning after breakfast and as late as 24 hours after alcohol consumption (65,66). Alcohol ingestion may mask the symptoms of hypoglycemia (67), reduce hepatic production of glucose and impair an individual's judgement.

NUTRITIONAL CONSIDERATIONS

A summary of nutritional considerations for people with diabetes is shown in Table 3.

RECOMMENDATIONS

1. Nutrition counselling by a registered dietitian is recommended for people with diabetes to lower A1C levels *[Grade B, Level 2 (3), for type 2 diabetes; Grade D, Consensus, for type 1 diabetes]*. Nutrition education is equally effective when given in a small group or one-on-one setting *[Grade B, Level 2 (9)]*.

2. Individuals with diabetes should be encouraged to follow *Eating Well with Canada's Food Guide* in order to meet their nutritional needs *[Grade D, Consensus]*.

3. People with type 1 diabetes should be taught how to match insulin to carbohydrate intake *[Grade B, Level 2 (23)]* or should maintain consistency in carbohydrate intake *[Grade D, Level 4 (18)]*. People with type 2 diabetes should be encouraged to maintain regularity in timing and spacing of meals to optimize glycemic control *[Grade D, Level 4 (19)]*.

4. People with type 1 or type 2 diabetes should choose food sources of carbohydrates with a low glycemic index, rather than a high glycemic index, more often to help optimize glycemic control *[Grade B, Level 2 (29,31)]*.

5. Sucrose and sucrose-containing foods can be substituted for other carbohydrates as part of mixed meals up to a maximum of 10% of total daily energy, provided adequate control of BG and lipids is maintained *[Grade B, Level 2 (38,39)]*.

6. Adults with diabetes should consume no more than 7% of total daily energy from saturated fats *[Grade D, Consensus]* and should limit intake of trans fatty acids to a minimum *[Grade D, Consensus]*.

7. People with type 1 diabetes should be informed of the risk of delayed hypoglycemia resulting from alcohol consumed with or after the previous evening's meal *[Grade C, Level 3 (62)]*, and should be advised on preventive actions such as carbohydrate intake and/or insulin dose adjustments, and increased BG monitoring *[Grade D, Consensus]*.

OTHER RELEVANT GUIDELINES

RELATED WEBSITES

Canadian Diabetes Association (http://www.diabetes.ca)
• Alcohol and Diabetes. Available at: http://www.diabetes.ca /files/CDAAlcoholFInal.pdf). Accessed September 1, 2008.

Table 3. Summary of nutritional considerations for people with diabetes

People with diabetes should follow Eating Well with Canada's Food Guide
- Eat at least 1 dark green and 1 orange vegetable each day; have vegetables and fruit more often than juice
- Make at least half of your grain products whole grain, each day
- Drink lower-fat milk or fortified soy beverages
- Have meat alternatives such as beans, lentils and tofu often
- Eat at least 2 servings of fish each week
- Achieve and maintain a healthy body weight by being active
- Enjoy foods with little or no added fat, sugar or salt
- Satisfy thirst with water

Carbohydrate (45–60% of energy)
- Up to 60 g of added fructose (e.g. fructose-sweetened beverages and foods) in place of an equal amount of sucrose is acceptable
- Intake of <10 g/day of sugar alcohols (maltitol, mannitol, sorbitol, lactitol, isomalt and xylitol) is acceptable
- The use of acesulfame potassium, aspartame, cyclamates, saccharin and sucralose is acceptable
- Include vegetables, fruit, whole grains and milk
- Within the same food category, consume low-glycemic-index foods in place of high-glycemic-index foods
- Increase dietary fibre to 25-50 g/day from a variety of sources, including soluble and cereal fibres
- Sucrose intake of up to 10% of total daily energy is acceptable

Protein (15–20% of energy)
- There is no evidence to suggest that usual recommended protein intake should be modified

Fat (<35% of energy)
- Restrict saturated fats to <7% of total daily energy intake and restrict trans fat intake to a minimum
- Limit polyunsaturated fat to <10% of energy intake
- Consume monounsaturated fats instead of saturated fats more often
- Include foods rich in polyunsaturated omega-3 fatty acids and plant oils

Vitamin and mineral supplements
- Routine supplementation is not necessary, except for vitamin D in persons aged >50 years and folic acid in women who could become pregnant
- In the case of an identified deficiency, limited dietary intake or special need, supplementation may be recommended

Alcohol
- People using insulin or insulin secretagogues should be aware of the risk of delayed hypoglycemia that can occur up to 24 hours after alcohol consumption
- Limit intake to 1–2 drinks per day (≤14 standard drinks per week for men and ≤9 per week for women)

- Basic Carbohydrate Counting for Diabetes Management. Available at: http://www.diabetes.ca/files/Carb_Counting_eng.qx.pdf. Accessed September 1, 2008.
- Cholesterol and Diabetes. Available at: http://www.diabetes.ca/files/CholesterolToolFINALEng.pdf. Accessed September 1, 2008.
- Eating Away from Home. Available at: http://www.diabetes.ca/files/EatingEnglish.pdf. Accessed September 1, 2008.
- The Glycemic Index. Available at: http://www.diabetes.ca/files/Diabetes_GL_FINAL2_CPG03.pdf. Accessed September 1, 2008.
- Handy Portion Guide. Available at: http://www.diabetes.ca. Accessed September 1, 2008.
- Just the Basics – Tips for healthy eating, diabetes prevention and management. Available at: http://www.diabetes.ca/ files/JTB17x_11_CPG03_1103.pdf. Accessed September 1, 2008.
- Sugars and Sweeteners. Available at: http://www.diabetes.ca/files/ en_sweeteners_final.pdf. Accessed September 1, 2008.

Canadian Diabetes Association, Dietitians of Canada. Nutrition Labelling Education Centre. Available at: http://www.healthy eatingisinstore.ca. Accessed September 1, 2008.

Health Canada. *Eating Well with Canada's Food Guide*. Available at: http://www.hc-sc.gc.ca/fn-an/food-guide-aliment/index_e.html. Accessed September 1, 2008.

REFERENCES

1. Pastors JG, Warshaw H, Daly A, et al. The evidence for the effectiveness of medical nutrition therapy in diabetes management. *Diabetes Care.* 2002;25:608-613.
2. Pi-Sunyer FX, Maggio CA, McCarron DA, et al. Multicenter randomized trial of a comprehensive prepared meal program in type 2 diabetes. *Diabetes Care.* 1999;22:191-197.
3. Franz MJ, Monk A, Barry B, et al. Effectiveness of medical nutrition therapy provided by dietitians in the management of non-insulin-dependent diabetes mellitus: a randomized, controlled clinical trial. *J Am Diet Assoc.* 1995;95:1009-1017.
4. Kulkarni K, Castle G, Gregory R, et al. Nutrition practice guide-

lines for type 1 diabetes mellitus positively affect dietitian practices and patient outcomes. The Diabetes Care and Education Dietetic Practice Group. *J Am Diet Assoc.* 1998;98:62-70.

5. Willaing I, Ladelund S, Jørgensen T, et al. Nutritional counselling in primary health care: a randomized comparison of an intervention by general practitioner or dietician. *Eur J Cardiovasc Prev Rehabil.* 2004;11:513-520.

6. Wilson C, Brown T, Acton K, et al. Effects of clinical nutrition education and educator discipline on glycemic control outcomes in the Indian health service. *Diabetes Care.* 2003;26: 2500-2504.

7. Brekke HK, Jansson PA, Lenner RA. Long-term (1- and 2-year) effects of lifestyle intervention in type 2 diabetes relatives. *Diabetes Res Clin Pract.* 2005;70:225-234.

8. Lemon CC, Lacey K, Lohse B, et al. Outcomes monitoring of health, behavior, and quality of life after nutrition intervention in adults with type 2 diabetes. *J Am Diet Assoc.* 2004;104:1805-1815.

9. Rickheim PL, Weaver TW, Flader JL, et al. Assessment of group versus individual diabetes education: a randomized study. *Diabetes Care.* 2002;25:269-274.

10. Norris SL, Engelgau MM, Narayan KM. Effectiveness of self-management training in type 2 diabetes: a systematic review of randomized controlled trials. *Diabetes Care.* 2001;24:561-587.

11. Ash S, Reeves MM, Yeo S, et al. Effect of intensive dietetic interventions on weight and glycaemic control in overweight men with Type II diabetes: a randomised trial. *Int J Obes Relat Metab Disord.* 2003;27:797-802.

12. Clement S. Diabetes self-management education. *Diabetes Care.* 1995;18:1204-1214.

13. Vallis TM, Higgins-Bowser I, Edwards L, et al. The role of diabetes education in maintaining lifestyle changes. *Can J Diabetes.* 2005;29:193-202.

14. Christensen NK, Terry RD, Wyatt S, et al. Quantitative assessment of dietary adherence in patients with insulin-dependent diabetes mellitus. *Diabetes Care.* 1983;6:245-250.

15. Toeller M, Klischan A, Heitkamp G, et al. Nutritional intake of 2868 IDDM patients from 30 centres in Europe. EURODIAB IDDM Complications Study Group. *Diabetologia.* 1996;39: 929-939.

16. Glazier RH, Bajcar J, Kennie NR, et al. A systematic review of interventions to improve diabetes care in socially disadvantaged populations. *Diabetes Care.* 2006;29:1675-1688.

17. Health Canada. *Eating Well with Canada's Food Guide.* Ottawa, ON: Health Products and Food Branch, Office of Nutrition and Promotion; 2007. Publication H39-166/1990E.

18. Wolever TM, Hamad S, Chiasson JL, et al. Day-to-day consistency in amount and source of carbohydrate associated with improved blood glucose control in type 1 diabetes. *J Am Coll Nutr.* 1999;18:242-247.

19. Savoca MR, Miller CK, Ludwig DA. Food habits are related to glycemic control among people with type 2 diabetes mellitus. *J Am Diet Assoc.* 2004;104:560-566.

20. Kalergis M, Schiffrin A, Gougeon R, et al. Impact of bedtime snack composition on prevention of nocturnal hypoglycemia in adults with type 1 diabetes undergoing intensive insulin management using lispro insulin before meals: a randomized, placebo-controlled, crossover trial. *Diabetes Care.* 2003;26:9-15.

21. Arnold L, Mann JI, Ball MJ. Metabolic effects of alterations in meal frequency in type 2 diabetes. *Diabetes Care.* 1997;20: 1651-1654.

22. Tunbridge FK, Home PD, Murphy M, et al. Does flexibility at mealtimes disturb blood glucose control on a multiple insulin injection regimen? *Diabet Med.* 1991;8:833-838.

23. DAFNE Study Group. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. *BMJ.* 2002;325:746.

24. Gillespie SJ, Kulkarni KD, Daly AE. Using carbohydrate counting in diabetes clinical practice. *J Am Diet Assoc.* 1998;98:897-905.

25. Kelley DE. Sugars and starch in the nutritional management of diabetes mellitus. *Am J Clin Nutr.* 2003;78:858S-864S.

26. Acceptable macronutrient distribution ranges. In: Otten J, Hellwig J, Meyer L, eds. *Dietary Reference Intakes.* Washington, DC: National Academies Press; 2006:70.

27. Barnard ND, Cohen J, Jenkins DJ, et al. A low-fat vegan diet improves glycemic control and cardiovascular risk factors in a randomized clinical trial in individuals with type 2 diabetes. *Diabetes Care.* 2006;29:1777-1783.

28. Luscombe ND, Noakes M, Clifton PM. Diets high and low in glycemic index versus high monounsaturated fat diets: effects on glucose and lipid metabolism in NIDDM. *Eur J Clin Nutr.* 1999;53:473-478.

29. Brand-Miller J, Hayne S, Petocz P, et al. Low glycemic index diets in the management of diabetes: a meta-analysis of randomized controlled trials. *Diabetes Care.* 2003;26:2261-2267.

30. Garg A, Bantle JP, Henry RR, et al. Effects of varying carbohydrate content of diet in patients with non-insulin-dependent diabetes mellitus. *JAMA.* 1994;271:1421-1428.

31. Opperman AM, Venter CS, Oosthuizen W, et al. Meta-analysis of the health effects of using the glycaemic index in meal-planning. *Br J Nutr.* 2004;92:367-381.

32. Brand JC, Colagiuri S, Crossman S, et al. Low-glycemic index foods improve long-term glycemic control in NIDDM. *Diabetes Care.* 1991;14:95-101.

33. Giacco R, Parillo M, Rivellese AA, et al. Long-term dietary treatment with increased amounts of fiber-rich low-glycemic index natural foods improves blood glucose control and reduces the number of hypoglycemic events in type 1 diabetic patients. *Diabetes Care.* 2000;23:1461-1466.

34. Anderson JW, Randles KM, Kendall CW, et al. Carbohydrate and fiber recommendations for individuals with diabetes: a quantitative assessment and meta-analysis of the evidence. *J Am Coll Nutr.* 2004;23:5-17.

35. Jacobs DR Jr, Meyer KA, Kushi LH, et al. Whole-grain intake may reduce the risk of ischemic heart disease death in postmenopausal women: the Iowa Women's Health Study. *Am J Clin Nutr.* 1998;68:248-257.

36. Chandalia M, Garg A, Lutjohann D, et al. Beneficial effects of

high dietary fiber intake in patients with type 2 diabetes mellitus. *N Engl J Med.* 2000;342:1392-1398.

37. Cooper PL, Wahlqvist ML, Simpson RW. Sucrose versus saccharin as an added sweetener in non-insulin-dependent diabetes: short- and medium-term metabolic effects. *Diabet Med.* 1988;5:676-680.

38. Chantelau EA, Gösseringer G, Sonnenberg GE, et al. Moderate intake of sucrose does not impair metabolic control in pump-treated diabetic out-patients. *Diabetologia.* 1985;28: 204-207.

39. Colagiuri S, Miller JJ, Edwards RA. Metabolic effects of adding sucrose and aspartame to the diet of subjects with non-insulin-dependent diabetes mellitus. *Am J Clin Nutr.* 1989;50: 474-478.

40. Coulston AM, Hollenbeck CB, Donner CC, et al. Metabolic effects of added dietary sucrose in individuals with noninsulin-dependent diabetes mellitus (NIDDM). *Metabolism.* 1985;34: 962-966.

41. Jellish WS, Emanuele MA, Abraira C. Graded sucrose/carbohydrate diets in overtly hypertriglyceridemic diabetic patients. *Am J Med.* 1984;77:1015-1022.

42. Nutrition Subcommittee of the British Diabetic Association's Professional Advisory Committee. Sucrose and fructose in the diabetic diet. *Diabet Med.* 1990;7:764-769.

43. Hawkins M, Gabriely I, Wozniak R, et al. Fructose improves the ability of hyperglycemia per se to regulate glucose production in type 2 diabetes. *Diabetes.* 2002;51:606-614.

44. Henry RR, Crapo PA, Thorburn AW. Current issues in fructose metabolism. *Annu Rev Nutr.* 1991;11:21-39.

45. Wang YM, van Eys J. Nutritional significance of fructose and sugar alcohols. *Annu Rev Nutr.* 1981;1:437-475.

46. Wolever TMS, Piekarz A, Hollands M, et al. Sugar alcohols and diabetes: a review. *Can J Diabetes.* 2002;26:356-362.

47. Wolever T, Barbeau M-C, Charron S, et al. Guidelines for the nutritional management of diabetes mellitus in the new millennium: a position statement by the Canadian Diabetes Association. *Can J Diabetes Care.* 1999;2:56-69.

48. Franz MJ, Bantle JP, Beebe CA, et al. Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. *Diabetes Care.* 2002;25:148-198.

49. Jackson AA. Limits of adaptation to high dietary protein intakes. *Eur J Clin Nutr.* 1999;53(suppl 1):S44-S52.

50. National Cholesterol Education Program. Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *Circulation.* 1994;89:1333-1445.

51. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA.* 2001;285:2486-2497.

52. de Lorgeril M, Salen P, Martin JL, et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation.* 1999;99:779-785.

53. Hu FB, Cho E, Rexrode KM, et al. Fish and long-chain omega-3 fatty acid intake and risk of coronary heart disease and total mortality in diabetic women. *Circulation.* 2003;107:1852-1857.

54. Grundy SM, Abate N, Chandalia M. Diet composition and the metabolic syndrome: what is the optimal fat intake? *Am J Med.* 2002;113(suppl 9B):25S-29S.

55. Howard BV. Dietary fat and diabetes: a consensus view. *Am J Med.* 2002;113(suppl 9B):38S-40S.

56. Garg A. High-monounsaturated-fat diets for patients with diabetes mellitus: a meta-analysis. *Am J Clin Nutr.* 1998;67(suppl 3):577S-582S.

57. Ros E. Dietary cis-monounsaturated fatty acids and metabolic control in type 2 diabetes. *Am J Clin Nutr.* 2003;78(suppl 3): 617S-625S.

58. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet.* 2002;360:23-33.

59. Rapola JM, Virtamo J, Ripatti S, et al. Randomised trial of alpha-tocopherol and beta-carotene supplements on incidence of major coronary events in men with previous myocardial infarction. *Lancet.* 1997;349:1715-1720.

60. Yusuf S, Dagenais G, Pogue J, et al. Vitamin E supplementation and cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med.* 2000;342:154-160.

61. Omenn GS, Goodman GE, Thornquist MD, et al. Risk factors for lung cancer and for intervention effects in CARET, the Beta-Carotene and Retinol Efficacy Trial. *J Natl Cancer Inst.* 1996;88:1550-1559.

62. Ashley MJ, Ferrence R, Room R, et al. Moderate drinking and health. Implications of recent evidence. *Can Fam Physician.* 1997; 43:687-694.

63. Bondy SJ, Rehm J, Ashley MJ, et al. Low-risk drinking guidelines: the scientific evidence. *Can J Public Health.* 1999;90:264-270.

64. Burge MR, Zeise TM, Sobhy TA, et al. Low-dose ethanol predisposes elderly fasted patients with type 2 diabetes to sulfonylurea-induced low blood glucose. *Diabetes Care.* 1999;22: 2037-2043.

65. Richardson T, Weiss M, Thomas P, et al. Day after the night before: influence of evening alcohol on risk of hypoglycemia in patients with type 1 diabetes. *Diabetes Care.* 2005;28:1801-1802.

66. Turner BC, Jenkins E, Kerr D, et al. The effect of evening alcohol consumption on next-morning glucose control in type 1 diabetes. *Diabetes Care.* 2001;24:1888-1893.

67. Kerr D, Macdonald IA, Heller SR, et al. Alcohol causes hypoglycaemic unawareness in healthy volunteers and patients with type 1 (insulin-dependent) diabetes. *Diabetologia.* 1990;33: 216-221.

Insulin Therapy in Type 1 Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee
This chapter was prepared by Alice Cheng MD FRCPC, Amir Hanna MB BCh FRCPC, Tina Kader MD FRCPC CDE and Cindy Richardson MD FRCPC

KEY MESSAGES

- Basal-prandial insulin regimens (e.g. multiple daily injections or continuous subcutaneous insulin infusion) are the insulin regimens of choice for all adults with type 1 diabetes.

- Insulin regimens should be tailored to the individual's treatment goals, lifestyle, diet, age, general health, motivation, hypoglycemia awareness status and ability for self-management.

- All individuals with type 1 diabetes should be counselled about the risk, prevention and treatment of insulin-induced hypoglycemia.

INTRODUCTION

Insulin therapy remains the mainstay of glycemic control in people with type 1 diabetes. Insulin preparations are primarily produced by recombinant DNA technology, and are formulated either as structurally identical to human insulin or as a modification of human insulin (insulin analogues) to alter their pharmacokinetics. Animal insulins are becoming less commercially available.

Insulin preparations are classified according to their duration of action, and are further differentiated by their time of onset and peak actions (Table 1). Premixed insulin preparations are available, but are not generally suitable for intensive treatment in patients with type 1 diabetes, who usually need to frequently change the individual components of their insulin regimens.

INSULIN DELIVERY SYSTEMS

Insulin can be administered by syringe, pen or pump (continuous subcutaneous insulin infusion [CSII]). Insulin pen devices facilitate the use of multiple injections of insulin. CSII therapy is a safe and effective method of intensive insulin therapy for selected patients and may provide some advantages over other methods of intensive therapy, particularly in individuals with higher baseline glycated hemoglobin (A1C) (1-5).

INITIATION OF INSULIN THERAPY

Patients must receive initial and ongoing education that includes comprehensive information on how to care for and use insulin; prevention, recognition and treatment of hypoglycemia; sick-day management; adjustments for food intake (e.g. carbohydrate counting) and physical activity; and self-monitoring of blood glucose (SMBG).

INSULIN REGIMENS

Insulin regimens should be tailored to the individual's treatment goals, lifestyle, diet, age, general health, motivation, hypoglycemia awareness status and ability for self-management. Social and financial aspects should also be considered. After insulin initiation, some patients go through a "honeymoon period," during which insulin requirements may decrease. This period is, however, transient (usually weeks to months), and insulin requirements will increase with time.

While fixed-dose regimens (conventional therapy) were once the most commonly used regimens and are occasionally still used, they are not preferred. The Diabetes Control and Complications Trial (DCCT) conclusively demonstrated that intensive treatment of type 1 diabetes significantly delays the onset and slows the progression of microvascular and macrovascular complications (6,7). The most successful protocols for type 1 diabetes rely on basal-bolus (basal-prandial) regimens that are used as a component of intensive diabetes therapy. Basal insulin is provided by an intermediate-acting insulin or a long-acting insulin analogue once or twice daily. Prandial (bolus) insulin is provided by a short-acting insulin or a rapid-acting insulin analogue given at each meal. Such protocols attempt to duplicate normal pancreatic insulin secretion. Prandial insulin dose must take into account the carbohydrate content and glycemic index of the carbohydrate consumed, exercise around mealtime and the fact that the carbohydrate to insulin ratio may not be the same for each meal (breakfast, lunch and dinner). Prandial insulins can also be used for correction doses to manage hyperglycemia.

Compared with regular insulin, insulin lispro or insulin aspart in combination with adequate basal insulin result in improved postprandial glycemic control and A1C, while minimizing the occurrence of hypoglycemia (8-11). Regular insulin should ideally be administered 30 to 45 minutes prior to a meal. In contrast, insulin aspart and insulin lispro should be administered 0 to 15 minutes before meals. In fact, their rapid onset of action allows for these insulins to be administered up to 15 minutes after a meal. However, preprandial injections achieve better postprandial control and possibly better overall glycemic control (12,13). Insulin aspart has been associated with improved quality of life (14). Insulin

glulisine, another short-acting analogue that has been approved but is not yet commercially available in Canada, has been shown to be equivalent to insulin lispro for glycemic control, with greater A1C reduction when given preprandially as opposed to postprandially (15,16).

When used as a basal insulin in patients with good glycemic control, the long-acting analogues insulin glargine and insulin detemir (with regular insulin or rapid-acting insulin analogues for meals), result in lower fasting plasma glucose (FPG) levels and less nocturnal hypoglycemia compared with once- or twice-daily NPH insulin (8,17-23). Given the potential severe consequences of nocturnal hypoglycemia (discussed below), the avoidance of this complication is of critical clinical importance. When compared with 4-times-daily NPH insulin, insulin glargine was associated with lower A1C and less hypoglycemia (21). Among people with type 1 diabetes, insulin glargine has been shown to have a longer duration of action compared with detemir (24). Insulin detemir has a flatter pharmacodynamic profile than NPH insulin (22). Twice-daily insulin detemir as the basal component of a basal-bolus insulin regimen has been shown

to reduce nocturnal hypoglycemia compared with twice-daily NPH insulin (23,25). There has been a trend towards improved A1C with both insulin glargine and insulin detemir that has reached significance in several studies (25-28). Due to concerns that alterations in the pharmacokinetics may occur, mixing glargine or detemir with other insulins in the same syringe is not recommended by the manufacturers.

In patients using CSII, insulin aspart and lispro have been shown to be superior to regular insulin by improving postprandial glycemic control and reducing hypoglycemia (29-32).

Although human insulins and insulin analogues are used by virtually all adults with type 1 diabetes, animal insulins are still accessible in Canada (see Related Website, page S49).

INHALED INSULIN

Inhaled insulin has been approved for use in Canada, but is not yet commercially available. It has been studied as a rapid-acting insulin administered before meals in a regimen that uses subcutaneous long-acting insulin either once or twice daily. Studies in adults have demonstrated equivalent glycemic control, reduced FPG levels and increased patient satisfaction

Table 1. Types of insulin			
Insulin type (trade name)	**Onset**	**Peak**	**Duration**
Prandial (bolus) insulins			
Rapid-acting insulin analogues (clear) • Insulin aspart (NovoRapid) • Insulin lispro (Humalog) • Insulin glulisine (Apidra)	10–15 min 10–15 min 10–15 min	1–1.5 h 1–2 h 1–1.5 h	3–5 h 3.5–4.75 h 3–5 h
Short-acting insulins (clear) • Humulin-R • Novolin ge Toronto	30 min	2–3 h	6.5 h
Inhaled insulin	10–20 min	2 h	6 h
Basal insulins			
Intermediate-acting (cloudy) • Humulin-N • Novolin ge NPH	1–3 h	5–8 h	Up to 18 h
Long-acting basal insulin analogues (clear) • Insulin detemir (Levemir) • Insulin glargine (Lantus)	90 min	Not applicable	Up to 24 h (glargine 24 h, detemir 16–24 h)
Premixed insulins			
Premixed regular insulin – NPH (cloudy) • Humulin 30/70 • Novolin ge 30/70, 40/60, 50/50	A single vial or cartridge contains a fixed ratio of insulin (% of rapid-acting or short-acting insulin to % of intermediate-acting insulin)		
Premixed insulin analogues (cloudy) • Biphasic insulin aspart (NovoMix 30) • Insulin lispro/lispro protamine (Humalog Mix25 and Mix50)			

Note: Physicians should refer to the most current edition of *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association; Ottawa, Ontario, Canada) and product monographs for detailed information.

compared with subcutaneous short-acting or rapid-acting insulins (33-36). The short-term safety data demonstrate no clinically significant pulmonary dysfunction (33,34,37). It is recommended, however, that inhaled insulin not be used in those with abnormal baseline spirometry (i.e. forced expiratory volume in 1 second [FEV1] <70% predicted) (38).

HYPOGLYCEMIA

Insulin-induced hypoglycemia is a major obstacle for individuals trying to achieve glycemic targets. Hypoglycemia can be severe and result in confusion, coma or seizure, requiring the assistance of other individuals. Significant risk of hypoglycemia often necessitates less stringent glycemic goals. The negative social and emotional impact of hypoglycemia may make patients reluctant to intensify therapy. The diabetes healthcare team should review the patient's experience with hypoglycemia at each visit. This should include an estimate of cause, frequency, symptoms, recognition, severity and treatment.

Intensive vs. conventional insulin therapy

Hypoglycemia is the most common adverse effect of intensive insulin therapy in patients with type 1 diabetes. In the DCCT, 35% of patients in the conventional treatment group and 65% in the intensive group experienced at least 1 episode of severe hypoglycemia (39,40). In a meta-analysis of 14 trials, the median incidence of severe hypoglycemia was 4.6 and 7.9 episodes per 100 patient-years in the conventionally treated and intensively treated patients, respectively (41). Studies have suggested that with adequate self-management education, appropriate glycemic targets, SMBG and professional support, intensive therapy may result in less hypoglycemia than reported in the DCCT (42-45).

Rapid-acting insulin analogues vs. regular insulin

Although there are no differences in the magnitude and temporal pattern of the physiologic, symptomatic and counterregulatory hormonal responses to hypoglycemia induced by regular human insulin or rapid-acting analogues (46,47), the frequency of hypoglycemic events has been shown to be reduced with rapid-acting insulin analogues compared with regular insulin (8-11).

Long-acting insulin analogues vs. intermediate-acting insulins

Studies have shown reduced incidence of nocturnal hypoglycemia when a long-acting insulin analogue is used in lieu of an intermediate-acting insulin as the basal insulin (48-51). This is an important clinical consideration, as nocturnal hypoglycemia has potential for significant adverse effects.

Lifestyle factors

Deviations from recommended or appropriate self-management behaviours (such as eating less food, taking more insulin, engaging in more activity) account for 85% of hypoglycemic episodes (52,53). For patients managed with fixed-dose insulin regimens, care should be taken to develop an individualized meal and activity plan that the person can and will follow (54). Adding bedtime snacks may be helpful to avoid nocturnal hypoglycemia among those taking NPH as the basal insulin, or in those individuals at high risk of severe hypoglycemia (regardless of insulin type), particularly when bedtime plasma glucose (PG) levels are <7.0 mmol/L (55,56).

Knowledge of the acute effects of exercise is mandatory. Low- to moderate-intensity exercise lowers blood glucose (BG) levels both during and after the activity, increasing the risk of a hypoglycemic episode. These effects on BG levels can be modified by altering diet, insulin and the type and timing of exercise. In contrast, high-intensity exercise raises BG levels during and immediately after the event. SMBG before, during and, especially for many hours after exercise is important for establishing response to exercise and guiding the appropriate management of exercise. If ketosis is present (urine ketone level >8.0 mmol/L or blood ketone level >3.0 mmol/L), exercise should not be performed, as metabolic deterioration will occur (57).

Hypoglycemia unawareness and nocturnal hypoglycemia

Asymptomatic hypoglycemia is the presence of a biochemically documented low BG level without any symptoms. Hypoglycemia unawareness occurs when the threshold for the development of autonomic warning symptoms is close to or lower than the threshold for the neuroglycopenic symptoms, such that the first signs of hypoglycemia will often be confusion or loss of consciousness. Severe hypoglycemic reactions are the primary barrier to achieving glycemic targets in people with type 1 diabetes (58). Severe hypoglycemic episodes occur frequently during sleep or in the absence of hypoglycemia awareness that alerts patients to take actions to correct their BG levels (59,60). The sympathoadrenal response to hypoglycemia is reduced during sleep (61). Asymptomatic nocturnal hypoglycemia is common and often lasts >4 hours (59,62-65). Severe hypoglycemia, resulting in seizures, is more likely to occur at night than during the day (66). To reduce the risk of asymptomatic nocturnal hypoglycemia, individuals using intensive insulin therapy should periodically monitor overnight BG levels at a time that corresponds with the peak action time of their overnight insulin.

In people with type 1 diabetes, hypoglycemia was reported to occur at a mean rate of approximately 2 episodes per week. Increasing frequency of hypoglycemia can lead to a decrease in the normal responses to hypoglycemia (67), which, in turn, can lead to decreased awareness of hypoglycemia and defective glucose counterregulation.

Hypoglycemia unawareness and defective glucose counterregulation are potentially reversible. Strict avoidance of hypoglycemia for a period of 2 days to 3 months has been

associated with improvement in the recognition of severe hypoglycemia, in the counterregulatory hormone responses, or both (42,67-73). Structured educational and psychobehavioural programs (e.g. blood glucose awareness training) may help improve detection of hypoglycemia and reduce frequency of severe hypoglycemia (74,75).

RECOMMENDATIONS

Insulin regimens for type 1 diabetes

1. To achieve glycemic targets in adults with type 1 diabetes, multiple daily insulin injections (prandial [bolus] and basal insulin) or the use of CSII as part of an intensive diabetes management regimen is the treatment of choice *[Grade A, Level 1A (6)]*.

2. Rapid-acting insulin analogues (aspart or lispro), in combination with adequate basal insulin, should be considered over regular insulin to improve A1C while minimizing the occurrence of hypoglycemia *[Grade B, Level 2 (9,11)]* and to achieve postprandial glucose targets *[Grade B, Level 2 (76)]*.

3. Insulin aspart or insulin lispro should be used when CSII is used in adults with type 1 diabetes *[Grade B, Level 2 (29,30)]*.

4. A long-acting insulin analogue (detemir, glargine) may be considered as an alternative to NPH as the basal insulin *[Grade B, Level 2 (17-20)]* to reduce the risk of hypoglycemia *[Grade B, Level 2 (50), for detemir; Grade C, Level 3 (51), for glargine]*, including nocturnal hypoglycemia *[Grade B, Level 2 (50), for detemir; Grade D, Consensus, for glargine]*.

Hypoglycemia

5. All individuals with type 1 diabetes should be counselled about the risk and prevention of insulin-induced hypoglycemia, and risk factors for severe hypoglycemia should be identified and addressed *[Grade D, Consensus]*.

6. In individuals with hypoglycemia unawareness, the following strategies should be implemented to reduce the risk of hypoglycemia and to attempt to regain hypoglycemia awareness:
   - Increased frequency of SMBG, including periodic assessment during sleeping hours *[Grade D, Consensus]*.
   - Less stringent glycemic targets with avoidance of hypoglycemia *[Grade C, Level 3 (72,73)]*.
   - Consideration of a psychobehavioural intervention program (blood glucose awareness training), if available *[Grade B, Level 2 (75)]*.

OTHER RELEVANT GUIDELINES

RELATED WEBSITE

Health Canada information about animal insulin:
http://hc-sc.gc.ca/dhp-mps/brgtherap/activit/fs-fi/qa_qr_insulin_02_2006_e.html Accessed September 1, 2008.

REFERENCES

1. Pickup J, Mattock M, Kerry S. Glycaemic control with continuous subcutaneous insulin infusion compared with intensive insulin injections in patients with type 1 diabetes: meta-analysis of randomised controlled trials. *BMJ*. 2002;324:705.

2. Tsui E, Barnie A, Ross S, et al. Intensive insulin therapy with insulin lispro: a randomized trial of continuous subcutaneous insulin infusion versus multiple daily insulin injection. *Diabetes Care*. 2001;24:1722-1727.

3. DeVries JH, Snoek FJ, Kostense PJ, et al; Dutch Insulin Pump Study Group. A randomized trial of continuous subcutaneous insulin infusion and intensive injection therapy in type 1 diabetes for patients with long-standing poor glycemic control. *Diabetes Care*. 2002;25:2074-2080.

4. Hirsch IB, Bode BW, Garg S, et al; Insulin Aspart CSII/MDI Comparison Study Group. Continuous subcutaneous insulin infusion (CSII) of insulin aspart versus multiple daily injection of insulin aspart/insulin glargine in type 1 diabetic patients previously treated with CSII. *Diabetes Care*. 2005;28:533-538.

5. Retnakaran R, Hochman J, DeVries JH, et al. Continuous subcutaneous insulin infusion versus multiple daily injections: the impact of baseline A1c. *Diabetes Care*. 2004;27:2590-2596.

6. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329:977-986.

7. Nathan DM, Cleary PA, Backlund JY, et al; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med*. 2005;353:2643-2653.

8. DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. *JAMA*. 2003;289:2254-2264.

9. Siebenhofer A, Plank J, Berghold A, et al. Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. *Cochrane Database Syst Rev*. 2006;(2):CD003287.

10. Heller SR, Colagiuri S, Vaaler S, et al. Hypoglycaemia with insulin aspart: a double-blind, randomised, crossover trial in subjects with type1 diabetes. *Diabet Med*. 2004;21:769-775.

11. Plank J, Siebenhofer A, Berghold A, et al. Systematic review and meta-analysis of short-acting insulin analogues in patients with diabetes mellitus. *Arch Intern Med*. 2005;165:1337-1344.

12. Schernthaner G, Wein W, Shnawa N, et al. Preprandial vs. post-

prandial insulin lispro – a comparative crossover trial in patients with type 1 diabetes. *Diabet Med.* 2004;21:279-284.

13. Jovanovic L, Giammattei J, Acquistapace M, et al. Efficacy comparison between preprandial and postprandial insulin aspart administration with dose adjustment for unpredictable meal size. *Clin Ther.* 2004;26:1492-1497.

14. Bott U, Ebrahim S, Hirschberger S, et al. Effect of the rapid-acting insulin analogue insulin aspart on quality of life and treatment satisfaction in patients with type 1 diabetes. *Diabet Med.* 2003;20:626-634.

15. Dreyer M, Prager R, Robinson A, et al. Efficacy and safety of insulin glulisine in patients with type 1 diabetes. *Horm Metab Res.* 2005;37:702-707.

16. Garg SK, Rosenstock J, Ways K. Optimized basal-bolus insulin regimens in type 1 diabetes: insulin glulisine versus regular human insulin in combination with basal insulin glargine. *Endocr Pract.* 2005;11:11-17.

17. Warren E, Weatherley-Jones E, Chilcott J, et al. Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine. *Health Technol Assess.* 2004;8:1-57.

18. Wang F, Carabino JM, Vergara CM. Insulin glargine: a systematic review of a long-acting insulin analogue. *Clin Ther.* 2003; 25:1541-1577.

19. Dunn CJ, Plosker GL, Keating GM, et al. Insulin glargine: an updated review of its use in the management of diabetes mellitus. *Drugs.* 2003;63:1743-1778.

20. Chapman TM, Perry CM. Insulin detemir: a review of its use in the management of type 1 and 2 diabetes mellitus. *Drugs.* 2004;64:2577-2595.

21. Rossetti P, Pampanelli S, Fanelli C, et al. Intensive replacement of basal insulin in patients with type 1 diabetes given rapid-acting insulin analog at mealtime: a 3-month comparison between administration of NPH insulin four times daily and glargine insulin at dinner or bedtime. *Diabetes Care.* 2003;26:1490-1496.

22. Plank J, Bodenlenz M, Sinner F, et al. A double-blind, randomized, dose-response study investigating the pharmacodynamic and pharmacokinetic properties of the long-acting insulin analog detemir. *Diabetes Care.* 2005;28:1107-1112.

23. De Leeuw I, Vague P, Selam JL, et al. Insulin detemir used in basal-bolus therapy in people with type 1 diabetes is associated with a lower risk of nocturnal hypoglycaemia and less weight gain over 12 months in comparison to NPH insulin. *Diabetes Obes Metab.* 2005;7:73-82.

24. Porcellati F, Rossetti P, Busciantella NR, et al. Comparison of pharmacokinetics and dynamics of the long-acting insulin analogs glargine and detemir at steady state in type 1 diabetes: a double-blind, randomized, crossover study. *Diabetes Care.* 2007;30:2447-2452.

25. Home P, Bartley P, Russell-Jones D, et al; Study to Evaluate the Administration of Detemir Insulin Efficacy, Safety and Suitability (STEADINESS) Study Group. Insulin detemir offers improved glycemic control compared with NPH insulin in people with type 1 diabetes: a randomized clinical trial. *Diabetes Care.* 2004;27:1081-1087.

26. Hermansen K, Fontaine P, Kukolja KK, et al. Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. *Diabetologia.* 2004;47:622-629.

27. Kudva YC, Basu A, Jenkins GD, et al. Randomized controlled clinical trial of glargine versus ultralente insulin in the treatment of type 1 diabetes. *Diabetes Care.* 2005;28:10-14.

28. Ashwell SG, Amiel SA, Bilous RW, et al. Improved glycaemic control with insulin glargine plus insulin lispro: a multicentre, randomized, cross-over trial in people with type 1 diabetes. *Diabet Med.* 2006;23:285-292.

29. Zinman B, Tildesley H, Chiasson JL, et al. Insulin lispro in CSII: results of a double-blind crossover study. *Diabetes.* 1997; 46:440-443.

30. Bode B, Weinstein R, Bell D, et al. Comparison of insulin aspart with buffered regular insulin and insulin lispro in continuous subcutaneous insulin infusion: a randomized study in type 1 diabetes. *Diabetes Care.* 2002;25:439-444.

31. Radermecker RP, Scheen AJ. Continuous subcutaneous insulin infusion with short-acting insulin analogues or human regular insulin: efficacy, safety, quality of life, and cost-effectiveness. *Diabetes Metab Res Rev.* 2004;20:178-188.

32. Siebenhofer A, Plank J, Berghold A, et al. Meta-analysis of short-acting insulin analogues in adult patients with type 1 diabetes: continuous subcutaneous insulin infusion versus injection therapy. *Diabetologia.* 2004;47:1895-1905.

33. Quattrin T, Bélanger A, Bohannon NJ, et al; Exubera Phase III Study Group. Efficacy and safety of inhaled insulin (Exubera) compared with subcutaneous insulin therapy in patients with type 1 diabetes: results of a 6-month, randomized, comparative trial. *Diabetes Care.* 2004;27:2622-2627.

34. Skyler JS, Weinstock RS, Raskin P, et al; Inhaled Insulin Phase III Type 1 Diabetes Study Group. Use of inhaled insulin in a basal/bolus insulin regimen in type 1 diabetic subjects: a 6-month, randomized, comparative trial. *Diabetes Care.* 2005; 28:1630-1635.

35. Gerber RA, Cappelleri JC, Kourides IA, et al. Treatment satisfaction with inhaled insulin in patients with type 1 diabetes: a randomized controlled trial. *Diabetes Care.* 2001;24:1556-1559.

36. Skyler JS, Jovanovic L, Klioze S, et al; Inhaled Human Insulin Type 1 Diabetes Study Group. Two-year safety and efficacy of inhaled human insulin (Exubera) in adult patients with type 1 diabetes. *Diabetes Care.* 2007;30:579-585.

37. Royle P, Waugh N, McAuley L, et al. Inhaled insulin in diabetes mellitus. *Cochrane Database Syst Rev.* 2004;(3):CD003890.

38. Exubera Product Monograph. Kirkland, QC: Pfizer Canada Inc.; 2007.

39. The Diabetes Control and Complications Trial Research Group. Adverse events and their association with treatment regimens in the Diabetes Control and Complications Trial. *Diabetes Care.* 1995;18:1415-1427.

40. The Diabetes Control and Complications Trial Research Group. Hypoglycemia in the Diabetes Control and Complications Trial.

Diabetes. 1997;46:271-286.

41. Egger M, Davey Smith G, Stettler C, et al. Risk of adverse effects of intensified treatment in insulin-dependent diabetes mellitus: a meta-analysis. *Diabet Med*. 1997;14:919-928.

42. Fanelli CG, Epifano L, Rambotti AM, et al. Meticulous prevention of hypoglycemia normalizes the glycemic thresholds and magnitude of most of neuroendocrine responses to, symptoms of, and cognitive function during hypoglycemia in intensively treated patients with short-term IDDM. *Diabetes*. 1993;42:1683-1689.

43. Bott S, Bott U, Berger M, et al. Intensified insulin therapy and the risk of severe hypoglycaemia. *Diabetologia*. 1997;40:926-932.

44. Ahern J, Tamborlane WV. Steps to reduce the risks of severe hypoglycemia. *Diabetes Spectrum*. 1997;10:39-41.

45. Bolli GB. How to ameliorate the problem of hypoglycemia in intensive as well as nonintensive treatment of type 1 diabetes. *Diabetes Care*. 1999;22(suppl 2):B43-B52.

46. Torlone E, Fanelli C, Rambotti AM, et al. Pharmacokinetics, pharmacodynamics and glucose counterregulation following subcutaneous injection of the monomeric insulin analogue [Lys(B28),Pro(B29)] in IDDM. *Diabetologia*. 1994;37:713-720.

47. McCrimmon RJ, Frier BM. Symptomatic and physiological responses to hypoglycaemia induced by human soluble insulin and the analogue lispro human insulin. *Diabet Med*. 1997;14:929-936.

48. Garg SK, Gottlieb PA, Hisatomi ME, et al. Improved glycemic control without an increase in severe hypoglycemic episodes in intensively treated patients with type 1 diabetes receiving morning, evening, or split dose insulin glargine. *Diabetes Res Clin Pract*. 2004;66:49-56.

49. Garg SK, Paul JM, Karsten JI, et al. Reduced severe hypoglycemia with insulin glargine in intensively treated adults with type 1 diabetes. *Diabetes Technol Ther*. 2004;6:589-595.

50. Goldman-Levine JD, Lee KW. Insulin detemir – a new basal insulin analog. *Ann Pharmacother*. 2005;39:502-507.

51. Mullins P, Sharplin P, Yki-Jarvinen H, et al. Negative binomial meta-regression analysis of combined glycosylated hemoglobin and hypoglycemia outcomes across eleven phase III and IV studies of insulin glargine compared with neutral protamine Hagedorn insulin in type 1 and type 2 diabetes mellitus. *Clin Ther*. 2007;29:1607-1619.

52. Clarke WL, Cox DJ, Gonder-Frederick LA, et al. The relationship between nonroutine use of insulin, food, and exercise and the occurrence of hypoglycemia in adults with IDDM and varying degrees of hypoglycemic awareness and metabolic control. *Diabetes Educ*. 1997;23:55-58.

53. Fritsche A, Stumvoll M, Renn W, et al. Diabetes teaching program improves glycemic control and preserves perception of hypoglycemia. *Diabetes Res Clin Pract*. 1998;40:129-135.

54. Cryer PE, Fisher JN, Shamoon H. Hypoglycemia. *Diabetes Care*. 1994;17:734-755.

55. Kaufman FR, Halvorson M, Kaufman ND. A randomized, blinded trial of uncooked cornstarch to diminish nocturnal hypoglycemia at diabetes camp. *Diabetes Res Clin Pract*. 1995;

30:205-209.

56. Kalergis M, Schiffrin A, Gougeon R, et al. Impact of bedtime snack composition on prevention of nocturnal hypoglycemia in adults with type 1 diabetes undergoing intensive insulin management using lispro insulin before meals: a randomized, placebo-controlled, crossover trial. *Diabetes Care*. 2003;26:9-15.

57. Berger M, Berchtold P, Cüppers HJ, et al. Metabolic and hormonal effects of muscular exercise in juvenile type diabetics. *Diabetologia*. 1977;13:355-365.

58. Cryer PE. Banting Lecture. Hypoglycemia: the limiting factor in the management of IDDM. *Diabetes*. 1994;43:1378-1389.

59. The DCCT Research Group. Epidemiology of severe hypoglycemia in the Diabetes Control and Complications Trial. *Am J Med*. 1991;90:450-459.

60. Daneman D, Frank M, Perlman K, et al. Severe hypoglycemia in children with insulin-dependent diabetes mellitus: frequency and predisposing factors. *J Pediatr*. 1989;115:681-685.

61. Berlin I, Sachon CI, Grimaldi A. Identification of factors associated with impaired hypoglycaemia awareness in patients with type 1 and type 2 diabetes mellitus. *Diabetes Metab*. 2005;31:246-251.

62. Porter PA, Byrne G, Stick S, et al. Nocturnal hypoglycaemia and sleep disturbances in young teenagers with insulin dependent diabetes mellitus. *Arch Dis Child*. 1996;75:120-123.

63. Gale EA, Tattersall RB. Unrecognised nocturnal hypoglycaemia in insulin-treated diabetics. *Lancet*. 1979;1:1049-1052.

64. Beregszàszi M, Tubiana-Rufi N, Benali K, et al. Nocturnal hypoglycemia in children and adolescents with insulin-dependent diabetes mellitus: prevalence and risk factors. *J Pediatr*. 1997;131:27-33.

65. Vervoort G, Goldschmidt HM, van Doorn LG. Nocturnal blood glucose profiles in patients with type 1 diabetes mellitus on multiple (> or = 4) daily insulin injection regimens. *Diabet Med*. 1996;13:794-799.

66. Davis EA, Keating B, Byrne GC, et al. Hypoglycemia: incidence and clinical predictors in a large population-based sample of children and adolescents with IDDM. *Diabetes Care*. 1997;20:22-25.

67. Ovalle F, Fanelli CG, Paramore DS, et al. Brief twice-weekly episodes of hypoglycemia reduce detection of clinical hypoglycemia in type 1 diabetes mellitus. *Diabetes*. 1998;47:1472-1479.

68. Dagogo-Jack S, Rattarasarn C, Cryer PE. Reversal of hypoglycemia unawareness, but not defective glucose counterregulation, in IDDM. *Diabetes*. 1994;43:1426-1434.

69. Fanelli C, Pampanelli S, Epifano L, et al. Long-term recovery from unawareness, deficient counterregulation and lack of cognitive dysfunction during hypoglycaemia, following institution of rational, intensive insulin therapy in IDDM. *Diabetologia*. 1994;37:1265-1276.

70. Dagogo-Jack S, Fanelli CG, Cryer PE. Durable reversal of hypoglycemia unawareness in type 1 diabetes. *Diabetes Care*. 1999;22:866-867.

71. Davis M, Mellman M, Friedman S, et al. Recovery of epineph-

rine response but not hypoglycemic symptom threshold after intensive therapy in type 1 diabetes. *Am J Med.* 1994;97:535-542.

72. Liu D, McManus RM, Ryan EA. Improved counter-regulatory hormonal and symptomatic responses to hypoglycemia in patients with insulin-dependent diabetes mellitus after 3 months of less strict glycemic control. *Clin Invest Med.* 1996;19:71-82.

73. Lingenfelser T, Buettner U, Martin J, et al. Improvement of impaired counterregulatory hormone response and symptom perception by short-term avoidance of hypoglycemia in IDDM. *Diabetes Care.* 1995;18:321-325.

74. Kinsley BT, Weinger K, Bajaj M, et al. Blood glucose awareness training and epinephrine responses to hypoglycemia during intensive treatment in type 1 diabetes. *Diabetes Care.* 1999;22: 1022-1028.

75. Schachinger H, Hegar K, Hermanns N, et al. Randomized controlled clinical trial of Blood Glucose Awareness Training (BGAT III) in Switzerland and Germany. *J Behav Med.* 2005; 28:587-594.

76. DeVries JH, Lindholm A, Jacobsen JL, et al; Tri-Continental Insulin Aspart Study Group. A randomized trial of insulin aspart with intensified basal NPH insulin supplementation in people with type 1 diabetes. *Diabet Med.* 2003;20:312-318.

Pharmacologic Management of Type 2 Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by William Harper MD FRCPC, Amir Hanna MB BCh FRCPC, Vincent Woo MD FRCPC, Keith G. Dawson MD PhD FRCPC, Jean-François Yale MD CSPQ, Lori MacCallum BScPhm PharmD, Maureen Clement MD CCFP, Scot Simpson BSP PharmD MSc and Maryann Hopkins BSP CDE

KEY MESSAGES

- If glycemic targets are not achieved within 2 to 3 months of lifestyle management, antihyperglycemic pharmacotherapy should be initiated.

- Timely adjustments to and/or additions of antihyperglycemic agents should be made to attain target A1C within 6 to 12 months.

- In patients with marked hyperglycemia (A1C ≥9.0%), antihyperglycemic agents should be initiated concomitantly with lifestyle management, and consideration should be given to either initiating combination therapy with 2 agents or initiating insulin.

INTRODUCTION

As people with type 2 diabetes form a heterogeneous group, treatment regimens and therapeutic targets should be individualized. Blood glucose (BG) levels close to the normal range should be the goal for individuals in whom it is deemed safe. As type 2 diabetes is characterized by insulin resistance and ongoing decline in beta cell function, glucose levels will likely worsen over time (1) and treatment must be dynamic. The number of available antihyperglycemic agents is expanding, requiring the clinician to consider many of the following factors when choosing medications: degree of hyperglycemia, risk of hypoglycemia, medication side effects, concomitant medical conditions, ability to adhere to regimen and patient preferences. Lifestyle modification, including nutritional therapy and physical activity, should continue to be emphasized while pharmacotherapy is being used.

TREATMENT REGIMENS

The diagnosis of type 2 diabetes is often delayed, and 20 to 50% of people with type 2 diabetes present with microvascular and/or macrovascular complications at the time of diagnosis (2,3). When lifestyle interventions fail to control BG levels adequately, pharmacologic treatment becomes necessary.

In the face of more severe hyperglycemia (i.e. glycated hemoglobin [A1C] ≥9.0%), combinations of agents are usually required. The lag period before adding other antihyperglycemic agent(s) should be kept to a minimum, taking into account the characteristics of the different medications. With timely adjustments to and/or additions of antihyperglycemic agents, the target A1C level should be attainable within 6 to 12 months.

In general, A1C will decrease by about 0.5 to 1.5% with monotherapy, depending on the agent used and the baseline A1C level (4). Generally, the higher the baseline A1C, the greater the A1C reduction for each given agent. In general, as A1C levels decrease toward normal levels (<7.3%), postprandial BG control assumes greater importance for further A1C reduction (5).

The initial use of combinations of submaximal doses of antihyperglycemic agents produces more rapid and improved glycemic control and fewer side effects compared to monotherapy at maximal doses (6-9). Furthermore, many patients on monotherapy with the late addition of another antihyperglycemic agent may not readily attain target BG levels (1). When combining antihyperglycemic agents with or without insulin, classes of agents that have different mechanisms of action should be used. Simultaneous use of agents from different classes but with similar mechanisms of action (e.g. sulfonylureas and meglitinides; and DPP-4 inhibitors) is currently untested and may be less effective at improving glycemia and is not recommended at this time.

There is debate over which antihyperglycemic agent (including insulin) should be used initially and which agents should be added subsequently. There is also debate over which agents within a given class might be preferred in specific situations. Symptomatic patients with high BG and A1C levels require agents that lower BG levels quickly (e.g. insulin). However, the issue of how to reach glycemic targets may be less important than the need to achieve that target. Improved BG and A1C levels are associated with better outcomes, even if recommended glycemic targets cannot be reached (3). Each of the agents listed in Table 1 (10-51) and Figure 1 has advantages and disadvantages (e.g. degree of BG lowering, risk of hypoglycemia and nonglycemic benefits/risks).

The recommendation to use metformin as the initial agent in most patients is based on its effectiveness in lowering BG, its relatively mild side effect profile and its demonstrated benefit in overweight patients (52). While monotherapy with an insulin sensitizer (thiazolidinedione [TZD]) produces more long-lasting glycemic control compared to metformin or sulfonylurea therapy (45), the edema, weight gain, small risk of congestive heart failure (CHF), increased risk of fractures in women (44,46) and inconsistent data regarding cardiovascular outcomes (53) offset the potential for this class to be recommended as first-line therapy. Although meta-analyses of

Table 1. Antihyperglycemic agents for use in type 2 diabetes

Class*	Drug (brand name)	Expected decrease in A1C with monotherapy	Hypoglycemia	Other therapeutic considerations
Alpha-glucosidase inhibitor	acarbose (Glucobay) (10-12)	↓	Negligible risk as monotherapy	• Not recommended as initial therapy in people with marked hyperglycemia (A1C ≥9.0%) • Often used in combination with other oral antihyperglycemic agents • Weight neutral as monotherapy • GI side effects
Incretin agent (13-15)	**DPP-4 inhibitor** sitagliptin (Januvia)	↓ to ↓↓	Negligible risk as monotherapy	• Weight neutral • Improved postprandial control • Newer agent with unknown long-term safety
Insulin (3,16-22)	**Rapid-acting analogues** aspart (NovoRapid) glulisine (Apidra) lispro (Humalog) **Short-acting** regular (Humulin-R, Novolin geToronto) **Intermediate-acting** NPH (Humulin-N, Novolin ge NPH) **Long-acting basal analogues** detemir (Levemir) glargine (Lantus) **Premixed** Premixed Regular-NPH (Humulin 30/70; Novolin ge 30/70, 40/60, 50/50) Biphasic insulin aspart (NovoMix 30) Insulin lispro/lispro protamine (Humalog Mix25, Mix50)	Depends on regimen, but up to ↓↓↓	Significant risk	• Potentially greatest A1C reduction and no maximal dose • Numerous formulations and delivery systems (including subcutaneous-injectable) allow for regimen flexibility • Hypoglycemia risk highest with regular and NPH insulin • When initiating insulin, consider adding bedtime intermediate-acting insulin or long-acting insulin analogue to daytime oral antihyperglycemic agents (although other regimens can be used) • Intensive insulin therapy regimen recommended if above fails to attain glycemic targets • Increased risk of weight gain relative to sulfonylureas and metformin
Insulin secretagogues	**Sulfonylureas** gliclazide (Diamicron, Diamicron MR, generic) (23,24)	↓↓	Minimal/moderate risk	• Relatively rapid BG-lowering response • All insulin secretagogues reduce glycemia similarly (except nateglinide, which is less effective) • Postprandial glycemia is especially reduced by nateglinide and repaglinide • Hypoglycemia and weight gain are especially common with glyburide • Consider using other class(es) of antihyperglycemic agents first in patients at high risk of hypoglycemia (e.g. the elderly, renal/hepatic failure) • If a sulfonylurea must be used in such individuals, gliclazide is associated with the lowest incidence of hypoglycemia (32) and glimepiride is associated with less hypoglycemia than glyburide (27) • Nateglinide and repaglinide are associated with less hypoglycemia in the context of missed meals
	glimepiride (Amaryl) (25-27)	↓↓	Moderate risk	
	glyburide (Diabeta, Euglucon, generic) (3)	↓↓	Significant risk	
	(note: chlorpropamide and tolbutamide are still available in Canada, but rarely used)			
	Meglitinides nateglinide (Starlix) (28) repaglinide (GlucoNorm) (29-31)	→↓ ↓↓	Minimal/moderate risk Minimal/moderate risk	

Class	Agent	A1C	Risk	Therapeutic considerations
Metformin	Glucophage, Glumetza, generic (33,34)	↓↓	Negligible risk as monotherapy	• Improved cardiovascular outcomes in overweight subjects • Contraindicated if CrCl/eGFR <30 mL/min or hepatic failure • Caution if CrCl/eGFR <60 mL/min • Weight neutral as monotherapy; promotes less weight gain when combined with other antihyperglycemic agents, including insulin • GI side effects
TZDs (35-45)	pioglitazone (Actos) rosiglitazone (Avandia)	↓↓	Negligible risk as monotherapy	• Longer duration of glycemic control with monotherapy compared to metformin or glyburide • Mild BP lowering • Between 6 and 12 weeks required to achieve full glycemic effect • Weight gain (waist-to-hip ratio not increased) • May induce edema and or heart failure • Avoid in patients with heart failure • Higher rates heart failure when combined with insulin[†] • Rare occurrence of macular edema • Rare occurrence of fractures in females (44,46) • Suggestion of increased risk of cardiovascular events with rosiglitazone awaits further study
Antiobesity agents	orlistat (Xenical) (47-49)	→	None	• Promote weight loss • Glycemic benefit may be limited to those who actually lose weight
	sibutramine (Meridia) (50,51)	→	None	• Orlistat can cause diarrhea and other GI side effects • Sibutramine can increase heart rate and BP
Combined formulations	Avandamet (metformin + rosiglitazone)	↓↓↓	Negligible risk as monotherapy	See metformin, TZDs, and sulfonylureas
	Avandaryl (glimepiride + rosiglitazone)	↓↓↓	Moderate risk	

*Listed in alphabetical order
†Combining insulin with a TZD is not an approved indication in Canada

↓: <1.0% reduction in A1C
↓↓: 1.0–2.0% reduction in A1C
↓↓↓: >2.0% reduction in A1C

A1C = glycated hemoglobin
BG = blood glucose
BP = blood pressure
CrCl = creatinine clearance
eGFR = estimated glomerular filtration rate
GI = gastrointestinal
TZD = thiazolidinedione

Note: Physicians should refer to the most recent edition of the *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association, Ottawa, Ontario, Canada) for product monographs and detailed prescribing information.

Figure 1. Management of hyperglycemia in type 2 diabetes

L I F E S T Y L E

Clinical assessment

Lifestyle intervention (initiation of nutrition therapy and physical activity)

| A1C <9.0% | A1C ≥9.0% | Symptomatic hyperglycemia with metabolic decompensation |

Initiate **metformin**

Initiate **pharmacotherapy** immediately without waiting for effect from lifestyle interventions:
- Consider initiating **metformin** concurrently with another agent from a different class; or
- Initiate **insulin**

Initiate **insulin ± metformin**

If not at target

Add an agent best suited to the individual based on the advantages/disadvantages listed below and the information contained in Table 1 (*agents listed in alphabetical order*)

Class	A1C	Hypoglycemia	Other advantages	Other disadvantages
Alpha-glucosidase inhibitor	↓	Rare	Improved postprandial control Weight neutral	GI side effects
Incretin agent: DPP-4 inhibitor	↓to↓↓	Rare	Improved postprandial control Weight neutral	New agent (unknown long-term safety)
Insulin	↓↓↓	Yes	No dose ceiling Many types, flexible regimens	Weight gain
Insulin secretagogue:				
Meglitinide	↓to↓↓	Yes*	Improved postprandial control Newer sulfonylureas (gliclazide, glimepiride) are associated with less hypoglycemia than glyburide	Requires TID to QID dosing Weight gain
Sulfonylurea	↓↓	Yes		
TZD	↓↓	Rare	Durable monotherapy	Requires 6–12 weeks for maximal effect Weight gain Edema, rare CHF, rare fractures in females
Weight loss agent	↓	None	Weight loss	GI side effects (orlistat) Increased heart rate/BP (sibutramine)

If not at target

- Add another drug from a different class; or
- Add bedtime basal insulin to other agent(s); or
- Intensify insulin regimen

Timely adjustments to and/or addition of antihyperglycemic agents should be made to attain target A1C within 6 to 12 months

A1C = glycated hemoglobin
BP = blood pressure
CHF = congestive heart failure
DPP-4 = dipeptidyl peptidase-4
GI = gastrointestinal
TZD = thiazolidinedione
↓ = <1.0% decrease in A1C
↓↓ = 1.0–2.0% decrease in A1C
↓↓↓ = >2.0% decrease in A1C

Note: Physicians should refer to the most recent edition of the *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association, Ottawa, Ontario, Canada) for product monographs and for detailed prescribing information

*Less hypoglycemia in the context of missed meals

smaller underpowered studies suggested possible cardiovascular harm specific to TZD use (54,55) this has not been demonstrated in larger randomized clinical trials (56-58).

In patients for whom hypoglycemia is a particular concern, agents associated with less hypoglycemia are preferred. Table 1 and Figure 1 provide information to aid decision-making.

A combination of oral antihyperglycemic agents and insulin often effectively controls glucose levels. When insulin is added to oral antihyperglycemic agent(s), a single injection of intermediate-acting (NPH) (6,59), or an extended long-acting insulin analogue (insulin glargine or insulin detemir) (19) may be added. This approach may result in better glycemic control with a smaller dose of insulin (60) and may induce less weight gain and less hypoglycemia than that seen when oral agents are stopped and insulin is used alone (33). The addition of bedtime insulin to metformin therapy leads to less weight gain than insulin plus a sulfonylurea or twice-daily NPH insulin (16). While combining insulin with a TZD is not an approved indication in Canada, the addition of such agents to insulin in carefully selected patients improves glycemic control and reduces insulin requirements (61). Such combination can result in increased weight, fluid retention and, in few patients, CHF. Inhaled insulin (approved, but not yet available in Canada) can also be added to oral antihyperglycemic therapy to help control BG levels, but can cause cough and slight reductions in pulmonary function tests (62). The use of inhaled insulin should be restricted to non-smokers and those without respiratory disorders. Pulmonary function tests should be done at baseline, 6 months and annually during inhaled insulin therapy.

Insulin can be used at diagnosis in individuals with marked hyperglycemia and can be used temporarily during illness, pregnancy, stress, or for a medical procedure or surgery. There is no evidence that exogenous insulin accelerates the risk of macrovascular complications of diabetes, and its appropriate use should be encouraged (63). When insulin is used in type 2 diabetes, the insulin regimen should be tailored to achieve good metabolic control while trying to avoid severe hypoglycemia. With intensive glycemic control, there is an increased risk of hypoglycemia, but this risk is lower in people with type 2 diabetes than in those with type 1 diabetes. The number of insulin injections (1–4 per day) and the timing of injections may vary depending on each individual's situation (64). The reduction in A1C achieved with insulin therapy depends on the dose and number of injections per day of insulin.

As type 2 diabetes progresses, insulin doses will likely need to be increased, additional doses of basal insulin (intermediate-acting or long-acting analogues) may need to be added, and prandial insulin (short-acting or rapid-acting analogues or inhaled insulin) may also be required.

RECOMMENDATIONS

1. In people with type 2 diabetes, if glycemic targets are not achieved using lifestyle management within 2 to 3 months, antihyperglycemic agents should be initiated [Grade A, Level 1A (3)]. In the presence of marked hyperglycemia (A1C ≥9.0%), antihyperglycemic agents should be initiated concomitantly with lifestyle management, and consideration should be given to initiating combination therapy with 2 agents or initiating insulin treatment in symptomatic individuals [Grade D, Consensus].

2. If glycemic targets are not attained when a single antihyperglycemic agent is used initially, an antihyperglycemic agent or agents from different classes should be added. The lag period before adding other agent(s) should be kept to a minimum, taking into account the characteristics of the different agents. Timely adjustments to and/or additions of antihyperglycemic agents should be made in order to attain target A1C within 6 to 12 months [Grade D, Consensus].

3. Pharmacological treatment regimens should be individualized taking into consideration the degree of hyperglycemia and the properties of the antihyperglycemic agents including: effectiveness in lowering BG, durability of glycemic control, side effects, contraindications, risk of hypoglycemia, presence of diabetes complications or comorbidities, and patient preferences [Grade D, Consensus]. The following factors and the information shown in Table 1 and Figure 1 should also be taken into account:
   • Metformin should be the initial drug used in both overweight patients [Grade A, Level 1A (52)] and nonoverweight patients [Grade D, Consensus].
   • Other classes of antihyperglycemic agents, including insulin, should be added to metformin, or used in combination with each other, if glycemic targets are not met, taking into account the information in Figure 1 and Table 1 [Grade D, Consensus].

4. When basal insulin is added to antihyperglycemic agents, long-acting analogues (insulin detemir or insulin glargine) may be considered instead of NPH to reduce the risk of nocturnal and symptomatic hypoglycemia [Grade A, Level 1A (71)].

5. The following antihyperglycemic agents (listed in alphabetical order), should be considered to lower postprandial BG levels:
   • Alpha-glucosidase inhibitor [Grade B, Level 2 (10)]
   • Premixed insulin analogues (i.e. biphasic insulin aspart and insulin lispro/protamine) instead of regular/NPH premixtures [Grade B, Level 2 (72,73)]
   • DPP-4 inhibitor [Grade A, Level 1 (13,14,74)].
   • Inhaled insulin [Grade B, Level 2 (20)].
   • Meglitinides (repaglinide, nateglinide) instead of sulfonylureas [Grade B, Level 2 (75,76)]
   • Rapid-acting insulin analogues (aspart, glulisine, lispro) instead of short-acting insulin (i.e. regular insulin) [Grade B, Level 2 (21,77,78)].

6. All individuals with type 2 diabetes currently using or starting therapy with insulin or insulin secretagogues should be counselled about the recognition and prevention of drug-induced hypoglycemia [Grade D, Consensus].

HYPOGLYCEMIA

Medication-induced hypoglycemia is the most common cause of hypoglycemia. It is estimated that hypoglycemia of any severity occurs annually in up to approximately 20% of patients taking insulin secretagogues (65). Although these hypoglycemic episodes are rarely fatal, they can be associated with serious clinical sequelae. Therefore, it is important to prevent, recognize and treat hypoglycemic episodes secondary to the use of insulin secretagogues. Few large, randomized clinical trials have compared the rates of hypoglycemia between these agents.

In the United Kingdom Prospective Diabetes Study (UKPDS), the proportion of adults with type 2 diabetes who experienced a severe hypoglycemic episode per year was significantly higher in the intensive group than in the conventional group (3), particularly for patients using insulin therapy. Although the risk of hypoglycemia was less than that seen in the patients with type 1 diabetes in the Diabetes Control and Complications Trial, each year approximately 3% of patients treated with insulin in the UKPDS experienced a severe hypoglycemic episode, and 40% had a hypoglycemic episode of any severity (3).

Lower rates of hypoglycemia have been observed in some studies of patients with type 2 diabetes treated with rapid-acting insulin analogues (insulin aspart, insulin lispro, insulin glulisine) compared to those treated with short-acting (regular) insulin (66,67). Use of long-acting basal insulin analogues (insulin detemir, insulin glargine) reduces the risk of nocturnal hypoglycemia compared to treatment with NPH insulin (19,68-70).

OTHER RELEVANT GUIDELINES

Targets for Glycemic Control, p. S29
Insulin Therapy in Type 1 Diabetes, p. S46
Hypoglycemia, p. S62
Management of Obesity in Diabetes, p. S77
Type 2 Diabetes in Children and Adolescents, p. S162
Diabetes and Pregnancy, p. S168
Diabetes in the Elderly, p. S181

RELEVANT APPENDIX

Appendix 3: Examples of Insulin Initiation and Titration Regimens in People With Type 2 Diabetes

REFERENCES

1. Turner RC, Cull CA, Frighi V, et al. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). *JAMA*. 1999;281:2005-2012.

2. Klein R, Klein BE, Moss SE, et al. The Wisconsin epidemiological study of diabetic retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. *Arch Ophthalmol*. 1984;102:527-532.

3. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352: 837-853.

4. Bloomgarden ZT, Dodis R, Viscoli CM, et al. Lower baseline glycemia reduces apparent oral agent glucose-lowering efficacy: a meta-regression analysis. *Diabetes Care*. 2006;29:2137-2139.

5. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA(1c). *Diabetes Care*. 2003;26:881-885.

6. Garber AJ, Larsen J, Schneider SH, et al. Simultaneous glyburide/metformin therapy is superior to component monotherapy as an initial pharmacological treatment for type 2 diabetes. *Diabetes Obes Metab*. 2002;4:201-208.

7. Rosenstock J, Goldstein BJ, Vinik AI, et al. Effect of early addition of rosiglitazone to sulphonylurea therapy in older type 2 diabetes patients (>60 years): the Rosiglitazone Early vs. Sulphonylurea Titration (RESULT) study. *Diabetes Obes Metab*. 2006;8:49-57.

8. Rosenstock J, Rood J, Cobitz A, et al. Initial treatment with rosiglitazone/metformin fixed-dose combination therapy compared with monotherapy with either rosiglitazone or metformin in patients with uncontrolled type 2 diabetes. *Diabetes Obes Metab*. 2006;8:650-660.

9. Rosenstock J, Rood J, Cobitz A, et al. Improvement in glycaemic control with rosiglitazone/metformin fixed-dose combination therapy in patients with type 2 diabetes with very poor glycaemic control. *Diabetes Obes Metab*. 2006;8:643-649.

10. Chiasson J-L, Josse RG, Hunt JA, et al. The efficacy of acarbose in the treatment of patients with non-insulin-dependent diabetes mellitus. A multicenter controlled clinical trial. *Ann Intern Med*. 1994;121:928-935.

11. Hoffmann J, Spengler M. Efficacy of 24-week monotherapy with acarbose, glibenclamide, or placebo in NIDDM patients. The Essen Study. *Diabetes Care*. 1994;17:561-566.

12. Holman RR, Cull CA, Turner RC. A randomized double-blind trial of acarbose in type 2 diabetes shows improved glycemic control over 3 years (U.K. Prospective Diabetes Study 44). *Diabetes Care*. 1999;22:960-964.

13. Aschner P, Kipnes MS, Lunceford JK, et al. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care*. 2006;29:2632-2637.

14. Charbonnel B, Karasik A, Liu J, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. *Diabetes Care*. 2006; 29:2638-2643.

15. Bosi E, Camisasca RP, Collober C, et al. Effects of vildagliptin on glucose control over 24 weeks in patients with type 2 diabetes inadequately controlled with metformin. *Diabetes Care*. 2007;30:890-895.

16. Yki-Järvinen H, Ryysy L, Nikkilä K, et al. Comparison of bed-time insulin regimens in patients with type 2 diabetes mellitus. A randomized, controlled trial. *Ann Intern Med*. 1999;130:389-396.

17. Wright A, Burden AC, Paisey RB, et al. Sulfonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the U.K. Prospective Diabetes Study (UKPDS 57). *Diabetes Care*. 2002;25:330-336.

18. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract*. 1995;28:103-117.

19. Rosenstock J, Schwartz SL, Clark CM Jr, et al. Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin glargine (HOE 901) and NPH insulin. *Diabetes Care*. 2001; 24:631-636.

20. Weiss SR, Cheng SL, Kourides IA, et al, for the Inhaled Insulin Phase II Study Group. Inhaled insulin provides improved glycemic control in patients with type 2 diabetes mellitus inadequately controlled with oral agents: a randomized controlled trial. *Arch Intern Med*. 2003;27:2277-2282.

21. Dailey G, Rosenstock J, Moses RG, et al. Insulin glulisine provides improved glycemic control in patients with type 2 diabetes. *Diabetes Care*. 2004;27:2363-2368.

22. Haak T, Tiengo A, Draeger E, et al. Lower within-subject variability of fasting blood glucose and reduced weight gain with insulin detemir compared to NPH insulin in patients with type 2 diabetes. *Diabetes Obes Metab*. 2005;7:56-64.

23. Harrower A. Gliclazide modified release: from once-daily administration to 24-hour blood glucose control. *Metabolism*. 2000;49(10 suppl 2):7-11.

24. Tessier D, Dawson K, Tétrault JP, et al. Glibenclamide vs gliclazide in type 2 diabetes of the elderly. *Diabet Med*. 1994; 11:974-980.

25. Schade DS, Jovanovic L, Schneider J. A placebo-controlled, randomized study of glimepiride in patients with type 2 diabetes mellitus for whom diet therapy is unsuccessful. *J Clin Pharmacol*. 1998;38:636-641.

26. Dills DG, Schneider J. Clinical evaluation of glimepiride versus glyburide in NIDDM in a double-blind comparative study. *Horm Metab Res*. 1996;28:426-429.

27. Holstein A, Plaschke A, Egberts EH. Lower incidence of severe hypoglycaemia in patients with type 2 diabetes treated with glimepiride versus glibenclamide. *Diabetes Metab Res Rev*. 2001; 17:467-473.

28. Horton ES, Clinkingbeard C, Gatlin M, et al. Nateglinide alone and in combination with metformin improves glycemic control by reducing mealtime glucose levels in type 2 diabetes. *Diabetes Care*. 2000;23:1660-1665.

29. Wolffenbuttel BHR, Landgraf R. A 1-year multicenter randomized double-blind comparison of repaglinide and glyburide for the treatment of type 2 diabetes. *Diabetes Care*. 1999;22:463-467.

30. Moses R, Slobodniuk R, Boyages S, et al. Effect of repaglinide addition to metformin monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care*. 1999;22:119-124.

31. Damsbo P, Clauson P, Marbury TC, et al. A double-blind randomized comparison of meal-related glycemic control by repaglinide and glyburide in well-controlled type 2 diabetic patients. *Diabetes Care*. 1999;22:789-794.

32. Schernthaner G, Grimaldi A, Di Mario U, et al. GUIDE study: double-blind comparison of once-daily gliclazide MR and glimepiride in type 2 diabetic patients. *Eur J Clin Invest*. 2004; 34:535-542.

33. United Kingdom Prospective Diabetes Study Group. United Kingdom Prospective Diabetes Study 24: a 6-year, randomized, controlled trial comparing sulfonylurea, insulin, and metformin therapy in patients with newly diagnosed type 2 diabetes that could not be controlled with diet therapy. *Ann Intern Med*. 1998;128:165-175.

34. Garber AJ, Duncan TG, Goodman AM, et al. Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose-response trial. *Am J Med*. 1997;103:491-497.

35. Aronoff S, Rosenblatt S, Braithwaite S, et al. Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes: a 6-month randomized placebo-controlled dose-response study. *Diabetes Care*. 2000;23:1605-1611.

36. Raskin P, Rappaport EB, Cole ST, et al. Rosiglitazone short-term monotherapy lowers fasting and post-prandial glucose in patients with type II diabetes. *Diabetologia*. 2000;43:278-284.

37. Nolan JJ, Jones NP, Patwardhan R, et al. Rosiglitazone taken once daily provides effective glycaemic control in patients with type 2 diabetes mellitus. *Diabet Med*. 2000;17:287-294.

38. Lebovitz HE, Dole JF, Patwardhan R, et al. Rosiglitazone monotherapy is effective in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2001;86:280-288.

39. Fonseca V, Rosenstock J, Patwardhan R, et al. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a randomized controlled trial. *JAMA*. 2000;283:1695-1702.

40. Kipnes MS, Krosnick A, Rendell MS, et al. Pioglitazone hydrochloride in combination with sulfonylurea therapy improves glycemic control in patients with type 2 diabetes mellitus: a randomized, placebo-controlled study. *Am J Med*. 2001;111:10-17.

41. Einhorn D, Rendell M, Rosenzweig J, et al. Pioglitazone hydrochloride in combination with metformin in the treatment of type 2 diabetes mellitus: a randomized, placebo-controlled study. *Clin Ther*. 2000;22:1395-1409.

42. Yale J-F, Valiquett TR, Ghazzi MN, et al. The effect of a thiazolidinedione drug, troglitazone, on glycemia in patients with type 2 diabetes mellitus poorly controlled with sulfonylurea and metformin. A multicenter, randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 2001;134:737-745.

43. Schwartz S, Raskin P, Fonseca V, et al. Effect of troglitazone in insulin-treated patients with type II diabetes mellitus. *N Engl J*

Med. 1998;338:861-866.

44. Meymeh RH, Wooltorton E. Diabetes drug pioglitazone (Actos): risk of fracture. *CMAJ*. 2007;177:723-724.

45. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med*. 2006;355:2427-2443.

46. Kahn SE, Zinman B, Lachin JM, et al; A Diabetes Outcome Progression Trial (ADOPT) Study Group. Rosiglitazone-associated fractures in type 2 diabetes: an analysis from A Diabetes Outcome Progression Trial. *Diabetes Care*. 2008;31:845-851.

47. Miles JM, Leiter L, Hollander P, et al. Effect of orlistat in overweight and obese patients with type 2 diabetes treated with metformin. *Diabetes Care*. 2002;25:1123-1128.

48. Kelley DE, Bray GA, Pi-Sunyer FX, et al. Clinical efficacy of orlistat therapy in overweight and obese patients with insulin-treated type 2 diabetes: A 1-year randomized controlled trial. *Diabetes Care*. 2002;25:1033-1041.

49. Hollander PA, Elbein SC, Hirsch IB, et al. Role of orlistat in the treatment of obese patients with type 2 diabetes. A 1-year randomized double-blind study. *Diabetes Care*. 1998;21:1288-1294.

50. Vettor R, Serra R, Fabris R, Pagano C, Federspil G. Effect of sibutramine on weight management and metabolic control in type 2 diabetes: a meta-analysis of clinical studies. *Diabetes Care*. 2005;28:942-999.

51. Finer N, Bloom SR, Frost GS, et al. Sibutramine is effective for weight loss and diabetic control in obesity with type 2 diabetes: a randomised, double-blind, placebo-controlled study. *Diabetes Obes Metab*. 2000;2:105-112.

52. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*. 1998;352:854-865.

53. *Avandia – Highlights of Prescribing Information. March 2008*. Research Triangle Park, NC: GlaxoSmithKline. Available at: http://www.gsk.com/products/prescription_medicines/us/medicines-ae.htm. Accessed September 1, 2008.

54. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med*. 2007;356:2457-2471.

55. Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA*. 2007;298:1189-1195.

56. Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet*. 2005;366:1279-1289.

57. Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone Evaluated for Cardiovascular Outcomes – An interim analysis. *N Engl J Med*. 2007;357:28-38.

58. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358:2545-2559.

59. Yki-Järvinen H, Kauppila M, Kujansuu E, et al. Comparison of insulin regimens in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med*. 1992;327:1426-1433.

60. Johnson JL, Wolf SL, Kabadi UM. Efficacy of insulin and sulfonylurea combination therapy in type II diabetes. A meta-analysis of the randomized placebo-controlled trials. *Arch Intern Med*. 1996;156:259-264.

61. Yu JG, Krusynska MT, Mulford MI, et al. A comparison of troglitazone and metformin on insulin requirements in euglycemic intensively insulin-treated type 2 diabetic patients. *Diabetes*. 1999;48:2414-2421.

62. Barnett AH, Dreyer M, Lange P, Serdarevic-Pehar M. An open, randomized, parallel-group study to compare the efficacy and safety profile of inhaled human insulin (Exubera) with metformin as adjunctive therapy in patients with type 2 diabetes poorly controlled on a sulfonylurea. *Diabetes Care*. 2006;29:1282-1287.

63. American Diabetes Association. Implications of the United Kingdom Prospective Diabetes Study. *Diabetes Care*. 1998;21:2180-2184.

64. Abraira C, Colwell JA, Nuttall FQ, et al. Veterans Affairs Cooperative Study on glycemic control and complications in type II diabetes (VA CSDM). Results of the feasibility trial. *Diabetes Care*. 1995;18:1113-1123.

65. Jennings AM, Wilson RM, Ward JD. Symptomatic hypoglycemia in NIDDM patients treated with oral hypoglycemic agents. *Diabetes Care*. 1989;12:203-208.

66. Anderson JH Jr, Brunelle RL, Keohane P, et al. Mealtime treatment with insulin analog improves postprandial hyperglycemia and hypoglycemia in patients with non-insulin-dependent diabetes mellitus. *Arch Intern Med*. 1997;157:1249-1255.

67. Anderson JH Jr, Brunelle RL, Koivisto VA, et al. Improved mealtime treatment of diabetes mellitus using an insulin analogue. *Clin Ther*. 1997;19:62-72.

68. Yki-Järvinen H, Dressler A, Ziemen M. Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. *Diabetes Care*. 2000;23:1130-1136.

69. Fritsche A, Schweitzer MA, Haring HU, et al. Glimepiride combined with morning insulin glargine, bedtime neutral protamine hagedorn insulin, or bedtime insulin glargine in patients with type 2 diabetes. A randomized, controlled trial. *Ann Int Med*. 2003;138:952-959.

70. Janka HU, Plewe G, Riddle MC, et al. Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. *Diabetes Care*. 2005;28:254-259.

71. Horvath K, Jeitler K, Berghold A, et al. A long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus (Review). *Cochrane Database Syst Rev*. 2007;(2):CD005613.

72. Roach P, Yue L, Arora V. Improved postprandial glycemic control during treatment with Humalog Mix25, a novel prota-

mine-based insulin lispro formulation. Humalog Mix25 Study Group. *Diabetes Care.* 1999;22:1258-1261.

73. Boehm BO, Home PD, Behrend C, et al. Premixed insulin aspart 30 vs. premixed human insulin 30/70 twice daily: a randomized trial in type 1 and type 2 diabetic patients. *Diabet Med.* 2002;19:393-399.

74. Ahren B, Gomis R, Standl E, et al. Twelve- and 52-week efficacy of the dipeptidyl peptidase IV inhibitor LAF237 in metformin-treated patients with type 2 diabetes. *Diabetes Care.* 2004;27:2874-2880.

75. Derosa G, Mugellini A, Ciccarelli L, et al. Comparison between repaglinide and glimepiride in patients with type 2 diabetes mellitus: a one-year, randomized, double-blind assessment of metabolic parameters and cardiovascular risk factors. *Clin Ther.* 2003;25:472-484.

76. Ristic S, Collober-Maugeais C, Pecher E, et al. Comparison of nateglinide and gliclazide in combination with metformin, for treatment of patients with Type 2 diabetes mellitus inadequately controlled on maximum doses of metformin alone. *Diabet Med.* 2006;23:757-762.

77. Ross SA, Zinman B, Campos RV, et al. A comparative study of insulin lispro and human regular insulin in patients with type 2 diabetes mellitus and secondary failure of oral hypoglycemic agents. *Clin Invest Med.* 2001;24:292-298.

78. Rosenfalck AM, Thorsby P, Kjems L, et al. Improved postprandial glycaemic control with insulin aspart in type 2 diabetic patients treated with insulin. *Acta Diabetol.* 2000;37:41-46.

Hypoglycemia

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee
The initial draft of this chapter was prepared by Jean-François Yale MD CSPQ

KEY MESSAGES

- It is important to prevent, recognize and treat hypo-glycemic episodes secondary to the use of insulin or insulin secretagogues.

- The goals of treatment for hypoglycemia are to detect and treat a low blood glucose (BG) level promptly by using an intervention that provides the fastest rise in BG to a safe level, to eliminate the risk of injury and to relieve symptoms quickly.

- It is important to avoid overtreatment, since this can result in rebound hyperglycemia and weight gain.

INTRODUCTION

Drug-induced hypoglycemia is a major obstacle for individuals (especially those with type 1 diabetes) trying to achieve glycemic targets. Hypoglycemia can be severe and result in confusion, coma or seizure requiring the assistance of other individuals. Significant risk of hypoglycemia often necessitates less stringent glycemic goals. The negative social and emotional impact of hypoglycemia may make patients reluctant to intensify therapy. As such, it is important to prevent, recognize and treat hypoglycemic episodes secondary to the use of insulin or insulin secretagogues. (See "Insulin Therapy in Type 1 Diabetes," p. S46, and "Pharmacologic Management of Type 2 Diabetes," p. S53, for further discussion of drug-induced hypoglycemia.)

DEFINITION OF HYPOGLYCEMIA

Hypoglycemia is defined by: 1) the development of autonomic or neuroglycopenic symptoms (Table 1); 2) a low plasma glucose (PG) level (<4.0 mmol/L for patients treated with insulin or an insulin secretagogue); and 3) symptoms responding to the administration of carbohydrate (1). The severity of hypoglycemia is defined by clinical manifestations (Table 2).

COMPLICATIONS OF SEVERE HYPOGLYCEMIA

Short-term risks of hypoglycemia include the dangerous situations that can arise while an individual is hypoglycemic, whether at home or work (e.g. driving, operating machinery). In addition, prolonged coma is sometimes associated with transient neurological symptoms such as paresis, convulsions and encephalopathy. The potential long-term complications of severe hypoglycemia are mild intellectual impairment and permanent neurologic sequelae such as hemiparesis and pontine dysfunction. The latter are rare and have been reported only in case studies.

Retrospective studies have suggested a link between frequent severe hypoglycemia (≥5 episodes since diagnosis) and a decrease in intellectual performance. These changes were small but, depending on an individual's occupation, could be clinically meaningful. In contrast, prospective studies have not found an association between intensive insulin therapy and cognitive function (2,3). A meta-analysis concluded that lowered cognitive performance in people with diabetes appeared to be associated with the presence of microvascular complications, but not with the occurrence of severe hypoglycemic episodes or with poor metabolic control (4).

The major risk factors for severe hypoglycemia in patients with type 1 diabetes include prior episode of severe hypoglycemia (5-7), current low glycated hemoglobin (A1C) (<6.0%) (6,8-10), hypoglycemia unawareness (11),

Table 1. Symptoms of hypoglycemia

Neurogenic (autonomic)	Neuroglycopenic
Trembling	Difficulty concentrating
Palpitations	Confusion
Sweating	Weakness
Anxiety	Drowsiness
Hunger	Vision changes
Nausea	Difficulty speaking
Tingling	Headache
	Dizziness

Table 2. Severity of hypoglycemia

Mild: Autonomic symptoms are present. The individual is able to self-treat.

Moderate: Autonomic and neuroglycopenic symptoms are present. The individual is able to self-treat.

Severe: Individual requires assistance of another person. Unconsciousness may occur. PG is typically <2.8 mmol/L.

PG = plasma glucose

long duration of diabetes (9,12), autonomic neuropathy (13), adolescence (14) and preschool-age children unable to detect and/or treat mild hypoglycemia on their own. Patients at high risk for severe hypoglycemia should be informed of their risk and counselled, along with their significant others, on preventing and treating hypoglycemia (including use of glucagon), preventing driving and industrial accidents through self-blood glucose monitoring and taking appropriate precautions prior to the activity, and documenting blood glucose (BG) readings taken during sleeping hours. Individuals may need to have their insulin regimen adjusted appropriately to lower their risk. Risk factors for severe hypoglycemia are shown in Table 3.

TREATMENT OF HYPOGLYCEMIA

The goals of treatment for hypoglycemia are to detect and treat a low BG level promptly by using an intervention that provides the fastest rise in BG to a safe level, to eliminate the risk of injury and to relieve symptoms quickly. It is also important to avoid overtreatment, since this can result in rebound hyperglycemia and weight gain.

Evidence suggests that 15 g of glucose (monosaccharide) is required to produce an increase in BG of approximately 2.1 mmol/L within 20 minutes, with adequate symptom relief for most people (Table 4) (15-19). This has not been well studied in patients with gastropathy. A 20-g oral glucose dose will produce a BG increment of approximately 3.6 mmol/L at 45 minutes (16,17). Other choices such as milk and orange juice are slower to increase BG levels and provide symptom relief (16,17). Glucose gel is quite slow (<1.0 mmol/L increase at 20 minutes) and must be swallowed to have a significant effect (15,20). Patients taking an alpha-glucosidase inhibitor (acarbose) must use glucose (dextrose) tablets (21) or, if unavailable, milk or honey to treat hypoglycemia. Glucagon 1 mg subcutaneously or intramuscularly produces a significant increase in BG (from 3.0 mmol/L to 12.0 mmol/L) within 60 minutes (22). The effect is impaired in individuals whom have consumed more than 2 standard alcoholic drinks in the previous few hours, or in those who have advanced liver disease (23).

Table 3. Risk factors for severe hypoglycemia in patients with type 1 diabetes

- Prior episode of severe hypoglycemia
- Current low A1C (<6.0%)
- Hypoglycemia unawareness
- Long duration of diabetes
- Autonomic neuropathy
- Low economic status
- Adolescence
- Preschool-age children unable to detect and/or treat mild hypoglycemia on their own

A1C = glycated hemoglobin

Table 4. Examples of 15 g of carbohydrate for the treatment of mild to moderate hypoglycemia

- 15 g of glucose in the form of glucose tablets
- 15 mL (3 teaspoons) or 3 packets of table sugar dissolved in water
- 175 mL (3/4 cup) of juice or regular soft drink
- 6 Life Savers (1=2.5 g of carbohydrate)
- 15 mL (1 tablespoon) of honey

RECOMMENDATIONS

1. Mild to moderate hypoglycemia should be treated by the oral ingestion of 15 g of carbohydrate, preferably as glucose or sucrose tablets or solution. These are preferable to orange juice and glucose gels *[Grade B, Level 2 (15)]*. Patients should be encouraged to wait 15 minutes, retest BG and retreat with another 15 g of carbohydrate if the BG level remains <4.0 mmol/L *[Grade D, Consensus]*.

2. Severe hypoglycemia in a conscious person should be treated by the oral ingestion of 20 g of carbohydrate, preferably as glucose tablets or equivalent. Patients should be encouraged to wait 15 minutes, retest BG and retreat with another 15 g of glucose if the BG level remains <4.0 mmol/L *[Grade D, Consensus]*.

3. Severe hypoglycemia in an unconscious individual >5 years of age, in the home situation, should be treated with 1 mg of glucagon subcutaneously or intramuscularly. Caregivers or support persons should call for emergency services and the episode should be discussed with the diabetes healthcare team as soon as possible *[Grade D, Consensus]*.

4. For individuals at risk of severe hypoglycemia, support persons should be taught how to administer glucagon by injection *[Grade D, Consensus]*.

5. To treat severe hypoglycemia with unconsciousness, when intravenous access is available, glucose 10 to 25 g (20 to 50 cc of D50W) should be given over 1 to 3 minutes *[Grade D, Consensus]*.

6. To prevent repeated hypoglycemia, once the hypoglycemia has been reversed, the person should have the usual meal or snack that is due at that time of the day. If a meal is >1 hour away, a snack (including 15 g of carbohydrate and a protein source) should be consumed *[Grade D, Consensus]*.

OTHER RELEVANT GUIDELINES

RELATED WEBSITE

Begg IS, Yale J-F, Houlden RL, et al. Canadian Diabetes Association's clinical practice guidelines for diabetes and private and commercial driving. *Can J Diabetes*. 2003;27:128-140. Available at: http://www.diabetes.ca/files/Driving GuidelinesBeggJune03.pdf. Accessed September 1, 2008.

REFERENCES

1. Hepburn DA. Symptoms of hypoglycaemia. In: Frier BM, Fisher BM, eds. *Hypoglycaemia and Diabetes: Clinical and Physiological Aspects*. London, UK: Edward Arnold; 1993:93-103.

2. The Diabetes Control and Complications Trial Research Group. Effects of intensive diabetes therapy on neuropsychological function in adults in the Diabetes Control and Complications Trial. *Ann Intern Med*. 1996;124:379-388.

3. Reichard P, Pihl M. Mortality and treatment side-effects during long-term intensified conventional insulin treatment in the Stockholm Diabetes Intervention Study. *Diabetes*. 1994;43:313-317.

4. Brands AM, Biessels GJ, de Haan EH, et al. The effects of type 1 diabetes on cognitive performance: a meta-analysis. *Diabetes Care*. 2005;28:726-735.

5. The Diabetes Control and Complications Trial Research Group. Adverse events and their association with treatment regimens in the Diabetes Control and Complications Trial. *Diabetes Care*. 1995;18:1415-1427.

6. The Diabetes Control and Complications Trial Research Group. Hypoglycemia in the Diabetes Control and Complications Trial. *Diabetes*. 1997;46:271-286.

7. Mühlhauser I, Overmann H, Bender R, et al. Risk factors of severe hypoglycaemia in adult patients with type I diabetes—a prospective population based study. *Diabetologia*. 1998;41:1274-1282.

8. The DCCT Research Group. Epidemiology of severe hypoglycemia in the Diabetes Control and Complications Trial. *Am J Med*. 1991;90:450-459.

9. Davis EA, Keating B, Byrne GC, et al. Hypoglycemia: incidence and clinical predictors in a large population-based sample of children and adolescents with IDDM. *Diabetes Care*. 1997;20:22-25.

10. Egger M, Davey Smith G, Stettler C, et al. Risk of adverse effects of intensified treatment in insulin-dependent diabetes mellitus: a meta-analysis. *Diabet Med*. 1997;14:919-928.

11. Gold AE, MacLeod KM, Frier BM. Frequency of severe hypoglycemia in patients with type I diabetes with impaired awareness of hypoglycemia. *Diabetes Care*. 1994;17:697-703.

12. Mokan M, Mitrakou A, Veneman T, et al. Hypoglycemia unawareness in IDDM. *Diabetes Care*. 1994;17:1397-1403.

13. Meyer C, Grossmann R, Mitrakou A, et al. Effects of autonomic neuropathy on counterregulation and awareness of hypoglycemia in type 1 diabetic patients. *Diabetes Care*. 1998;21:1960-1966.

14. Diabetes Control and Complications Trial Research Group. Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. *J Pediatr*. 1994;125:177-188.

15. Slama G, Traynard PY, Desplanque N, et al. The search for an optimized treatment of hypoglycemia. Carbohydrates in tablets, solution, or gel for the correction of insulin reactions. *Arch Intern Med*. 1990;150:589-593.

16. Wiethop BV, Cryer PE. Alanine and terbutaline in treatment of hypoglycemia in IDDM. *Diabetes Care*. 1993;16:1131-1136.

17. Brodows RG, Williams C, Amatruda JM. Treatment of insulin reactions in diabetics. *JAMA*. 1984;252:3378-3381.

18. Special problems. In: Skyler JS, ed. *Medical Management of Type 1 Diabetes*. 3rd ed. Alexandria, VA: American Diabetes Association; 1998:134-143.

19. Canadian Diabetes Association. The role of dietary sugars in diabetes mellitus. *Beta Release*. 1991;15:117-123.

20. Gunning RR, Garber AJ. Bioactivity of instant glucose. Failure of absorption through oral mucosa. *JAMA*. 1978;240:1611-1612.

21. Glucobay® (acarbose) [product monograph]. Toronto, ON: Bayer Inc.; 2007.

22. Cryer PE, Fisher JN, Shamoon H. Hypoglycemia. *Diabetes Care*. 1994;17:734-755.

23. Glucagon [product monograph]. Toronto, ON: Eli Lilly Canada Inc.; 2007.

Hyperglycemic Emergencies in Adults

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Jeannette Goguen MD MEd FRCPC and Danièle Pacaud MD FRCPC

KEY MESSAGES

- Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) should be suspected in ill patients with diabetes. If either DKA or HHS is diagnosed, precipitating factors must be sought and treated.

- DKA and HHS are medical emergencies that require treatment and monitoring for multiple metabolic abnormalities and vigilance for complications.

- Ketoacidosis requires insulin administration (0.1 U/kg/hour) for resolution; bicarbonate therapy should be considered only for extreme acidosis (pH ≤7.0).

Note to readers: Although the diagnosis and treatment of diabetic ketoacidosis (DKA) in adults and in children share general principles, there are significant differences in their application, largely related to the increased risk of life-threatening cerebral edema with DKA in children and adolescents. The specific issues related to treatment of DKA in children and adolescents are addressed in "Type 1 Diabetes in Children and Adolescents," p. S150.

INTRODUCTION

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are diabetes emergencies with overlapping features. With insulin deficiency, hyperglycemia causes urinary losses of water and electrolytes (sodium, potassium, chloride) and the resultant extracellular fluid volume (ECFV) depletion. Potassium is shifted out of cells, and ketoacidosis occurs as a result of elevated glucagon levels and absolute insulin deficiency (in the case of type 1 diabetes) or high catecholamine levels suppressing insulin release (in the case of type 2 diabetes). In DKA, ketoacidosis is prominent, while in HHS the main features are ECFV depletion and hyperosmolarity.

Risk factors for DKA include new diagnosis of diabetes mellitus, insulin omission, infection, myocardial infarction, abdominal crisis, trauma and possibly treatment with insulin infusion pumps.

HHS is much less common than DKA (1,2). In addition to the precipitating factors noted above for DKA, HHS has also been reported following cardiac surgery, and with the use of certain drugs, including diuretics, glucocorticoids, lithium and atypical antipsychotics.

The clinical presentation of DKA includes symptoms of hyperglycemia, Kussmaul respiration, acetone-odoured breath, ECFV contraction, nausea, vomiting and abdominal pain. There may be a decreased level of consciousness. In HHS, there is often more profound ECFV contraction and decreased level of consciousness (proportional to the elevation in plasma osmolality). In addition, in HHS there can be a variety of neurological presentations, including seizures and a stroke-like state that can resolve once osmolality returns to normal (2-4). In both conditions, there may also be evidence of a precipitating condition.

DIAGNOSIS

DKA or HHS should be suspected whenever patients have significant hyperglycemia, especially if they are ill or highly symptomatic (see above). As outlined in Figure 1, to make the diagnosis and determine the severity of DKA or HHS, the following should be assessed: plasma levels of electrolytes (and anion gap), glucose, creatinine, osmolality and beta-hydroxybutyric acid (beta-OHB) (if available), blood gases, serum and urine ketones, fluid balance, level of consciousness, precipitating factors and complications (5).

There are no definitive criteria for the diagnosis of DKA. Typically, the arterial pH is ≤7.3, serum bicarbonate is ≤15 mmol/L, and the anion gap is >12 mmol/L with positive serum and/or urine ketones (5-7). Plasma glucose is usually ≥14.0 mmol/L, but can be lower (8). DKA is more challenging to diagnose in the presence of the following conditions: 1) mixed acid-base disorders (such as associated vomiting, which will raise the bicarbonate level); 2) if there has been a shift in the redox potential favouring the presence of beta-OHB (rendering serum ketone testing negative); or 3) if the loss of ketoanions with sodium or potassium in osmotic diuresis has occurred, leading to a return of the plasma anion gap towards normal. It is therefore important to measure ketones in both the serum and urine. If there is an elevated anion gap, and serum ketones are negative, beta-OHB levels should be measured. Measurement of serum lactate should be considered in hypoxic states. In HHS, a more prolonged duration of relative insulin insufficiency and inadequate fluid intake (or high glucose intake) results in higher glucose levels (typically ≥34.0 mmol/L) and greater ECFV contraction, but minimal acid-base disturbance (5,6).

Figure 1. Management of DKA in adults

Diagnose DKA

↑glucose, ↑anion gap* + ↑serum/urine ketones and/or ↑serum beta-OHB, ↓pH or ↓bicarbonate

Monitor

Plasma electrolytes, anion gap, glucose, creatinine, plasma osmolality, fluid balance, level of consciousness every 2–4 h
Precipitating factors (Table 1)
Complications (Table 1)

Manage

Acidosis

pH <7.0

NaHCO₃
1 ampoule/h
until pH ≥7.0
Avoid
hypokalemia

If [K⁺] <3.3 mmol/L,
correct hypokalemia
before starting insulin

If [K⁺] ≥3.3 mmol/L,
administer IV short-
acting insulin
0.1 U/kg/h

Adjust rate of insulin infusion based
on anion gap resolution
Avoid hypokalemia and hypoglycemia

Serum [K⁺]

<3.3 mmol/L

Give 40 mmol/L KCl
(max 40 mmol/h) +
no insulin until [K⁺]
≥3.3 mmol/L

>3.3 mmol/L but <5.0–5.5 mmol/L

Give 10–40 mmol/L
KCl (max 40 mmol/h)
Less aggressive KCl
given in renal failure

IV fluids

↓ECFV

Severe deficit (shock)

0.9% NaCl 1–2 L/h to
correct hypotension/
shock, then....

Mild to moderate deficit

0.9% NaCl 500 mL/h × 4 h,
then 250 mL/hr × 4 h

Once euvolemic

Corrected plasma [Na⁺]†
is normal or high; and
Rate of fall of effective plasma
osmolality‡ is <3 mmol/kg/h

Switch to 0.45% NaCl to
replace ongoing losses

Corrected plasma [Na⁺]†
is low; or
Rate of fall of effective plasma
osmolality‡ is ≥3 mmol/kg/h

Continue with 0.9% NaCl to
replace ongoing losses

Once plasma glucose reaches 14.0 mmol/L

Add D5W or D10W to IV fluids to maintain
plasma glucose of 12.0–14.0 mmol/L

*Anion gap = plasma [Na⁺] – plasma [Cl⁻] – plasma [HCO₃⁻]
†Corrected plasma [Na⁺] = measured [Na⁺] + 3/10 × ([glucose (mmol/L) – 5)
‡Effective plasma osmolality = [Na⁺] × 2 + [glucose (mmol/L)], reported as mmol/kg

Beta-OHB = beta-hydroxybutyric acid
DKA = diabetic ketoacidosis
ECFV = extracellular fluid volume
IV = intravenous

MANAGEMENT

Objectives of management include restoration of normal ECFV and tissue perfusion; resolution of ketoacidosis; correction of electrolyte imbalances and hyperglycemia; and the diagnosis and treatment of coexistent illness. The issues that must be addressed in the patient presenting with DKA or HHS are outlined in Table 1. A summary of fluid therapy is outlined in Table 2, and a management algorithm and formulas for calculating key measurements are provided in Figure 1.

Table 1. Priorities* to be addressed in the management of patients presenting with hyperglycemic emergencies		
Metabolic	*Precipitating cause of DKA/HHS*	*Other complications of DKA/HHS*
•ECFV contraction •Potassium deficit and abnormal concentration •Metabolic acidosis •Hyperosmolality (water deficit leading to increased corrected sodium concentration plus hyperglycemia)	•New diagnosis of diabetes •Insulin omission •Infection •Myocardial infarction •Drugs	•Hyper/hypokalemia •ECFV overexpansion •Cerebral edema •Hypoglycemia •Pulmonary emboli •Aspiration •Hypocalcemia (if phosphate used) •Stroke •Acute renal failure •Deep vein thrombosis

*Severity of issue will dictate priority of action

DKA = diabetic ketoacidosis
ECFV = extracellular fluid volume
HHS = hyperosmolar hyperglycemic state

Table 2. Summary of fluid therapy for DKA and HHS in adults
1. Administer IV normal saline initially. If the patient is in shock, give 1 to 2 L/hour initially to correct shock; otherwise, give 500 mL/hour for 4 hours, then 250 mL/hour for 4 hours.
2. Add potassium immediately if patient is normo- or hypokalemic. Otherwise, if initially hyperkalemic, only add potassium once serum potassium falls to <5 to 5.5 mmol/L and patient is diuresing.
3. Once plasma glucose reaches 14.0 mmol/L, add glucose to maintain plasma glucose at 12.0 to 14.0 mmol/L.
4. After hypotension has been corrected, switch normal saline to half-normal saline (with potassium chloride). However, if plasma osmolality is falling more rapidly than 3 mmol/kg/hour and/or the corrected plasma sodium is reduced, maintain IV fluids at higher osmolality (i.e. may need to maintain on normal saline).

DKA = diabetic ketoacidosis
HHS = hyperosmolar hyperglycemic state
IV = intravenous

Patients with DKA and HHS are best managed in an intensive care unit (ICU) or step-down setting (5-7) with specialist care (9,10). Volume status (including fluid intake and output), vital signs, neurologic status, plasma concentrations of electrolytes, anion gap, osmolality and glucose need to be monitored closely, initially as often as every 2 hours (5-7). Precipitating factors must be diagnosed and treated (5-7).

ECFV contraction

The sodium deficit is typically 7.0 to 10.0 mmol/kg in DKA (11) and 5 to 13 mmol/kg in HHS (12), which along with water losses (100 mL/kg and 100–200 mL/kg, respectively) (11,12) results in decreased ECFV, usually with decreased intracellular fluid volume. Restoring ECFV improves tissue perfusion and reduces plasma glucose levels by both dilution and by increasing urinary glucose losses. ECFV re-expansion using a rapid rate of initial fluid administration was associated with an increased risk of cerebral edema (CE) in 1 study (13) but not in another (14). In adults, one should initially administer intravenous (IV) normal saline 1 to 2 L/hour to correct shock, otherwise 500 mL/hour for 4 hours, then 250 mL/hour of IV fluids (15,16).

Potassium deficit

The typical potassium deficit range is 2 to 5 mmol/kg in DKA and 4 to 6 mmol/kg in HHS (12,13). There have been no randomized trials that have studied strategies for potassium replacement. Typical recommendations suggest that potassium supplementation should be started for plasma potassium <5.0 to 5.5 mmol/L once diuresis has been established, usually with the second litre of saline. If the patient at presentation is normo- or hypokalemic, potassium should be given immediately, at concentrations in the IV fluid between 10 and 40 mmol/L, at a maximum rate of 40 mmol/hour. In the case of frank hypokalemia (potassium <3.3 mmol/L), insulin should be withheld until potassium replacement at 40 mmol/hour has restored plasma potassium to ≥3.3 mmol/L (5,6). It is reasonable to treat the potassium deficit of HHS in the same way.

Metabolic acidosis

Metabolic acidosis is a prominent component of DKA. Patients with HHS have minimal or no acidosis. Insulin is used to stop ketoacid production; IV fluid alone has no impact on parameters of ketoacidosis (17). Short-acting insulin (0.1 U/kg/h) is recommended (18-20). Although the use of an initial bolus of IV insulin is recommended in some reviews (5), the effectiveness of this step has not been studied in adults. In children, using an initial bolus of IV insulin does not result in faster resolution of ketoacidosis (21,22). The use of subcutaneous boluses of rapid-acting insulin analogues at 1- to 2-hour intervals results in similar duration of ketoacidosis with no more frequent occurrence of hypoglycemia compared to short-acting IV insulin 0.1 U/kg/hour (23-25). The

dose of insulin should subsequently be adjusted based on ongoing acidosis (26), using the plasma anion gap or beta-OHB measurements. Plasma glucose levels will fall due to multiple mechanisms, including ECFV re-expansion (27), glucose losses via osmotic diuresis (17) and insulin-mediated reduced glucose production and increased cellular uptake of glucose. Once plasma glucose reaches 14.0 mmol/L, IV glucose should be started to avoid hypoglycemia, targeting a plasma glucose of 12.0 to 14.0 mmol/L.

Similar doses of IV insulin can be used to treat HHS, although subjects are not acidemic and the fall in plasma glucose concentration is predominantly due to re-expansion of ECFV and osmotic diuresis (27). Insulin has been withheld successfully in HHS (28), but generally its use is recommended to reduce plasma glucose levels (5,6).

Use of IV sodium bicarbonate to treat acidosis did not affect outcome in randomized controlled trials (29-31). Sodium bicarbonate therapy can be considered in adult patients in shock or with arterial pH ≤7.0. For example, one can administer 1 ampoule (50 mmol) of sodium bicarbonate added to 200 mL of D5W (or sterile water, if available) over 1 hour, repeated every 1 to 2 hours until pH is ≥7.0 (5,6). Potential risks associated with the use of sodium bicarbonate include hypokalemia (32) and delayed occurrence of metabolic alkalosis.

Hyperosmolality

Hyperosmolality is due to hyperglycemia and a water deficit. However, serum sodium concentration may be reduced due to shift of water out of cells. The concentration of sodium needs to be corrected for the level of glycemia to determine if there is also a water deficit (see Figure 1). In patients with DKA, plasma osmolality is usually ≤320 mmol/kg. In HHS, plasma osmolality is typically >320 mmol/kg. Because of the risk of CE with rapid reductions in osmolality (33), it has been recommended that the plasma osmolality be lowered no faster than 3 mmol/kg/hour (5,6). This can be achieved by monitoring plasma osmolality, by adding glucose to the infusions when plasma glucose reaches 14.0 mmol/L to maintain it at that level, and selecting the correct concentration of IV saline. Typically, after volume re-expansion, IV fluid is switched to half-normal saline because urinary losses of electrolytes in the setting of osmotic diuresis are usually hypotonic. The potassium in the infusion will also add to the osmolality. If osmolality falls too rapidly despite the administration of glucose, consideration should be given to increasing the sodium concentration of the infusing solution (5,6). Water imbalances can also be monitored using the corrected plasma sodium.

Phosphate deficiency

There is currently no evidence to support the use of phosphate therapy for DKA (34-36), and there is no evidence that hypophosphatemia causes rhabdomyolysis in DKA (37).

However, because hypophosphatemia has been associated with rhabdomyolysis in other states, administration of potassium phosphate in cases of severe hypophosphatemia could be considered for the purpose of trying to prevent rhabdomyolysis.

COMPLICATIONS

In Ontario, in-hospital mortality in patients hospitalized for acute hyperglycemia ranged from <1% at ages 20 to 49 years old to 16% in those over age 75 (38). Reported mortality in DKA ranges from 0.65 to 3.3% (2,9,39-41). In HHS, recent studies found mortality rates to be 12 to 17%, but included patients with mixed DKA and hyperosmolality (1,3,42). About 50% of deaths occur in the first 48 to 72 hours. Mortality is usually due to the precipitating cause, to electrolyte imbalances (especially hypo- and hyperkalemia) and to CE.

RECOMMENDATIONS

1. In patients with DKA, a protocol incorporating the principles illustrated in Figure 1 should be followed *[Grade D, Consensus]*. For HHS, a similar protocol can be used; however, in this case, the plasma glucose level is used to titrate the insulin dose *[Grade D, Consensus]*.

2. In individuals with DKA, IV 0.9% sodium chloride should be administered initially at 500 mL/hour for 4 hours, then 250 mL/hour for 4 hours *[Grade B, Level 2 (15)]* with consideration of a higher initial rate (1–2 L/hour) in the presence of shock *[Grade D, Consensus]*. For persons with a HHS, IV fluid administration should be individualized based on the patient's needs *[Grade D, Consensus]*.

3. In patients with DKA, IV short-acting insulin should be administered at an initial dose of 0.1 U/kg/hour *[Grade B, Level 2 (19,20)]*. The insulin infusion rate should be maintained until the resolution of ketosis *[Grade B, Level 2 (24)]* as measured by the normalization of the plasma anion gap *[Grade D, Consensus]*. Once the plasma glucose concentration reaches 14.0 mmol/L, IV dextrose should be started to avoid hypoglycemia *[Grade D, Consensus]*.

OTHER RELEVANT GUIDELINES

Type 1 Diabetes in Children and Adolescents, p. S150

REFERENCES

1. Hamblin PS, Topliss DJ, Chosich N, et al. Deaths associated with diabetic ketoacidosis and hyperosmolar coma, 1973-1988. *Med J Aust*. 1989;151:439-444.

2. Holman RC, Herron CA, Sinnock P. Epidemiologic characteristics of mortality from diabetes with acidosis or coma, United States, 1970-78. *Am J Public Health*. 1983;73:1169-1173.

3. Wachtel TJ, Tetu-Mouradjian LM, Goldman DL, et al. Hyperosmolarity and acidosis in diabetes mellitus: a three year experience in Rhode Island. *J Gen Med*. 1991;6:495-502.

4. Malone ML, Gennis B, Goodwin JS. Characteristics of diabetic

ketoacidosis in older versus younger adults. *J Am Geriatr Soc.* 1992;40:1100-1104.

5. Kitabchi AE, Umpierrez GE, Murphy MB, et al. Management of hyperglycemic crises in patients with diabetes. *Diabetes Care.* 2001;24:131-153.

6. Chiasson JL, Aris-Jilwan N, Belanger R, et al. Diagnosis and treatment of diabetic ketoacidosis and the hyperglycemic hyperosmolar state. *CMAJ.* 2003;168:859-866.

7. Lebovitz HE, Diabetic ketoacidosis. *Lancet.* 1995;345:767-772.

8. Munro JF, Campbell IW, McCuish AC, et al. Euglycemic diabetic ketoacidosis. *BMJ.* 1973;2:578-580.

9. May ME, Young C, King J. Resource utilization in treatment of diabetic ketoacidosis in adults. *Am J Med Sci.* 1993;306:287-294.

10. Levetan CS, Jablonski KA, Passaro MD, et al. Effect of physician specialty on outcomes in diabetic ketoacidosis. *Diabetes Care.* 1999;22:1790-1795.

11. Kreisberg RA. Diabetic ketoacidosis: new concepts and trends in pathogenesis and treatment. *Ann Intern Med.* 1978;88:681-695.

12. Ennis ED, Stahl EJ, Kreisberg RA. The hyperosmolar hyperglycemic syndrome. *Diabetes Rev.* 1994;2:115-126.

13. Mahoney CP, Vlcek BW, DelAguila M. Risk factors for developing brain herniation during diabetic ketoacidosis. *Pediatr Neurol.* 1999;2:721-727.

14. Rosenbloom AL. Intracerebral crises during treatment of diabetic ketoacidosis. *Diabetes Care.* 1990;13:22-33.

15. Adrogue HJ, Barrero J, Eknoyan G. Salutary effects of modest fluid replacement in the treatment of adults with diabetic ketoacidosis. *JAMA.* 1989;262:2108-2113.

16. Fein IA, Rackow EC, Sprung CL, et al. Relation of colloid osmotic pressure to arterial hypoxemia and cerebral edema during crystalloid volume loading of patients with diabetic ketoacidosis. *Ann Intern Med.* 1982;96:570-575.

17. Owen OE, Licht JH, Sapir DG. Renal function and effects of partial rehydration during diabetic ketoacidosis. *Diabetes.* 1981;30:510-518.

18. Kitabchi AE, Ayyagari V, Guerra SM, et al. The efficacy of low dose versus conventional therapy of insulin for treatment of diabetic ketoacidosis. *Ann Intern Med.* 1976;84:633-638.

19. Heber D, Molitch ME, Sperling MA. Low-dose continuous insulin therapy for diabetic ketoacidosis. Prospective comparison with "conventional" insulin therapy. *Arch Intern Med.* 1977;137:1377-1380.

20. Butkiewicz EK, Leibson CL, O'Brien PC, et al. Insulin therapy for diabetic ketoacidosis. Bolus insulin injection versus continuous insulin infusion. *Diabetes Care.* 1995;18:1187-1190.

21. Fort P, Waters SM, Lifshitz F. Low-dose insulin infusion in the treatment of diabetic ketoacidosis: bolus versus no bolus. *J Pediatr.* 1980;96:36-40.

22. Lindsay R, Bolte RG. The use of an insulin bolus in low-dose insulin infusion for pediatric diabetic ketoacidosis. *Pediatr Emerg Care.* 1989;5:77-79.

23. Della Manna T, Steinmetz L, Campos PR, et al. Subcutaneous use of a fast-acting insulin analog: an alternative treatment for

pediatric patients with diabetic ketoacidosis. *Diabetes Care.* 2005; 28:1856-1861.

24. Umpierrez GE, Latif K, Stoever J, et al. Efficacy of subcutaneous insulin lispro versus continuous intravenous regular insulin for the treatment of patients with diabetic ketoacidosis. *Am J Med.* 2004;117:291-296.

25. Umpierrez GE, Cuervo R, Karabell A, et al. Treatment of diabetic ketoacidosis with subcutaneous insulin aspart. *Diabetes Care.* 2004;27:1873-1888.

26. Wiggam MI, O'Kane MJ, Harper R, et al. Treatment of diabetic ketoacidosis using normalization of blood 3-hydroxybutyrate concentration as the endpoint of emergency management. *Diabetes Care.* 1997;20:1347-1352.

27. Waldhäusl W, Kleinberger G, Korn A, et al. Severe hyperglycemia: effects of rehydration on endocrine derangements and blood glucose concentration. *Diabetes.* 1979;28:577-584.

28. Gerich JE, Martin MM, Recant LL. Clinical and metabolic characteristics of hyperosmolar nonketotic coma. *Diabetes.* 1971; 20:228-238.

29. Morris LR, Murphy MB, Kitabchi AE. Bicarbonate therapy in severe diabetic ketoacidosis. *Ann Intern Med.* 1986;105:836-840.

30. Gamba G, Oseguera J, Castrejon M, et al. Bicarbonate therapy in severe diabetic ketoacidosis: a double blind, randomized placebo controlled trial. *Revista Investig Clinica.* 1991;43:234-248.

31. Hale PJ, Crase J, Nattrass M. Metabolic effects of bicarbonate in the treatment of diabetic ketoacidosis. *Br Med J Clin Res Ed.* 1984;289:1035-1038.

32. Soler NG, Bennet MA, Dixon K, et al. Potassium balance during treatment of diabetic ketoacidosis with special reference to the use of bicarbonate. *Lancet.* 1972;2:665-667.

33. Carlotti AP, Bohn D, Mallie JP, et al. Tonicity balance, and not electrolyte-free water calculations, more accurately guides therapy for acute changes in natremia. *Intensive Care Med.* 2001; 27:921-924.

34. Keller U, Berger W. Prevention of hypophosphatemia by phosphate infusion during treatment of diabetic ketoacidosis and hyperosmolar coma. *Diabetes.* 1980;29:87-95.

35. Wilson HK, Keuer SP, Lea AS, et al. Phosphate therapy in diabetic ketoacidosis. *Arch Intern Med.* 1982;142:517-520.

36. Fisher JN, Kitabchi AE. A randomized study of phosphate therapy in the treatment of diabetic ketoacidosis. *J Clin Endocrinol Metab.* 1983;57:177-180.

37. Singhal PC, Abromovici M, Ayer S, et al. Determinants of rhabdomyolysis in the diabetic state. *Am J Nephrol.* 1991;11: 447-450.

38. Booth GL, Fang J. Acute complications of diabetes. In: Hux JE, Booth GL, Slaughter PM, et al, eds. *Diabetes in Ontario: An ICES Practice Atlas.* Toronto, ON: Institute for Clinical Evaluative Sciences; 2003:2.19-2.50. Available at http://www.ices.on.ca. Accessed September 1, 2008.

39. Bagg W, Sathu A, Streat S, et al. Diabetic ketoacidosis in adults at Auckland Hospital, 1988-1996. *Aust N Z J Med.* 1998;28: 604-608.

40. Umpierrez GE, Kelly JP, Navarrete JE, et al. Hyperglycemic crises in urban blacks. *Arch Intern Med.* 1997;157;669-675.

41. Musey VC, Lee JK, Crawford R, et al. Diabetes in urban African-Americans. I. Cessation of insulin therapy is the major precipitating cause of diabetic ketoacidosis. *Diabetes Care.* 1995;18:483-489.

42. Wachtel TJ, Silliman RA, Lamberton P. Predisposing factors for the diabetic hyperosmolar state. *Arch Intern Med.* 1987;147: 499-501.

In-hospital Management of Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Alun Edwards MB MRCP (UK) FRCPC, Alice Y.Y. Cheng MD FRCPC, Maureen Clement MD CCFP, Amir Hanna MB BCh FRCPC, Robyn Houlden MD FRCPC and Jacqueline James MD MEd FRCPC

KEY MESSAGES

- Diabetes increases the risk for disorders that predispose individuals to hospitalization, including cardiovascular diseases, nephropathy, infection and lower-extremity amputations.

- Use of "sliding scale" insulin therapy, although common, treats hyperglycemia after it has occurred. A proactive approach to management with the use of basal, bolus and correction insulin is preferred.

- Hypoglycemia remains a major impediment to achieving optimal glycemic control in hospitalized patients. Healthcare institutions should have standardized treatment protocols that address mild, moderate and severe hypoglycemia.

INTRODUCTION

Diabetes increases the risk for disorders that predispose individuals to hospitalization, including cardiovascular disease (CVD), nephropathy, infection and lower-extremity amputations. The majority of hospitalizations for patients with diabetes are not directly related to the metabolic state, and diabetes management is rarely the primary focus of care. Therefore, glycemic control and other diabetes care issues are often not adequately addressed (1). A rapidly growing body of literature supports targeted glycemic control in the hospital setting, with potential for improved mortality, morbidity and healthcare economic outcomes (2).

The precise prevalence of diabetes in hospitalized adult patients is not known. One study reported a prevalence of 26% of known diabetes in hospitalized patients in a community teaching hospital (3). An additional 12% of patients had unrecognized diabetes or hospital-related hyperglycemia that reverted to normoglycemia after discharge. Diabetes has been reported to be the fourth most common comorbid condition listed on all hospital discharges (4).

ROLE OF ORAL ANTIHYPERGLYCEMIC AGENTS

No large studies have investigated the potential roles of various oral antihyperglycemic agents (OHAs) on outcomes in hospitalized patients with diabetes. However, OHAs may have a role in stable patients who had good glycemic control on OHAs prior to admission (unless newly developed conditions, such as renal, hepatic or cardiac disturbances, represent contraindications to their use).

ROLE OF SUBCUTANEOUS INSULIN

Patients with type 1 diabetes must be maintained on insulin therapy during hospitalization to prevent diabetic ketoacidosis. Stable patients who are able to eat should typically receive the same dose of subcutaneous basal insulin (NPH, glargine, detemir) they were taking at home. Bolus (prandial) insulin (regular, lispro, aspart) may require adjustment depending on the patient's intercurrent illness and ability to consume meals. Correction-dose (supplemental) insulin is useful to treat unanticipated hyperglycemia in hospitalized patients (2,5). This involves the adjustment of the patient's usual scheduled or programmed insulin to compensate for unanticipated hyperglycemia. If correction doses are frequently required, the scheduled insulin doses should be increased. If patients are not able to eat their usual meals, prandial insulin doses might also need to be adjusted to avoid hypoglycemia.

Stable patients with type 2 diabetes using insulin at home should also continue their pre-admission insulin regimen, with adjustment as needed.

The use of "sliding scale" insulin therapy for inpatient management of diabetes is a common practice. Sliding scale insulin therapy treats hyperglycemia after it has occurred. Studies have shown that this reactive approach is associated with higher rates of hyper- and hypoglycemia (6).

ROLE OF INTRAVENOUS INSULIN INFUSION

Intravenous (IV) insulin infusion therapy should be considered during critical illness, or other illness requiring prompt glycemic control, or prolonged fasting (NPO status) (7). IV insulin infusion therapy should be administered only where frequent blood glucose (BG) monitoring and close nursing supervision are possible. Staff education is a critical component of the implementation of an IV insulin infusion protocol. IV insulin protocols should take into account the current and previous BG levels (and, therefore, the rate of change), and the patient's usual insulin dose. BG determinations should be performed every 1 to 2 hours until BG stability has been demonstrated.

For NPO patients not receiving enteral or parenteral

nutrition, dextrose infusions should be provided.

To maintain effective blood levels of insulin, short- or rapid-acting insulin should be administered 30 minutes to 2 hours before discontinuation of IV insulin infusion. The initial dose of subcutaneous insulin given after discontinuation of IV insulin infusion should be based on previously established dose requirements or the rate and pattern of in-hospital IV insulin infusion. Other parameters that affect subcutaneous insulin dose determination include body weight, stress of illness and other comorbid conditions such as renal insufficiency.

ORGANIZATION OF CARE

Healthcare institutions should implement a program to improve glycemic control in the inpatient setting. This should include the formation of a multidisciplinary steering committee to provide educational programs, implement policies to assess and monitor the quality of glycemic management, and produce standardized order sets, protocols and algorithms for diabetes care within the institution. The timely consultation of such teams has been demonstrated to improve quality, reduce length of stay and lower costs (8,9).

Self-management in the hospital may be appropriate for competent adult patients who successfully conduct self-management of diabetes at home, have a stable level of consciousness, and have the physical skills needed to self-administer insulin and perform self-monitoring of blood glucose (SMBG). A physician order for self-management should be written with respect to selection of food, SMBG, self-determination and administration of insulin dose and type.

Bedside BG monitoring

No study has compared the effect of frequency of bedside BG testing on the incidence of hyper- or hypoglycemia in the hospital. The frequency and timing of bedside BG monitoring should be individualized. Healthcare institutions must implement and maintain a quality-control program to ensure the accuracy of bedside BG testing (10,11).

Safety – hypoglycemia

Hypoglycemia remains a major impediment to achieving optimal glycemic control in hospitalized patients. Healthcare institutions should have standardized treatment protocols that address mild, moderate and severe hypoglycemia. Healthcare workers should be educated about factors that increase the risk of hypoglycemia, such as sudden reduction in oral intake or discontinuation of enteral or parenteral nutrition, unexpected transfer from nursing unit after rapid-acting insulin administration, and reduction in corticosteroid dose (12).

Safety – insulin administration errors

Insulin is identified as 1 of the top 5 "high-risk medications" in the hospital setting. A systems approach may work to reduce errors. This includes preprinted, approved, un-ambiguous standard orders for insulin administration, or computerized order entry (13).

THE CRITICALLY ILL PATIENT

Acute hyperglycemia in the intensive care setting is not unusual and results from a number of factors, including stress-induced counterregulatory hormone secretion, and possibly the effect of medications administered in the intensive care unit (ICU) (14). Hyperglycemia in this setting has effects on multiple systems, including the CV, neurologic and immune systems (14). Van den Berghe and colleagues (15) demonstrated impressive benefits of intensive glycemic control with IV insulin infusion among predominantly surgical patients admitted to the ICU and requiring mechanical ventilation. A subsequent analysis of a heterogeneous ICU population with predominantly medical patients and utilizing historical controls demonstrated a reduction in mortality, length of stay, renal dysfunction and requirement of transfusion among those receiving intensive glycemic control with an IV insulin infusion protocol (16).

A meta-analysis of studies looking at the effects of insulin therapy for critically ill adult patients also demonstrated an overall reduction in mortality, particularly among those with diabetes and if glycemic control was a primary goal (17). However, this meta-analysis did not include any randomized controlled trials (RCTs) of intensive insulin therapy in a medical ICU. To date, there has been only 1 RCT of intensive insulin therapy and glycemic control among medical ICU patients (18). There was no difference in the primary outcome of in-hospital mortality between the groups. However, there was a significant reduction in the prespecified secondary outcomes of renal dysfunction, length of stay and prolonged mechanical ventilation. Mortality was increased among patients who stayed in the ICU for <3 days and decreased in patients who stayed in the ICU for >3 days.

Perioperative glycemic control

The management of individuals with diabetes at the time of surgery poses a number of challenges. Acute hyperglycemia is common secondary to the physiologic stress associated with surgery. Pre-existing diabetes-related complications and comorbidities may also influence clinical outcomes. Acute hyperglycemia has been shown to adversely affect immune function (19) and wound healing (20) in animal models. Observational studies in humans have shown that hyperglycemia increases the risk of postoperative infections (21-23) and renal allograft rejection (24), and is associated with increased resource utilization (25).

In patients undergoing coronary artery bypass surgery, a pre-existing diagnosis of diabetes has been identified as a risk factor for postoperative sternal wound infections, delirium, renal dysfunction, respiratory insufficiency and prolonged

hospital stay (26-28). Intraoperative hyperglycemia during cardiopulmonary bypass has been associated with increased morbidity and mortality rates in individuals with and without diabetes (29-31).

Studies investigating the role of diabetes as an independent risk factor for short- and long-term mortality rates post-coronary artery bypass surgery yield mixed results (26,32,33). Patients with known diabetes, undiagnosed diabetes and impaired fasting glucose identified by preoperative fasting plasma glucose (FPG) determination carry a higher risk of postoperative mortality than those with normal preoperative FPG levels (34). A diagnosis of diabetes may not influence early and midterm mortality in patients after off-pump coronary artery bypass (35).

In patients undergoing major noncardiac surgery, diabetes may increase the risk of postoperative complications, including mortality (36,37).

Major surgery

In patients undergoing coronary artery bypass surgery, improved intraoperative and postoperative glycemic control with a continuous IV insulin infusion or glucose insulin potassium (GIK) infusion to achieve plasma glucose (PG) levels between 5.5 and 10.0 mmol/L has been shown to decrease the rate of deep sternal wound infections and mortality (38-40). The use of GIK to maintain PG levels between 6.9 and 11.1 mmol/L was also associated with decreased rates of recurrent ischemia, atrial fibrillation and length of stay (40). However, among those without diabetes, tight intraoperative glycemic control initiated when PG levels rose above 5.6 mmol/L during coronary artery bypass surgery failed to decrease neurologic complications associated with the surgery (41). Among those with and without diabetes undergoing coronary artery bypass surgery, an RCT using a continuous IV insulin infusion to maintain intraoperative glycemic control between 4.4 and 5.6 mmol/L was compared with conventional intraoperative glycemic control (<11.1 mmol/L) (42). There was no additional benefit to more aggressive control.

Minor and moderate surgery

The appropriate perioperative glycemic targets for minor or moderate surgeries are less clear. There are few intervention studies assessing the impact of tight glycemic control on morbidity or mortality in these settings; however, a number of small studies that compared different methods of achieving glycemic control during minor and moderate surgeries did not demonstrate any adverse effects of maintaining perioperative glycemic levels between 5.0 and 11.0 mmol/L (43-45).

Rapid institution of perioperative control should be carefully considered in patients with poorly controlled type 2 diabetes undergoing monocular phacoemulsification cataract surgery with moderate to severe nonproliferative diabetic retinopathy, because of the possible increased risk of postoperative progression of retinopathy and maculopathy (46). The outcome of vitrectomy does not appear to be influenced by perioperative control (47).

Given the data supporting tighter perioperative glycemic control during major surgeries and the compelling data showing the adverse effects of hyperglycemia, it is reasonable to target glycemic levels between 5.0 and 11.0 mmol/L for minor and moderate surgeries. However, the benefits of improved perioperative glycemic control must be weighed against the risk of perioperative hypoglycemia. Anesthetic agents and postoperative analgesia may alter the patient's level of consciousness and awareness of hypoglycemia. The risk of hypoglycemia can be reduced by frequent BG monitoring and carefully designed management protocols.

Acute stroke

Diabetes is well recognized as a major contributor to atherothrombotic cerebrovascular disease. About 21% of patients admitted with acute ischemic stroke have previously diagnosed diabetes; undiagnosed diabetes may increase the overall prevalence to >50% (48,49). Observational studies suggest that diabetes might increase the risk of mortality (50,51), infarct size or neurological impairment (49,50, 52,53) and reduce the benefit from acute thrombolytic revascularization (54). However, the results are inconsistent, and recent studies have failed to show an effect of diabetes on stroke morbidity or mortality (49,55).

Patients with diabetes who have higher BG values in the days following a cerebral infarction are more likely to exhibit infarct expansion, cerebral edema and worse short-term outcome (52,53). In 1 small study of 25 patients, mean PG levels >7.0 mmol/L were associated with increased infarct size (52). These observations indicate the need for studies to determine the effect of aggressive BG lowering in the early stages of stroke management.

A randomized trial performed on 933 patients with increased PG values (6.0 to 17.0 mmol/L) at the time of admission with acute stroke, compared the effect of GIK infusion with saline infusion. No reduction in mortality or significant disability at 90 days was observed, even though BG and blood pressure (BP) values were significantly better in the GIK group (56). This confirmed the findings of a smaller pilot study (57).

Patients with undefined neurological conditions admitted to an ICU and managed with IV insulin infusion to achieve intensive glycemic targets also showed no improvement in mortality compared to the control group (18).

At present, the apparent association between in-hospital hyperglycemia and adverse outcomes for ischemic stroke has not been accompanied by evidence that therapy to correct hyperglycemia is beneficial. In view of this, no specific recommendation regarding glycemic management during acute stroke can be made.

RECOMMENDATIONS

1. Provided that their medical conditions, dietary intake and glycemic control are acceptable, patients with diabetes should be maintained on their prehospitalization oral antihyperglycemic agents or insulin regimens *[Grade D, Consensus]*.

2. For hospitalized patients with diabetes treated with insulin, a proactive approach that may include basal, prandial and correction-dose insulin, along with pattern management, is preferred over the "sliding scale" reactive approach using only short- or rapid-acting insulin *[Grade D, Consensus]*.

3. To maintain intraoperative glycemic levels between 5.5 and 10.0 mmol/L for patients with diabetes undergoing coronary artery bypass surgery, a continuous IV insulin infusion alone *[Grade C, Level 3 (38,39)]* or with the addition of glucose and potassium *[Grade B, Level 2 (40)]*, with an appropriate protocol and trained staff to ensure the safe and effective implementation of this therapy and to minimize the likelihood of hypoglycemia, should be used.

4. A continuous IV insulin infusion should be used to achieve glycemic levels of 4.5 to 6.0 mmol/L in post-operative ICU patients with hyperglycemia (random PG >6.1 mmol/L) requiring mechanical ventilation to reduce morbidity and mortality *[Grade A, Level 1A (15)]*, and in medical ICU patients with hyperglycemia (random PG >6.1 mmol/L) to reduce morbidity *[Grade B, Level 2 (18)]*.

5. Perioperative glycemic levels should be maintained between 5.0 and 11.0 mmol/L for most other surgical situations, with an appropriate protocol and trained staff to ensure the safe and effective implementation of this therapy and minimize the likelihood of hypoglycemia *[Grade D, Consensus]*.

6. In hospitalized patients, efforts must be made to ensure that patients using insulin or insulin secretagogues have ready access to an appropriate form of glucose at all times, particularly when NPO or during diagnostic procedures *[Grade D, Consensus]*.

7. Measures to assess, monitor and improve glycemic control within the inpatient setting should be implemented, and include hypoglycemia management protocols and diabetes-specific discharge planning *[Grade D, Consensus]*. Glucagon should be available for any patient at risk for severe hypoglycemia when IV access is not readily available *[Grade D, Consensus]*.

OTHER RELEVANT GUIDELINES

Pharmacologic Management of Type 2 Diabetes,
 p. S53
Management of Acute Coronary Syndromes, p. S119
Treatment of Diabetes in Patients With Heart Failure,
 p. S123

REFERENCES

1. Roman SH, Chassin MR. Windows of opportunity to improve diabetes care when patients with diabetes are hospitalized for other conditions. *Diabetes Care*. 2001;24:1371-1376.

2. Campbell KB, Braithwaite SS. Hospital management of hyperglycemia. *Clin Diabetes*. 2004;22:81-88.

3. Umpierrez GE, Isaacs SD, Bazargan N, et al. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab*. 2002;87: 978-982.

4. Vasa F. Systematic strategies for improved outcomes for the hyperglycemic hospitalized patient with diabetes mellitus. *Am J Cardiol*. 2005;96:41E-46E.

5. Magee MF, Clement S. Subcutaneous insulin therapy in the hospital setting: issues, concerns, and implementation. *Endocr Pract*. 2004;10(suppl 2):81-88.

6. Queale WS, Seidler AJ, Brancati FL. Glycemic control and sliding scale insulin use in medical inpatients with diabetes mellitus. *Arch Intern Med*. 1997;157:545-552.

7. Garber AJ, Moghissi ES, Bransome ED Jr, et al; American College of Endocrinology Task Force on Inpatient Diabetes Metabolic Control. American College of Endocrinology position statement on inpatient diabetes and metabolic control. *Endocr Pract*. 2004;10:77-82.

8. Levetan CS, Salas JR, Wilets IF, et al. Impact of endocrine and diabetes team consultation on hospital length of stay for patients with diabetes. *Am J Med*. 1995;99:22-28.

9. Koproski J, Pretto Z, Poretsky L. Effects of an intervention by a diabetes team in hospitalized patients with diabetes. *Diabetes Care*. 1997;20:1553-1555.

10. Lewandrowski K, Cheek R, Nathan DM, et al. Implementation of capillary blood glucose monitoring in a teaching hospital and determination of program requirements to maintain quality testing. *Am J Med*. 1992;93:419-426.

11. Rumley AG. Improving the quality of near-patient blood glucose measurement. *Ann Clin Biochem*. 1997;34:281-286.

12. Clement S, Braithwaite SS, Magee MF, et al; American Diabetes Association Diabetes in Hospitals Writing Committee. Management of diabetes and hyperglycemia in hospitals. *Diabetes Care*. 2004;27:553-591.

13. Bates DW, Leape LL, Cullen DJ, et al. Effect of computerized physician order entry and a team intervention on prevention of serious medication errors. *JAMA*. 1998;280:1311-1316.

14. Lewis KS, Lane-Gill SL, Bobek MG, et al. Intensive insulin therapy for critically ill patients. *Ann Pharmacother*. 2004;38: 1243-1251.

15. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med*. 2001;345: 1359-1367.

16. Krinsley JS. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. *Mayo Clin Proc*. 2004;79:992-1000.

17. Pittas AG, Siegel RD, Lau J. Insulin therapy for critically ill hospitalized patients: a meta-analysis of randomized controlled

trials. *Arch Intern Med.* 2004;164:2005-2011.

18. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med.* 2006;354: 449-461.

19. Kwoun MO, Ling PR, Lydon E, et al. Immunologic effects of acute hyperglycemia in nondiabetic rats. *J Parenter Enteral Nutr.* 1997;21:91-95.

20. Verhofstad MH, Hendriks T. Complete prevention of impaired anastomotic healing in diabetic rats requires preoperative blood glucose control. *Br J Surg.* 1996;83:1717-1721.

21. Golden SH, Peart-Vigilance C, Kao WH, et al. Perioperative glycemic control and the risk of infectious complications in a cohort of adults with diabetes. *Diabetes Care.* 1999;22:1408-1414.

22. Pomposelli JJ, Baxter JK 3rd, Babineau TJ, et al. Early postoperative glucose control predicts nosocomial infection rate in diabetic patients. *J Parenter Enteral Nutr.* 1998;22:77-81.

23. McAlister FA, Man J, Bistritz L, et al. Diabetes and coronary artery bypass surgery: an examination of perioperative glycemic control and outcomes. *Diabetes Care.* 2003;26:1518-1524.

24. Thomas MC, Mathew TH, Russ GR, et al. Early peri-operative glycaemic control and allograft rejection in patients with diabetes mellitus: a pilot study. *Transplantation.* 2001;72:1321-1324.

25. Estrada CA, Young JA, Nifong LW, et al. Outcomes and perioperative hyperglycemia in patients with or without diabetes mellitus undergoing coronary artery bypass grafting. *Ann Thorac Surg.* 2003;75:1392-1399.

26. Brandt M, Harder K, Walluscheck KP, et al. Coronary artery bypass surgery in diabetic patients. *J Card Surg.* 2004;19:36-40.

27. Bucerius J, Gummert JF, Walther T, et al. Diabetes in patients undergoing coronary artery bypass grafting. Impact on perioperative outcome. *Z Kardiol.* 2005;94:575-582.

28. Bucerius J, Gummert JF, Walther T, et al. Impact of diabetes mellitus on cardiac surgery outcome. *Thorac Cardiovasc Surg.* 2003;51:11-16.

29. Doenst T, Wijeysundera D, Karkouti K, et al. Hyperglycemia during cardiopulmonary bypass is an independent risk factor for mortality in patients undergoing cardiac surgery. *J Thorac Cardiovasc Surg.* 2005;130:1144.

30. Gandhi GY, Nuttall GA, Abel MD, et al. Intraoperative hyperglycemia and perioperative outcomes in cardiac surgery patients. *Mayo Clin Proc.* 2005;80:862-866.

31. Ouattara A, Lecomte P, Le Manach Y, et al. Poor intraoperative blood glucose control is associated with a worsened hospital outcome after cardiac surgery in diabetic patients. *Anesthesiology.* 2005;103:687-694.

32. Kubal C, Srinivasan AK, Grayson AD, et al. Effect of risk-adjusted diabetes on mortality and morbidity after coronary artery bypass surgery. *Ann Thorac Surg.* 2005;79:1570-1576.

33. Calafiore AM, Di Mauro M, Di Giammarco G, et al. Effect of diabetes on early and late survival after isolated first coronary bypass surgery in multivessel disease. *J Thorac Cardiovasc Surg.* 2003;125:144-154.

34. Anderson RE, Klerdal K, Ivert T, et al. Are even impaired fasting blood glucose levels preoperatively associated with increased mortality after CABG surgery? *Eur Heart J.* 2005;26:1513-1518.

35. Choi JS, Cho KR, Kim KB. Does diabetes affect the postoperative outcomes after total arterial off-pump coronary bypass surgery in multivessel disease? *Ann Thorac Surg.* 2005;80:1353-1360.

36. Ganesh SP, Pietrobon R, Cecilio WA, et al. The impact of diabetes on patient outcomes after ankle fracture. *J Bone Joint Surg Am.* 2005;87:1712-1718.

37. Juul AB, Wetterslev J, Kofoed-Enevoldsen A. Long-term postoperative mortality in diabetic patients undergoing major non-cardiac surgery. *Eur J Anaesthesiol.* 2004;21:523-529.

38. Furnary AP, Zerr KJ, Grunkemeier GL, et al. Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures. *Ann Thorac Surg.* 1999;67:352-360.

39. Furnary AP, Gao G, Grunkemeier GL, et al. Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg.* 2003;125:1007-1021.

40. Lazar HL, Chipkin SR, Fitzgerald CA, et al. Tight glycemic control in diabetic coronary artery bypass graft patients improves perioperative outcomes and decreases recurrent ischemic events. *Circulation.* 2004;109:1497-1502.

41. Butterworth J, Wagenknecht LE, Legault C, et al. Attempted control of hyperglycemia during cardiopulmonary bypass fails to improve neurologic or neurobehavioral outcomes in patients without diabetes mellitus undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg.* 2005;130:1319.

42. Gandhi GY, Nuttall GA, Abel MD, et al. Intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery: a randomized trial. *Ann Intern Med.* 2007;146:233-243.

43. Raucoules-Aimé M, Lugrin D, Boussofara M, et al. Intraoperative glycaemic control in non-insulin-dependent and insulin-dependent diabetes. *Br J Anaesth.* 1994;73:443-449.

44. Hemmerling TM, Schmid MC, Schmidt J, et al. Comparison of a continuous glucose-insulin-potassium infusion versus intermittent bolus application of insulin on perioperative glucose control and hormone status in insulin-treated type 2 diabetics. *J Clin Anesth.* 2001;13:293-300.

45. Christiansen CL, Schurizek BA, Malling B, et al. Insulin treatment of the insulin-dependent diabetic patient undergoing minor surgery. Continuous intravenous infusion compared with subcutaneous administration. *Anaesthesia.* 1988;43:533-537.

46. Suto C, Hori S, Kato S, et al. Effect of perioperative glycemic control in progression of diabetic retinopathy and maculopathy. *Arch Ophthalmol.* 2006;124:38-45.

47. Kamio S, Kawasaki R, Yamashita H. Influence of systemic conditions and glycemic control on complications of vitrectomy

for diabetic retinopathy [Japanese]. *Folia Ophthalmologica Japonica.* 2004;55:105-109.

48. Gray CS, Scott JF, French JM, et al. Prevalence and prediction of unrecognised diabetes mellitus and impaired glucose tolerance following acute stroke. *Age Ageing.* 2004;33:71-77.

49. Megherbi SE, Milan C, Minier D, et al; European BIOMED Study of Stroke Care Group. Association between diabetes and stroke subtype on survival and functional outcome 3 months after stroke: data from the European BIOMED Stroke Project. *Stroke.* 2003;34:688-694.

50. Capes SE, Hunt D, Malmberg K, et al. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. *Stroke.* 2001;32:2426-2432.

51. Hamidon BB, Raymond AA. The impact of diabetes mellitus on in-hospital stroke mortality. *J Postgrad Med.* 2003;49:307-309.

52. Baird TA, Parsons MW, Phanh T, et al. Persistent poststroke hyperglycemia is independently associated with infarct expansion and worse clinical outcome. *Stroke.* 2003;34:2208-2214.

53. Dora B, Mihci E, Eser A, et al. Prolonged hyperglycemia in the early subacute period after cerebral infarction: effects on short term prognosis. *Acta Neurol Belg.* 2004;104:64-67.

54. Alvarez-Sabín J, Molina CA, Montaner J, et al. Effects of admission hyperglycemia on stroke outcome in reperfused tissue plasminogen activator-treated patients. *Stroke.* 2003;34: 1235-1241.

55. Karapanayiotides T, Piechowski-Jozwiak B, van Melle G. Stroke patterns, etiology, and prognosis in patients with diabetes mellitus. *Neurology.* 2004;62:1558-1562.

56. Gray CS, Hildreth AJ, Sandercock PA, et al; GIST Trialists Collaboration. Glucose-potassium-insulin infusions in the management of post-stroke hyperglycaemia: the UK Glucose Insulin in Stroke Trial (GIST-UK). *Lancet Neurol.* 2007;6:397-406.

57. Scott JF, Robinson GM, French JM, et al. Glucose potassium insulin infusions in the treatment of acute stroke patients with mild to moderate hyperglycemia: the Glucose Insulin in Stroke Trial (GIST). *Stroke.* 1999;30:793-799.

Management of Obesity in Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Robyn Houlden MD FRCPC and David C.W. Lau MD PhD FRCPC

KEY MESSAGES

- An estimated 80 to 90% of persons with type 2 diabetes are overweight or obese.

- A modest weight loss of 5 to 10% of initial body weight can substantially improve insulin sensitivity and glycemic, blood pressure and lipid control.

- A comprehensive healthy lifestyle intervention program should be implemented in overweight and obese people with diabetes to achieve and maintain a healthy body weight. The addition of a pharmacologic agent should be considered for appropriate overweight or obese adults who are unable to attain clinically important weight loss with lifestyle modification.

- Adults with severe obesity may be considered for bariatric surgery when other interventions fail to result in achieving weight goals.

INTRODUCTION

An estimated 80 to 90% of persons with type 2 diabetes are overweight or obese. Furthermore, intensive insulin therapy is associated with weight gain (1). Weight loss has been shown to improve glycemic control by increasing insulin sensitivity and glucose uptake, and diminishing hepatic glucose output (2,3). The risk of death from all causes, cardiovascular disease (CVD) and some forms of cancer increases with excessive body fat (4). This relationship between increasing body fat accumulation and adverse health outcomes exists throughout the range of overweight and obese men and women in all age groups, including those ≥75 years of age (5). While the relationship between increasing adiposity and adverse health effects has not been extensively examined in people with diabetes, it is likely that similar, if not greater, benefits are conferred on people with diabetes with lower body fat content or body mass index (BMI).

ASSESSMENT OF BODY WEIGHT

The initial assessment of people with diabetes should include height and weight measurements, calculation of BMI (kg/m^2) (see Table 1) (6), and waist circumference (WC) to assess the degree of abdominal fat (Table 2) (6). Metabolic comorbidities, such as hypertension, dyslipidemia and CVD, should also be assessed since they are highly correlated with increasing BMI (7,8). Excessive upper body fat, or abdominal obesity, is a strong independent predictor of metabolic comorbidities (9,10). Cutoff values for WC vary among expert guidelines. The National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) guidelines (11,12) and Health Canada (6) identify WC values ≥102 cm (40 inches) in men and ≥88 cm (35 inches) in women as being associated with substantially increased abdominal fat accumulation and health risks (Table 2). The International Diabetes Federation (13) has proposed population-specific WC cutoff values that are associated with increased risk of complications and are lower than the NCEP-ATP III guidelines (Table 3) (13). Neither set of WC values has been fully validated against the development of clinical events, and considerable population-based research is needed in this area.

Table 1. *Canadian Guidelines for Body Weight Classification in Adults* **using BMI (6)**

Classification	BMI* category (kg/m^2)	Risk of developing health problems
Underweight	<18.5	Increased
Normal weight	18.5–24.9	Least
Overweight	25.0–29.9	Increased
Obese Class I Class II Class III	≥30.0 30.0–34.9 35.0–39.9 ≥40.0	 High Very high Extremely high

*BMI values are age and gender independent, and may not be correct for all ethnic populations

BMI = body mass index

Table 2. WC and risk of developing health problems (6)	
WC cutoff points*†	**Risk of developing health problems**
Men ≥102 cm (40 inches)	Increased
Women ≥88 cm (35 inches)	Increased

*WC cutoffs may be lower in some populations (e.g. older individuals, Asian population [See Table 3]), especially in the presence of the metabolic syndrome (such as hypertriglyceridemia)
†Increased WC can also be a marker for increased risk, even in persons with normal weight

WC = waist circumference

TREATMENT OF OBESITY

The goals of therapy for overweight and obese people with diabetes are to reduce body fat, attain and maintain a healthy or lower body weight for the long term, and prevent weight regain. In general, obese people with diabetes have greater difficulty with weight loss compared to similarly obese people without diabetes (14). A modest weight loss of 5 to 10% of initial body weight can substantially improve insulin sensitivity, glycemic control, high blood pressure (BP) and dyslipidemia (15-19). The optimal rate of weight loss is 1 to 2 kg/month. A negative energy balance of 500 kcal/day is typically required to achieve a weight loss of 0.45 kg/week (20).

Lifestyle interventions

Lifestyle intervention is recommended for weight loss in order to improve health status and quality of life (20,21). In people with diabetes who are overweight or obese, achieving a healthy weight through an active lifestyle promotes a general sense of well-being and cardiovascular (CV) fitness, along with other benefits, such as reducing CVD, morbidity,

mortality and other complications attributable to obesity (22). Lifestyle interventions that combine dietary modification, increased and regular physical activity and behaviour therapy are the most effective (23-25). Structured interdisciplinary programs have demonstrated the best short- and long-term results (24). Ongoing follow-up with the healthcare team is important to plan individualized dietary and activity changes to facilitate weight loss. Adjustments to antihyperglycemic agents may be required as the individual with diabetes loses weight (26).

All weight-loss diets must be well balanced and nutritionally adequate to ensure optimal health. In general, a carbohydrate intake of at least 100 g/day is required to spare protein breakdown and muscle wasting, and to avoid large shifts in fluid balance and ketosis. High-fibre foods that take longer to eat and digest are associated with greater satiety. Adequate protein intake is required to maintain lean body mass and other essential physiological processes. Reduced intake of saturated fat and energy-dense foods should be emphasized to achieve the required daily energy deficit to promote weight loss. Very low-calorie diets with <900 kcal/day are not recommended, except under medical supervision.

Because confusion over portion size of foods and beverages (27) may lead to overeating, people with diabetes should be counselled by a dietitian on appropriate serving sizes and on how to select meals, preferably nutrient-rich meals (i.e. containing whole grains and legumes), which are associated with greater satiety and lower caloric intake (28).

Behavioural therapy

Two large-scale reviews of >100 individual studies evaluating behaviour modification techniques support their effectiveness in promoting weight loss as adjuncts to lifestyle intervention (29,30).

Members of the healthcare team should consider using a structured approach to providing advice and feedback on physical activity, healthy eating habits and weight loss (31-34).

Table 3. Ethnic-specific values for WC (13)		
Country or ethnic group	**Central obesity as defined by WC**	
	Men	**Women**
Europid*	≥94 cm	≥80 cm
South Asian, Chinese, Japanese	≥90 cm	≥80 cm
South and Central American	Use South Asian cutoff points until more specific data are available	
Sub-Saharan African	Use Europid cutoff points until more specific data are available	
Eastern Mediterranean and Middle East (Arab)	Use Europid cutoff points until more specific data are available	

*NCEP-ATP III guidelines (11,12) and Health Canada (6) define central obesity as WC values ≥102 cm (40 inches) in men and ≥88 cm (35 inches)

WC = waist circumference

Pharmacotherapy

Pharmacotherapy for overweight people with diabetes not only improves glycemic control, but also results in a significant reduction in the doses of antihyperglycemic agents (26). Pharmacotherapy is an acceptable adjunct in the short- and long-term management of obesity when lifestyle measures fail to achieve the desired weight loss after an adequate trial of 3 to 6 months (20,35). Pharmacotherapy can be considered for people with BMI ≥30.0 kg/m^2 with no obesity-related comorbidities or risk factors, or BMI ≥27.0 kg/m^2 with obesity-related comorbidities or risk factors (20). Antiobesity drug therapy may be considered as an adjunct to nutrition therapy, physical activity and behaviour modification to achieve a target weight loss of 5 to 10% of initial body weight and for weight maintenance (20,35).

Two medications, orlistat and sibutramine, have been approved in Canada for long-term management of obesity (Table 4). Drug therapy leads to even greater weight loss when coupled with lifestyle intervention and behaviour modification therapy. Both drugs have been shown to be effective in obese people with type 2 diabetes, improving glycemic and metabolic control, and resulting in favourable changes in lipid levels, BP profile and fat distribution (26,36,37). In obese people with impaired glucose tolerance (IGT), orlistat also improves glucose tolerance and reduces the progression to type 2 diabetes (38). Clinical trials with antiobesity agents have confirmed a smaller degree of weight loss in people with diabetes compared with obese people who do not have diabetes (14,26).

When pharmacotherapy is being considered in the treatment of the obese or overweight person with type 2 diabetes, the choice of drug should be based on the individual's CV risk profile, dietary habits and concomitant disease(s).

People with irregular eating habits, such as those who "snack" frequently, may be better suited to sibutramine therapy because of its long-acting satiety-enhancing properties. Combining orlistat and sibutramine therapy is not advocated for clinical use. Sibutramine should be avoided in patients with ischemic heart disease, congestive heart failure or other major cardiac disease. Orlistat should be avoided in patients with inflammatory or other chronic bowel disease.

Other available antiobesity drugs, such as diethylpropion and phentermine, are sympathomimetic noradrenergic appetite suppressants that are approved only for short-term use of a few weeks. They are not recommended because of modest efficacy and frequent adverse side effects.

Currently, a number of new molecular entities that target receptors and metabolic processes relevant to energy metabolism are being developed for the treatment of obesity. Among these emerging strategies, cannabinoid type 1 receptor antagonists currently appear to be the most promising (39).

Surgery

Individuals who are candidates for surgical procedures should be carefully selected after evaluation by an interdisciplinary team with medical, surgical, psychiatric and nutritional expertise. Surgery is usually reserved for people with class III obesity (BMI ≥40.0 kg/m^2), or class II obesity (BMI=35.0–39.9 kg/m^2) in the presence of comorbidities (40) and the inability to achieve weight-loss goals following an adequate trial of lifestyle intervention. Long-term, if not lifelong, medical surveillance after surgical therapy is necessary for most people. Preferred surgical options for weight loss include laparoscopic vertical banded gastroplasty and laparoscopic Roux-en-Y gastric bypass (41-43).

Table 4. Medications approved for the treatment of obesity in type 2 diabetes				
Class	*Generic (trade) name*	*Recommended regimen*	*Action*	*Adverse effects*
Gastrointestinal lipase inhibitor	orlistat (Xenical)	120 mg TID (during or up to 1 hour after each meal)	• Nonsystemic pancreatic lipase inhibitor that exerts its therapeutic activity in the stomach and gastrointestinal tract by reducing dietary fat digestion and absorption by about 30%	• Abdominal bloating, pain and cramping • Steatorrhea • Fecal incontinence
Norepinephrine and serotonin reuptake inhibitor	sibutramine (Meridia)	10–15 mg OD (in the morning)	• Reduces food intake by enhancing satiety • May increase thermogenesis • May prevent decline in energy expenditure with weight loss	• Xerostomia • Increase heart rate and blood pressure • Constipation • Dizziness

RECOMMENDATIONS

1. A comprehensive healthy lifestyle intervention program (including a hypocaloric, nutritionally balanced diet, regular physical activity or exercise, and behavioural modification techniques) for overweight and obese people with, or at risk for diabetes, should be implemented to achieve and maintain a healthy body weight *[Grade D, Consensus]*. Members of the healthcare team should consider using a structured approach to providing advice and feedback on physical activity, healthy eating habits and weight loss *[Grade C, Level 3 (31-34)]*.

2. In overweight or obese adults with type 2 diabetes, a pharmacologic agent such as orlistat *[Grade A, Level 1A (26)]* or sibutramine *[Grade B, Level 2 (37)]* should be considered as an adjunct to lifestyle modifications to facilitate weight loss and improve glycemic control.

3. Adults with class III obesity (BMI ≥40.0 kg/m²) or class II obesity (BMI 35.0 to 39.9 kg/m²) with other comorbidities may be considered for bariatric surgery when other lifestyle interventions are inadequate in achieving weight goals *[Grade C, Level 3 (43)]*.

OTHER RELEVANT GUIDELINES

Physical Activity and Diabetes, p. S37
Nutrition Therapy, p. S40

RELATED WEBSITES

Health Canada. Canadian Guidelines for Body Weight Classification in Adults. Quick Reference for Professionals. Available at: http://www.hc-sc.gc.ca/fn-an/alt_formats/hpfb-dgpsa/pdf/nutrition/cg_quick_ref-ldc_rapide_ref_e.pdf. Accessed September 1, 2008.

OBESITY CANADA GUIDELINES

2006 Canadian Clinical Practice Guidelines on the Management and Prevention of Obesity in Adults and Children. Available at: http://www.cmaj.ca/cgi/content/full/176/8/S1/DC1. Accessed September 1, 2008.

REFERENCES

1. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352: 837-853.

2. Ruderman N, Chisholm D, Pi-Sunyer X, et al. The metabolically obese, normal-weight individual revisited. *Diabetes*. 1998; 47:699-713.

3. Markovic TP, Jenkins AB, Campbell LV, et al. The determinants of glycemic responses to diet restriction and weight loss in obesity and NIDDM. *Diabetes Care*. 1998;21:687-694.

4. Calle EE, Rodriguez C, Walker-Thurmond K, et al. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med*. 2003; 348:1625-1638.

5. Stevens J, Cai J, Pamuk ER, et al. The effect of age on the association between body-mass index and mortality. *N Engl J Med*. 1998;338:1-7.

6. Health Canada. *Canadian Guidelines for Body Weight Classification in Adults*. Ottawa, ON: Health Canada; 2003. Publication H49-179/2003E.

7. Rabkin SW, Chen Y, Leiter L, et al. Risk factor correlates of body mass index. Canadian Heart Health Surveys Research Group. *CMAJ*. 1997;157(suppl 1):S26-S31.

8. World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser*. 2000;894:i-xii,1-253.

9. Reeder BA, Senthilselvan A, Després JP, et al. The association of cardiovascular disease risk factors with abdominal obesity in Canada. Canadian Heart Health Surveys Research Group. *CMAJ*. 1997;157(suppl 1):S39-S45.

10. Després JP, Lemieux I, Prud'homme D. Treatment of obesity: need to focus on high risk abdominally obese patients. *BMJ*. 2001;322:716-720.

11. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486-2497.

12. Grundy SM, Cleeman JI, Daniels SR, et al; American Heart Association; National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation*. 2005;112:2735-2752.

13. International Diabetes Federation. *The IDF Consensus Worldwide Definition of the Metabolic Syndrome*. Brussels: IDF Communications; 2006. Available at: http://www.idf.org/web data/docs/IDF_Meta_def_final.pdf. Accessed September 1, 2008.

14. Wing RR, Marcus MD, Epstein LH, et al. Type II diabetic subjects lose less weight than their overweight nondiabetic spouses. *Diabetes Care*. 1987;10:563-566.

15. Dattilo AM, Kris-Etherton PM. Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. *Am J Clin Nutr*. 1992;56:320-328.

16. Goldstein DJ. Beneficial health effects of modest weight loss. *Int J Obes Relat Metab Disord*. 1992;16:397-415.

17. Elmer PJ, Grimm R Jr, Laing B, et al. Lifestyle intervention: results of the Treatment of Mild Hypertension Study (TOMHS). *Prev Med*. 1995;24:378-388.

18. Tuomilehto J, Lindström J, Eriksson JG, et al; Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med*. 2001;344:1343-1350.

19. Knowler WC, Barrett-Connor E, Fowler SE, et al; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or met-

formin. *N Engl J Med.* 2002;346:393-403.

20. National Institutes of Health. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults – The Evidence Report. *Obes Res.* 1998;6 (suppl 2):51S-209S.

21. Willett WC, Dietz WH, Colditz GA. Guidelines for healthy weight. *N Engl J Med.* 1999;341:427-434.

22. Williamson DF, Thompson TJ, Thun M, et al. Intentional weight loss and mortality among overweight individuals with diabetes. *Diabetes Care.* 2000;23:1499-1504.

23. Pavlou KN, Krey S, Steffee WP. Exercise as an adjunct to weight loss and maintenance in moderately obese subjects. *Am J Clin Nutr.* 1989;49(5 suppl):1115-1123.

24. Wing RR, Hill JO. Successful weight loss maintenance. *Annu Rev Nutr.* 2001;21:323-341.

25. Wing RR, Goldstein MG, Acton KJ, et al. Behavioral science research in diabetes: lifestyle changes related to obesity, eating behavior, and physical activity. *Diabetes Care.* 2001;24:117-123.

26. Hollander PA, Elbein SC, Hirsch IB, et al. Role of orlistat in the treatment of obese patients with type 2 diabetes. A 1-year randomized double-blind study. *Diabetes Care.* 1998;21:1288-1294.

27. Rolls BJ, Morris EL, Roe LS. Portion size of food affects energy intake in normal-weight and overweight men and women. *Am J Clin Nutr.* 2002;76:1207-1213.

28. Rolls BJ, Roe LS, Meengs JS. Salad and satiety: energy density and portion size of a first-course salad affect energy intake at lunch. *J Am Diet Assoc.* 2004;104:1570-1576.

29. Wing RR, Jeffery RW. Outpatient treatments of obesity: a comparison of methodology and clinical results. *Int J Obes.* 1979; 3:261-279.

30. Bennett GA. Behaviour therapy for obesity: a quantitative review of the effects of selected treatment characteristics on outcome. *Behav Ther.* 1986;17:554-562.

31. Swinburn BA, Walter LG, Arroll B, et al. The green prescription study: a randomized controlled trial of written exercise advice provided by general practitioners. *Am J Public Health.* 1998;88: 288-291.

32. Logsdon DN, Lazaro CM, Meier RV. The feasibility of behavioral risk reduction in primary medical care. *Am J Prev Med.* 1989;5: 249-256.

33. Campbell MK, DeVellis BM, Strecher VJ, et al. Improving dietary behavior: the effectiveness of tailored messages in primary care settings. *Am J Public Health.* 1994;84:783-787.

34. Lewis BS, Lynch WD. The effect of physician advice on exercise behavior. *Prev Med.* 1993;22:110-121.

35. National Task Force on the Prevention and Treatment of Obesity. Long-term pharmacotherapy in the management of obesity. *JAMA.* 1996;276:1907-1915.

36. Scheen AJ, Lefèbvre PJ. Antiobesity pharmacotherapy in the management of type 2 diabetes. *Diabetes Metab Res Rev.* 2000;16: 114-124.

37. Finer N, Bloom SR, Frost GS, et al. Sibutramine is effective for weight loss and diabetic control in obesity with type 2 diabetes: a randomised, double-blind, placebo-controlled study. *Diabetes Obes Metab.* 2000;2:105-112.

38. Heymsfield SB, Segal KR, Hauptman J, et al. Effects of weight loss with orlistat on glucose tolerance and progression to type 2 diabetes in obese adults. *Arch Intern Med.* 2000;160:1321-1326.

39. Van Gaal LF, Rissanen AM, Scheen AJ, et al; RIO-Europe Study Group. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. *Lancet.* 2005;365:1389-1397.

40. Melissas J, Christodoulakis M, Spyridakis M, et al. Disorders associated with clinically severe obesity: significant improvement after surgical weight reduction. *South Med J.* 1998;91: 1143-1148.

41. Chapman AE, Kiroff G, Game P, et al. Laparoscopic adjustable gastric banding in the treatment of obesity: a systematic literature review. *Surgery.* 2004;135:326-351.

42. Maggard MA, Shugarman LR, Suttorp M, et al. Meta-analysis: surgical treatment of obesity. *Ann Intern Med.* 2005;142:547-559.

43. Sjöström CD, Lissner L, Wedel H, et al. Reduction in incidence of diabetes, hypertension and lipid disturbances after intentional weight loss induced by bariatric surgery: the SOS Intervention Study. *Obes Res.* 1999;7:477-484.

Psychological Aspects of Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Helen Jones RN MSN CDE, Peter Hall PhD, Barry Simon MD and Beth Mitchell PhD

KEY MESSAGES

- Significant behavioural demands and challenging psychosocial factors affect nearly all aspects of diabetes management and subsequent glycemic control.

- All individuals with diabetes and their families should be regularly screened for symptoms of psychological distress.

- Preventive interventions such as participative decision-making, feedback and psychological support should be incorporated into all primary care and self-management education interventions to enhance adaptation to diabetes and reduce stress.

INTRODUCTION

Significant behavioural demands and challenging psychosocial factors affect nearly all aspects of diabetes management and subsequent diabetes control (1,2). Psychological issues related to the diagnosis and/or self-care demands may present anywhere on a continuum from impairment in quality of life to clinically significant depressive and/or anxiety disorders.

ADJUSTMENT PROBLEMS

Both adults and children face challenges associated with adjustment to diabetes. Some children and/or their parents have adjustment problems soon after the diagnosis of diabetes (3,4). Those who do not solve these problems within the first year of diagnosis are at risk for poor adaptation to diabetes, including regimen adherence problems, poor glycemic control and continued psychosocial difficulties (5,6). Stress (general and diabetes-specific) (7,8), inadequate social and family interactions (9,10), inappropriate beliefs about the nature of diabetes (10), and poor coping skills (11,12) may have a negative impact on self-care behaviours and glycemic control.

Adults with type 1 and 2 diabetes across many cultures report significant psychological distress related to the diagnosis of diabetes, with a negative impact on diabetes self-management (13).

The diagnosis of diabetes may precipitate or exacerbate existing psychological disorders (14,15). As quality of life is adversely affected by the presence of comorbid psychological disorders and health complications (14,15), the identifi-

cation of potential psychiatric conditions, such as depression, anxiety and eating disorders, is critical.

Depression

Depressive symptoms are common in people with diabetes compared with the general population (14,16,17), and major depressive disorder is present in approximately 15% of patients with diabetes (18). Depressive disorders in adults and children are associated with poorer self-care behaviour (19,20), poorer glycemic control, health complications, decreased quality of life and psychological well-being (14,21), increased family problems, and higher healthcare costs (22-25).

Anxiety

Emerging evidence suggests that the prevalence of phobic disorders (24,26) and generalized anxiety disorders (3) is elevated in people with type 1 diabetes. Generalized anxiety disorder appears to be increased in individuals with diabetes compared with the general population (14 vs. 3 to 4%, respectively) (27). As many as 40% of patients have at least some anxiety symptoms (27), and fear of hypoglycemia (28,29) is not uncommon in those with diabetes. A recent meta-analysis suggested that the presence of clinically significant anxiety disorders among those with type 1 and 2 diabetes is associated with poor glycemic control (28).

Eating disorders

Eating disorders are frequently observed in young women and adolescent females with type 1 diabetes (30,31) and are associated with poorer glycemic control (31,32) and an increased risk of long-term complications (33). A meta-analysis of controlled studies of eating disorders and diabetes showed a higher prevalence of bulimia in girls with diabetes compared with healthy controls (34). Other studies have demonstrated prevalence rates of full syndrome and subthreshold eating disorders that are twice as high as those in peers without diabetes (30,35). Young women and adolescent females with type 1 diabetes should, therefore, be regularly screened for eating disorders with the Eating Disorders Inventory (36). Those with an identified or suspected eating disorder should be referred to a medical team or mental health professional knowledgeable in treating such disorders.

SCREENING

All individuals with diabetes and their families should be regularly screened for symptoms of psychological and social distress (2,20). Healthcare professionals should actively explore psychological factors by asking empathetic but frank open-ended questions about stress, social support, unhealthy self-care behaviours, health beliefs about risk of complications, treatment efficacy and the degree of interference with normal functioning (37). People with diabetes should be screened for depression and anxiety regularly, either through direct queries (e.g. "During the past month, have you often been bothered by feeling down, depressed, or hopeless?" and "During the past month, have you often been bothered by little interest or pleasure in doing things?") (38), or with a standardized questionnaire (e.g. Beck Depression Inventory [39], the Problem Areas in Diabetes scale [37], the Child Health Questionnaire [CHQ] [40], Behaviour Assessment System for Children [BASC] [40]).

INTERVENTIONS

Preventive psychological interventions should be incorporated into all primary care and self-management education interventions to enhance adaptation to diabetes and reduce stress. Educational and psychological interventions often share a theoretical basis around increasing readiness to change and self-efficacy (41,42).

Effective interventions for children and adults include psychosocial support, feedback and reinforcement (20,43-45); coping skills training (46); cognitive-behavioural therapy (CBT) (47); and family behaviour therapy (48). Approaches that increase patient participation in decision-making regarding care and education have been shown to be more effective than a "do as I say" approach in enhancing psychological adjustment to diabetes, and potentially preventing psychological distress (49-51).

For those with suboptimal self-care or significant psychological symptoms, focused interventions using CBT or family behaviour therapy need to be considered (43,52). These issues should be addressed using psychosocial services within diabetes teams or resources in the community. In pediatric populations, intensive case management with psychoeducation may be required (43,52). In-home, multisystemic therapy can be used to reduce diabetes-related stress (53), improve glycemic control and reduce inpatient admissions for adolescents with poor glycemic control (2,54). Antidepressant medication (55) and CBT have each been shown to be specifically effective in treating depression in adults with diabetes (56). Risk of significant weight gain during extended use of selective serotonin reuptake inhibitor antidepressants may be greater for paroxetine (57); sertraline or fluoxetine may be preferred in this weight-sensitive population.

RECOMMENDATIONS

1. Individuals with diabetes should be regularly screened for subclinical psychological distress and psychiatric disorders (e.g. depressive and anxiety disorders) by interview *[Grade D, Consensus]* or with a standardized questionnaire *[Grade B, Level 2 (39)]*.

2. Patients diagnosed with depression, anxiety or eating disorders should be referred to mental health professionals who are either part of the diabetes team or are in the community *[Grade D, Consensus]*. Those diagnosed with depression should be offered treatment with CBT *[Grade B, Level 2 (56)]* and/or antidepressant medication *[Grade A, Level 1A (55)]*.

3. Multidisciplinary team members with required expertise should offer CBT-based techniques, such as stress management strategies and coping skills training *[Grade A, Level 1A for type 2 diabetes (42); Grade B, Level 2, for type 1 diabetes (46)]*, family behaviour therapy *[Grade B, Level 2 (48,53)]* and case management *[Grade B, Level 2 (43,53)]* to improve glycemic control and/or psychological outcomes in individuals with suboptimal self-care behaviours, suboptimal glycemic control and/or psychological distress.

OTHER RELEVANT GUIDELINES

Organization of Diabetes Care, p. S20
Self-management Education, p.S25
Type 1 Diabetes in Children and Adolescents, p. S150
Type 2 Diabetes in Children and Adolescents, p. S162

REFERENCES

1. Delamater AM, Jacobson AM, Anderson B, et al. Psychosocial therapies in diabetes. Report of the Psychosocial Therapies Working Group. *Diabetes Care.* 2001;24:1286-1292.

2. Wysocki T, Buckloh LM, Lochrie AS, et al. The psychologic context of pediatric diabetes. *Pediatr Clinic North Am.* 2005;52: 1755-1778.

3. Kovacs M, Goldston D, Obrosky DS, et al. Psychiatric disorders in youths with IDDM: rates and risk factors. *Diabetes Care.* 1997;20:36-44.

4. Landolt MA, Vollrath, Laimbacher J, et al. Prospective study of posttraumatic stress disorder in parents of children with newly diagnosed type 1 diabetes. *J Am Acad Child Adolesc Psychiatry* 2005;44:682-689.

5. Grey M, Cameron ME, Lipman TH, et al. Psychosocial status of children with diabetes in the first 2 years after diagnosis. *Diabetes Care.* 1995;18:1330-1336.

6. Jacobson AM, Hauser ST, Lavori P, et al. Family environment and glycemic control: a four-year prospective study of children and adolescents with insulin-dependent diabetes mellitus. *Psychosom Med.* 1994;56:401-409.

7. Lloyd CE, Dyer PH, Lancashire RJ, et al. Association between stress and glycemic control in adults with type 1 (insulin-dependent) diabetes. *Diabetes Care.* 1999;22:1278-1283.

8. Seiffge-Krenke I, Stemmler M. Coping with everyday stress

and links to medical and psychosocial adaptation in diabetic adolescents. *J Adolesc Health*. 2003;33:180-188.

9. Schafer LC, McCaul KD, Glasgow RE. Supportive and non-supportive family behaviors: relationships to adherence and metabolic control in persons with type I diabetes. *Diabetes Care*. 1986;9:179-185.

10. Skinner TC, Hampson SE. Social support and personal models of diabetes in relation to self-care and well-being in adolescents with type I diabetes mellitus. *J Adolesc*. 1998;21:703-715.

11. Peyrot MF, McMurry JF Jr. Stress buffering and glycemic control. The role of coping styles. *Diabetes Care*. 1992;15:842-846.

12. Graue M, Wentzel-Larsen T, Bru E, et al. The coping styles of adolescents with type 1 diabetes are associated with degree of metabolic control. *Diabetes Care* 2004; 27;1313-1317.

13. Peyrot, M, Rubin RR, Lauritzen T, et al. Psychosocial problems and barriers to improved diabetes management: results of the Cross-National Diabetes Attitudes, Wishes and Needs (DAWN) Study. *Diabet Med*. 2005;22:1379-1385.

14. Goldney RD, Phillips PJ, Fisher LJ, et al. Diabetes, depression, and quality of life: a population study. *Diabetes Care*. 2004;27: 1066-1070.

15. Northam EA, Matthews LK, Anderson PJ, et al. Psychiatric morbidity and health outcome in type 1 diabetes – perspectives from a prospective longitudinal study. *Diabet Med*. 2005; 22:152-157.

16. Anderson RJ, Freedland KE, Clouse RE, et al. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care*. 2001;24:1069-1078.

17. Dantzer C, Swendsen J, Maurice-Tison S, et al. Anxiety and depression in juvenile diabetes: a critical review. *Clin Psychol Rev*. 2003;23:787-800.

18. Garvard JA, Lustman PJ, Clouse RE. Prevalence of depression in adults with diabetes. An epidemiological evaluation. *Diabetes Care*. 1993;16:1167-1178.

19. McKellar JD, Humphreys K, Piette JD. Depression increases diabetes symptoms by complicating patients' self-care adherence. *Diabetes Educ*. 2004;30:485-492.

20. Wysocki T. Behavioural assessment and intervention in pediatric diabetes. *Behav Modif*. 2006;30:72-92.

21. Grey M, Whittemore R, Tamborlane W. Depression in type 1 diabetes in children: natural history and correlates. *J Psychosom Res*. 2002;53:907-911.

22. Egede LE, Zheng D, Simpson K. Comorbid depression is associated with increased health care use and expenditures in individuals with diabetes. *Diabetes Care*. 2002;25:464-470.

23. Garrison MM, Katon WJ, Richardson LP. The impact of psychiatric comorbidities on readmissions for diabetes in youth. *Diabetes Care*. 2005;28:2150-2154.

24. Popkin MK, Callies AL, Lentz RD, et al. Prevalence of major depression, simple phobia, and other psychiatric disorders in patients with long-standing type I diabetes mellitus. *Arch Gen Psychiatry*. 1988;45:64-68.

25. Cote MP, Mullins LL, Hartman V, et al. Psychosocial correlates of health care utilization for children and adolescents with type

1 diabetes mellitus. *Children's Health Care*. 2003;32:1-16.

26. Mollema ED, Snoek FJ, Adèr HJ, et al. Insulin-treated diabetes patients with fear of self-injecting or fear of self-testing: psychological comorbidity and general well-being. *J Psychosom Res*. 2001;51:665-672.

27. Grigsby AB, Anderson RJ, Freedland KE, et al. Prevalence of anxiety in adults with diabetes: a systematic review. *J Psychosom Res*. 2002;53:1053-1060.

28. Anderson RJ, DeGroot M, Grigsby AB, et al. Anxiety and poor glycemic control: a meta-analytic review of the literature. *Int J Psychiatry Med*. 2002:32:235-247.

29. Leiter LA, Yale J-F, Chiasson J-L, et al. Assessment of the impact of fear of hypoglycemic episodes on glycemic and hypoglycemia management. *Can J Diabetes*. 2005;29:186-192.

30. Jones JM, Lawson ML, Daneman D, et al. Eating disorders in adolescent females with and without type 1 diabetes: cross sectional study. *BMJ*. 2000;320:1563-1566.

31. Daneman D, Olmsted M, Rydall A, et al. Eating disorders in young women with type 1 diabetes. Prevalence, problems and prevention. *Horm Res*. 1998;50(suppl 1):79-86.

32. Affenito SG, Backstrand JR, Welch GW, et al. Subclinical and clinical eating disorders in IDDM negatively affect metabolic control. *Diabetes Care*. 1997;20:183-184.

33. Rydall AC, Rodin GM, Olmsted MP, et al. Disordered eating behavior and microvascular complications in young women with insulin-dependent diabetes mellitus. *N Engl J Med*. 1997; 336:1849-1854.

34. Mannucci E, Rotella F, Ricca V, et al. Eating disorders in patients with type 1 diabetes: a meta-analysis. *J Endocrinol Invest*. 2005;28:417-419.

35. Rodin G, Olmsead MP, Rydall AC, et al. Eating disorders in young women with type 1 diabetes mellitus. *J Psychoso Res*. 2002;53: 943-949.

36. Garner DM, Olmstead MP. Eating Disorder Inventory (EDI) manual. Odessa, FL: Psychological Assessment Resources. 1984.

37. Welch GW, Jacobson AM, Polonsky WH. The Problem Areas in Diabetes scale. An evaluation of its clinical utility. *Diabetes Care*. 1997;20:760-766.

38. Whooley MA, Avins AL, Miranda J, et al. Case-finding instruments for depression. Two questions are as good as many. *J Gen Intern Med*. 1997;12:439-445.

39. Lustman PJ, Clouse RE, Griffith LS, et al. Screening for depression in diabetes using the Beck Depression Inventory. *Psychosom Med*. 1997;59:24-31.

40. Cameron FJ, Smidts D, Hesketh K, et al. Early detection of emotional and behavioural problems in children with diabetes: the validity of the Child Health Questionnaire as a screening instrument. *Diabet Med*. 2003;20:646-650.

41. Steed L, Cooke D, Newman S. A systematic review of psychosocial outcomes following education, self-management and psychological interventions in diabetes mellitus. *Patient Educ Couns*. 2003;51:5-15.

42. Ismail K, Winkley K, Rabe-Hesketh S. Systematic review and meta-analysis of randomized controlled trials of psychological

interventions to improve glycaemic control in patients with type 2 diabetes. *Lancet*. 2004;363:1589-1597.

43. Svoren BM, Butler D, Levine BS, et al. Reducing acute adverse outcomes in youths with type 1 diabetes: a randomized, controlled trial. *Pediatrics*. 2003;112:914-922.

44. Piette JD, Weinberger M, McPhee SJ. The effect of automated calls with telephone nurse follow-up on patient-centered outcomes of diabetes care: a randomized, controlled trial. *Med Care*. 2000;38:218-230.

45. Jones H, Edwards L, Vallis TM, et al. Changes in diabetes self-care behaviors make a difference in glycemic control: the Diabetes Stages of Change (DiSC) study. *Diabetes Care*. 2003; 26:732-737.

46. Grey M, Boland EA, Davidson M, et al. Short-term effects of coping skills training as adjunct to intensive therapy in adolescents. *Diabetes Care*. 1998;21:902-908.

47. Fosbury JA, Bosley CM, Ryle A, et al. A trial of cognitive analytic therapy in poorly controlled type 1 patients. *Diabetes Care*. 1997;20:959-964.

48. Wysocki T, Harris MA, Greco P, et al. Randomized, controlled trial of behavior therapy for families of adolescents with insulin-dependent diabetes mellitus. *J Pediatric Psychol*. 2000; 25:23-33.

49. Norris SL, Engelgau MM, Narayan KM. Effectiveness of self-management training in type 2 diabetes: a systematic review of randomized controlled trials. *Diabetes Care*. 2001;24:561-587.

50. Anderson BJ, Brackett J, Ho J, et al. An office-based intervention to maintain parent-adolescent teamwork in diabetes management. Impact on parent involvement, family conflict, and subsequent glycemic control. *Diabetes Care*. 1999;22:713-721.

51. Greenfield S, Kaplan SH, Ware JE Jr, et al. Patients' participation in medical care: effects on blood sugar control and quality of life in diabetes. *J Gen Intern Med*. 1988;3:448-457.

52. Gage H, Hampson S, Skinner TC, et al. Educational and psychosocial programmes for adolescents with diabetes: approaches, outcomes and cost-effectiveness. *Patient Educ Couns*. 2004;53:333-346.

53. Ellis DA, Frey MA, Naar-King S, et al. The effects of multisystemic therapy on diabetes stress among adolescents with chronically poorly controlled type 1 diabetes: findings from a randomized, controlled trial. *Pediatrics*. 2005;16:826-832.

54. Ellis DA, Frey MA, Naar-King S, et al. Use of multisystemic therapy to improve regimen adherence among adolescents with type 1 diabetes in chronic poor metabolic control: a randomized controlled trial. *Diabetes Care*. 2005;28:1604-1610.

55. Lustman PJ, Freedland KE, Griffith LS, et al. Fluoxetine for depression in diabetes: a randomized double-blind placebo-controlled trial. *Diabetes Care*. 2000;23:618-623.

56. Lustman PJ, Griffith LS, Freedland KE, et al. Cognitive behavior therapy for depression in type 2 diabetes mellitus. A randomized, controlled trial. *Ann Intern Med*. 1998;129:613-621.

57. Fava M, Judge R, Hoog S, et al. Fluoxetine versus sertraline and paroxetine in major depressive disorders: changes in weight with long term treatment. *J Clin Psychiatry*. 2000; 61:863-867.

Influenza and Pneumococcal Immunization

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee
The initial draft of this chapter was prepared by Vincent Woo MD FRCPC

KEY MESSAGES

- Studies in high-risk individuals, which included people with diabetes, have shown that influenza vaccination can reduce hospitalizations by approximately 40%.

- As people with diabetes are at least as susceptible to pneumococcal infection as other people with chronic diseases, the use of the pneumococcal vaccine is encouraged.

- A one-time pneumococcal revaccination is recommended for individuals >65 years of age if the original vaccine was administered when they were <65 years of age and >5 years earlier.

INTRODUCTION

People with diabetes, especially those with renal and cardiac complications, are at high risk for morbidity and mortality from influenza and pneumococcal disease (1). Studies in high-risk individuals, which included people with diabetes, have shown that influenza vaccination can reduce hospitalizations by about 40% (2). However, there are few randomized controlled trials that have specifically evaluated the use and benefit of influenza or pneumococcal immunization in people with diabetes (1). Clinical practice recommendations for people with diabetes must therefore be extrapolated from recommendations for individuals at high risk of complications associated with these infectious diseases (3-5).

INFLUENZA IMMUNIZATION IN ADULTS

The majority of studies on influenza immunization rely on observational reports of increased death rates in people with diabetes during influenza epidemics (6-9). One case-control study of people with diabetes showed a 6-fold increased risk of hospitalization during influenza outbreaks compared to nonepidemic years (9).

A retrospective case-control study demonstrated the effectiveness of influenza vaccination in reducing rates of hospitalization of people with diabetes for influenza, pneumonia or diabetes-related events during 2 influenza epidemics in Leicestershire, England, United Kingdom (10). The study detected a 79% reduction in hospitalization rates during the 2 epidemics in people with diabetes who had been immunized against influenza during the period immediately preceding the epidemic. Another nested case-control study in the Netherlands demonstrated that vaccination was associated with a 56% reduction in any complication, a 54% reduction in hospitalizations and a 58% reduction in deaths in people with type 2 diabetes (11).

PNEUMOCOCCAL IMMUNIZATION IN ADULTS

Numerous studies have demonstrated the efficacy of immunization in reducing pneumococcal bacteremia in the general population (12-15). There is widespread acceptance that people with diabetes are at least as susceptible to pneumococcal infection as other people with chronic diseases (1), and therefore the use of the pneumococcal vaccine is encouraged in this population. A one-time revaccination is recommended for individuals >65 years of age if the original vaccine was administered when they were <65 years of age and >5 years earlier.

RECOMMENDATIONS

1. People with diabetes should receive an annual influenza vaccine to reduce the risk of complications associated with influenza epidemics *[Grade D, Consensus]*.

2. People with diabetes should be considered for vaccination against pneumococcus *[Grade D, Consensus]*.

RELATED WEBSITES

National Advisory Committee on Immunization. *Canadian Immunization Guide*. 7th ed. Ottawa, ON: Canadian Medical Association; 2006. Available at: http://www.phac-aspc.gc.ca/publicat/cig-gci/index.html. Accessed September 1, 2008.

REFERENCES

1. Smith SA, Poland GA. Use of influenza and pneumococcal vaccines in people with diabetes. *Diabetes Care*. 2000;23:95-108.
2. Nichol KL, Nordin J, Mullooly J, et al. Influenza vaccination and reduction in hospitalizations for cardiac disease and stroke among the elderly. *N Engl J Med*. 2003;348:1322-1332.
3. Casey JI. Host defense abnormalities in diabetic patients. In: Rifkin H, Raskin P, eds. *Diabetes Mellitus*. Vol 5. Bowie, MD: Robert J. Brady Company; 1981:219-223.
4. Heymann AD, Shapiro Y, Chodick G, et al. Reduced hospitalizations and death associated with influenza vaccination among patients with and without diabetes. *Diabetes Care*. 2004;27:2581-2584.

5. Smith SA, Poland GA, American Diabetes Association. Influenza and pneumococcal immunization in diabetes. *Diabetes Care*. 2004;27:S111-S113.

6. Eickhoff TC, Sherman IL, Serfing RE. Observations on excess mortality associated with epidemic influenza. *JAMA*. 1961;176:104-110.

7. Martin WJ. Recent changes in the death rate from influenza. *Br Med J*. 1950;1:267-268.

8. Stocks P, Camb MD. Influenza epidemics on the certified causes of death. *Lancet*. 1935:ii;386-395.

9. Bouter KP, Diepersloot RJA, van Romunde LKJ, et al. Effect of epidemic influenza on ketoacidosis, pneumonia and death in diabetes mellitus: a hospital register survey of 1976–1979 in The Netherlands. *Diabetes Res Clin Pract*. 1991;12:61-68.

10. Colquhoun AJ, Nicholson KG, Botha JL, et al. Effectiveness of influenza vaccine in reducing hospital admissions in people with diabetes. *Epidemiol Infect*. 1997;119:335-341.

11. Looijmans-Van den Akker I, Verheij TJ, Buskens E, et al. Clinical effectiveness of first and repeat influenza vaccination in adult and elderly diabetic patients. *Diabetes Care*. 2006;29:1771-1776.

12. Bolan G, Broome CV, Facklam RR, et al. Pneumococcal vaccine efficacy in selected populations in the United States. *Ann Intern Med*. 1986;104:1-6.

13. Forrester HL, Jahnigen DW, LaForce FM. Inefficacy of pneumococcal vaccine in a high-risk population. *Am J Med*. 1987;83:425-430.

14. Schwartz JS. Pneumococcal vaccine: clinical efficacy and effectiveness. *Ann Intern Med*. 1982;96:208-220.

15. Shapiro ED, Clemens JD. A controlled evaluation of the protective efficacy of pneumococcal vaccine for patients at high risk of serious pneumococcal infections. *Ann Intern Med*. 1984;101:325-330.

Pancreas and Islet Transplantation

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Breay W. Paty MD FRCPC, Erin Keely MD FRCPC and Charlotte McDonald MD FRCPC

KEY MESSAGES

- Pancreas transplant can result in prolonged insulin independence and a possible reduction in the progression of secondary complications of diabetes.

- Islet transplant can result in transient insulin independence and can reliably stabilize blood glucose concentrations in people with glycemic lability.

- The risks of chronic immunosuppression must be carefully weighed against the potential benefits of pancreas or islet transplant for each individual.

INTRODUCTION

Beta cell replacement as a means of restoring endogenous insulin secretion, either by whole organ pancreas transplant or islet transplant, has a number of potential advantages over standard exogenous insulin therapy for the treatment of type 1 diabetes, including improved glycemic control and the potential for insulin independence. However, any advantages must be weighed against the risks and adverse effects of surgery and chronic immunosuppressive therapy that accompany these treatments. Unfortunately, the absence of data from randomized controlled trials (RCTs) makes it difficult to draw firm conclusions regarding the efficacy of these therapies compared with intensive medical management of diabetes. Nevertheless, some general recommendations can be made regarding the role of pancreas and islet transplant in the context of current clinical experience.

WHOLE PANCREAS TRANSPLANTATION

Pancreas transplantation has progressed significantly in terms of surgical technique and immunosuppression since it was first introduced in the 1960s (1). It is most commonly categorized on the basis of the presence or absence of a kidney transplant and the relative timing of the procedures: simultaneous pancreas kidney (SPK) transplant; pancreas after kidney (PAK) transplant; or pancreas transplant alone (PTA), in the absence of a kidney transplant. Worldwide, non-controlled pancreas graft and patient survival rates differ slightly among these 3 categories (2). However, in the absence of large RCTs, it is unclear whether these differences are clinically significant.

Metabolic studies demonstrate a marked improvement in glycemic control and glycated hemoglobin (A1C) after suc-cessful whole pancreas transplant, with most recipients achieving insulin independence that can last for many years (3,4). A reduction in albuminuria has been shown at 1 year posttransplant (5). Similarly, improvements in the histologic changes of diabetic nephropathy have been reported after 5 to 10 years posttransplant (6). Studies also show an improvement and/or stabilization of diabetic retinopathy (7) after an initial risk of worsening due to a rapid reduction in glycemia (8). The benefits of pancreas transplant are less clear in patients with advanced retinal disease (9). Peripheral sensory and motor neuropathies have been shown to improve after pancreas transplant (10,11). Improvements in autonomic neuropathy are less consistent and may take longer to achieve (12,13). There is growing evidence that pancreas transplant improves cardiovascular (CV) function (14) and may reduce cardiac events (15). However, studies have generally been small and nonrandomized. It remains uncertain whether pancreas transplant improves overall mortality rates (16). Finally, diabetes-related quality of life appears to improve after pancreas transplant, although overall quality of life may not change (17).

ISLET TRANSPLANTATION

Islet transplantation is a less invasive procedure than pancreas transplantation. It involves the infusion of islets isolated from cadaveric pancreata via the portal vein into the liver (18). Unlike whole pancreas transplant recipients, most islet transplant recipients require at least 2 islet infusions to achieve insulin independence, although there has been recent short-term success using single islet donors in some centres (19). The rate of posttransplant insulin independence at the most experienced centres is approximately 80% at 1 year, but declines to about 10% at 5 years (20-22). Rates of insulin independence may be lower at less experienced centres (23,24). Most transplant recipients continue to have some endogenous insulin secretion even after insulin independence is lost. However, there are very few long-term data regarding function of the transplanted islets after 5 years. Most published studies involve islet transplant in the absence of a kidney transplant (islet transplant alone [ITA]). There is some evidence suggesting that islet transplant performed at the same time as a kidney transplant (simultaneous islet kidney [SIK]) or after a kidney transplant (islet after kidney [IAK]) may have comparable results (25,26).

The principal benefit of islet transplant is stabilization of blood glucose control in individuals with severe glycemic lability or hypoglycemia unawareness. This benefit is evident and persists in most recipients, even in the absence of insulin independence (27,28). The impact of islet transplantation on diabetes complications remains uncertain. Renal function appears to decline after ITA in patients with significant pre-existing renal dysfunction, although the degree of decline can vary (29,30). For this reason, particular caution may be warranted for patients with pre-existing renal dysfunction. There is some evidence that IAK transplant recipients show improved endothelial and CV function compared to kidney transplant recipients (31,32). Kidney graft survival rates also appear to improve with concomitant islet transplant (33). The impact of islet transplantation on diabetic retinopathy and neuropathy is still uncertain. Quality of life appears to improve initially after islet transplantation, due primarily to a reduced fear of hypoglycemia, but declines with the loss of insulin independence (34,35).

RISKS OF PANCREAS AND ISLET TRANSPLANTATION

Pancreas transplantation is associated with significant perioperative risks, including graft pancreatitis, peripancreatic abscess, duodenal stump leak, venous or arterial thrombosis, and conversion from bladder to enteric drainage (36). Islet transplantation is associated with fewer procedural risks, which may include intraperitoneal hemorrhage, partial portal vein thrombosis, gallbladder puncture and a transient elevation of liver enzymes (37). Both pancreas and islet transplantation require chronic immunosuppression, which is associated with a number of risks and side effects, including increased risk of infection and malignancy, nephrotoxicity, diarrhea, oral ulcers (in the case of islet transplant) and many others. These risks must be carefully weighed against the potential benefits of transplant for each individual.

RECOMMENDATIONS

1. For individuals with type 1 diabetes and end-stage renal disease who are undergoing or have undergone successful kidney transplant, pancreas transplant should be considered [Grade D, Consensus].

2. For individuals with type 1 diabetes and preserved renal function, but with persistent metabolic instability characterized by severe glycemic lability and/or severe hypoglycemia unawareness despite best efforts to optimize glycemic control, pancreas transplant [Grade D, Level 4 (4)] or islet transplant [Grade D, Level 4 (21)] may be considered.

REFERENCES

1. Larsen JL. Pancreas transplantation: indications and consequences. *Endocr Rev.* 2004;25:919-946.

2. Gruessner AC, Sutherland DE. Pancreas transplant outcomes for United States (US) and non-US cases as reported to the United Network for Organ Sharing (UNOS) and the International Pancreas Transplant Registry (IPTR) as of June 2004. *Clin Transplant.* 2005;19:433-455.

3. Robertson RP, Abid M, Sutherland DE, et al. Glucose homeostasis and insulin secretion in human recipients of pancreas transplantation. *Diabetes.* 1989;38(suppl 1):97-98.

4. Robertson RP, Sutherland DE, Lanz KJ. Normoglycemia and preserved insulin secretory reserve in diabetic patients 10-18 years after pancreas transplantation. *Diabetes.* 1999;48:1737-1740.

5. Coppelli A, Giannarelli R, Vistoli F, et al. The beneficial effects of pancreas transplant alone on diabetic nephropathy. *Diabetes Care.* 2005;28:1366-1370.

6. Fioretto P, Steffes MW, Sutherland DE, et al. Reversal of lesions of diabetic nephropathy after pancreas transplantation. *N Engl J Med.* 1998;339:69-75.

7. Giannarelli R, Coppelli A, Sartini M, et al. Effects of pancreas-kidney transplantation on diabetic retinopathy. *Transpl Int.* 2005;18:619-622.

8. Landgraf R, Nusser J, Scheuer R, et al. Metabolic control and effect on secondary complications of diabetes mellitus by pancreatic transplantation. *Baillieres Clin Gastroenterol.* 1989;3:865-876.

9. Bandello F, Vigano C, Secchi A, et al. Effect of pancreas transplantation on diabetic retinopathy: a 20-case report. *Diabetologia.* 1991;34(suppl 1):S92-S94.

10. Kennedy WR, Navarro X, Goetz FC, et al. Effects of pancreatic transplantation on diabetic neuropathy. *N Engl J Med.* 1990;322:1031-1037.

11. Navarro X, Sutherland DE, Kennedy WR. Long-term effects of pancreatic transplantation on diabetic neuropathy. *Ann Neurol.* 1997;42:727-736.

12. Solders G, Tydén G, Persson A, et al. Improvement of nerve conduction in diabetic neuropathy. A follow-up study 4 yr after combined pancreatic and renal transplantation. *Diabetes.* 1992;41:946-951.

13. Tydén G, Bolinder J, Solders G, et al. Improved survival in patients with insulin-dependent diabetes mellitus and end-stage diabetic nephropathy 10 years after combined pancreas and kidney transplantation. *Transplantation.* 1999;67:645-648.

14. Coppelli A, Giannarelli R, Mariotti R, et al. Pancreas transplant alone determines early improvement of cardiovascular risk factors and cardiac function in type 1 diabetic patients. *Transplantation.* 2003;76:974-976.

15. La Rocca E, Fiorina P, di Carlo V, et al. Cardiovascular outcomes after kidney-pancreas and kidney-alone transplantation. *Kidney Int.* 2001;60:1964-1971.

16. Venstrom JM, McBride MA, Rother KI, et al. Survival after pancreas transplantation in patients with diabetes and preserved kidney function. *JAMA.* 2003;290:2817-2823.

17. Sureshkumar KK, Mubin T, Mikhael N, et al. Assessment of quality of life after simultaneous pancreas-kidney transplantation. *Am J Kidney Dis.* 2002;39:1300-1306.

18. Robertson RP. Islet transplantation as a treatment for diabetes – a work in progress. *N Engl J Med.* 2004;350:694-705.

19. Hering BJ, Kandaswamy R, Ansite JD, et al. Single-donor, marginal-dose islet transplantation in patients with type 1 diabetes. *JAMA.* 2005;293:830-835.

20. Markmann JF, Deng S, Huang X, et al. Insulin independence following isolated islet transplantation and single islet infusions. *Ann Surg.* 2003;237:741-749.

21. Ryan EA, Paty BW, Senior PA, et al. Five-year follow-up after clinical islet transplantation. *Diabetes.* 2005;54:2060-2069.

22. Shapiro AM, Ricordi C, Hering BJ, et al. International trial of the Edmonton protocol for islet transplantation. *N Engl J Med.* 2006;355:1318-1330.

23. Close NC, Hering BJ, Eggerman TL. Results from the inaugural year of the Collaborative Islet Transplant Registry. *Transplant Proc.* 2005;37:1305-1308.

24. Hirshberg B, Rother KI, Digon BJ 3rd, et al. Benefits and risks of solitary islet transplantation for type 1 diabetes using steroid-sparing immunosuppression: the National Institutes of Health experience. *Diabetes Care.* 2003;26:3288-3295.

25. Lehmann R, Weber M, Berthold P, et al. Successful simultaneous islet-kidney transplantation using a steroid-free immunosuppression: two-year follow-up. *Am J Transplant.* 2004;4: 1117-1123.

26. Toso C, Baertschiger R, Morel P, et al. Sequential kidney/islet transplantation: efficacy and safety assessment of a steroid-free immunosuppression protocol. *Am J Transplant.* 2006;6:1049-1058.

27. Ryan EA, Shandro T, Green K, et al. Assessment of the severity of hypoglycemia and glycemic lability in type 1 diabetes subjects undergoing islet transplantation. *Diabetes.* 2004;53: 955-962.

28. Paty BW, Senior PA, Lakey JR, et al. Assessment of glycemic control after islet transplantation using the continuous glucose monitor in insulin-independent versus insulin-requiring type 1 diabetes subjects. *Diabetes Technol Ther.* 2006;8:165-173.

29. Rother KI, Harlan DM. Challenges facing islet transplantation for the treatment of type 1 diabetes mellitus. *J Clin Invest.* 2004;114:877-883.

30. Senior PA, Zeman M, Paty BW, et al. Changes in renal function after clinical islet transplantation: four-year observational study. *Am J Transplant.* 2007;7:91-98.

31. Fiorina P, Folli F, Bertuzzi F, et al. Long-term beneficial effect of islet transplantation on diabetic macro-/microangiopathy in type 1 diabetic kidney-transplanted patients. *Diabetes Care.* 2003;26:1129-1136.

32. Fiorina P, Gremizzi C, Maffi P, et al. Islet transplantation is associated with an improvement of cardiovascular function in type 1 diabetic kidney transplant patients. *Diabetes Care.* 2005; 28:1358-1365.

33. Fiorina P, Folli F, Zerbini G, et al. Islet transplantation is associated with improvement of renal function among uremic patients with type I diabetes mellitus and kidney transplants. *J Am Soc Nephrol.* 2003;14:2150-2158.

34. Johnson JA, Kotovych M, Ryan EA, et al. Reduced fear of hypoglycemia in successful islet transplantation. *Diabetes Care.* 2004;27:624-625.

35. Poggioli R, Faradji RN, Ponte G, et al. Quality of life after islet transplantation. *Am J Transplant.* 2006;6:371-378.

36. Humar A, Kandaswamy R, Granger D, et al. Decreased surgical risks of pancreas transplantation in the modern era. *Ann Surg.* 2000;231:269-275.

37. Ryan EA, Paty BW, Senior PA, et al. Risks and side effects of islet transplantation. *Curr Diab Rep.* 2004;4:304-309.

Complementary and Alternative Medicine in the Management of Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee
The initial draft of this chapter was prepared by Jeannette Goguen MD MEd FRCPC

KEY MESSAGES

• Up to 30% of patients with diabetes use complementary and alternative medicine (CAM) for various indications.

• Most CAM studies have small sample sizes and are of short duration, and therefore may have missed harmful side effects.

• Certain CAM in common use for disorders other than diabetes can result in side effects and drug interactions.

INTRODUCTION

Complementary and alternative medicine (CAM) has been defined as "medicine that does not conform to the standards of the medical community, is not widely taught in North American medical schools and is not available in North American hospitals" (1). It involves the use of herbal medications as well as dietary supplements, including minerals, vitamins and other micronutrients. When used in a traditional system (e.g. Chinese, Tibetan, Ayurvedic), an herb is often only one of a number of interventions, which could also include acupuncture, yoga and multiple other herbs.

MANAGEMENT

CAM in the management of diabetes has been included in these guidelines, as it includes potential new therapeutic agents, and because studies have suggested that up to 30% of patients with diabetes use CAM for multiple indications (2), leading to potential side effects, drug interactions and increased cost to the patient. In 1 Canadian study in predominantly Caucasian subjects, the most commonly used alternative trace element for glycemic control was chromium (6%), followed by magnesium (2.2%) and vanadium (1%) (2). Herbs were rarely used.

There are several issues unique to CAM that have implications in the assessment of the evidence for its use: trials are typically of short duration, with small sample sizes and unique patient populations that may not be generalizable (3); publications are often difficult to access, with only 10% referenced in MEDLINE (4); and there is a lack of standardization and purity of available compounds, including their contamination with regular medications and toxic compounds (5).

The following herbs have been shown to improve glycemic control in adults with type 2 diabetes: *Aloe vera* (6,7); *Ipomoea*

batatas (caiapo) (8); *Coccinia indica* (9); *Ganoderma lucidum* (10); *Gymnema sylvestre* (11); *Ocimum tenuiflorum* (holy basil or tulsi) (12); *Salacia reticulata* (13); pinitol (14); touchi (15); and *Pterocarpus marsupium* (vijayasar) (16). However, as all of the studies were small and of short duration, it is premature to recommend the use of these agents.

The following herbs have been shown to be ineffective for glycemic control in adults with type 2 diabetes: *Syzgium cumini* (17); *Tinospora crispa* (18); French maritime pine bark (19); garlic (20); and soy phytoestrogens (21). The following dietary supplements have been shown to be ineffective: coenzyme Q10 (22) and vitamin E (23-26). Glucosamine sulfate, used to treat osteoarthritis, does not affect glycemic control (27).

The following herbs have conflicting evidence with regards to glycemic control in adults with type 2 diabetes: *Cinnamomum cassia* (Chinese cinnamon) (28-31); *Momordica charantia* (bitter melon or bitter gourd) (32,33); *Trigonella foenum-graecum* (fenugreek) (34,35); and ginseng (36,37). The following dietary supplements have conflicting evidence: chromium (38-46); vanadium (47); magnesium (48-52); lipoic acid (53); vitamin C (52,54); and carnitine (55,56).

Studies have examined the combinations of herbs as used by traditional practitioners. These studies included Tibetan traditional medicine (57), Chinese plants (58,59) and Ayurvedic pancreas extract (60). Methodological concerns make the results of these studies difficult to interpret.

COMPLICATIONS

It is important to consider potential harm from the use of CAM. Most studies were of small sample size and short duration, and thus may have missed harmful side effects. The use of *Tinospora crispa* was associated with markedly elevated liver enzymes in 2 patients and should be avoided (18). Alternative medications should not be used in pregnancy – some are abortifacts (e.g. *Momordica charantia*) (61). As well, there are case reports of severe hypoglycemia with the use of bitter melon in children (61).

Impurities of substances are another concern. Contamination with regular medications and with heavy metals has been documented in several publications (5). Finally, certain CAM in common use for disorders other than diabetes can result in side effects and drug interactions. Agents that have been associated with elevations in blood pressure include the following: ginseng, licorice, yohimbine

and yerba mate. It is important to be aware of the following drug interactions: *Hypericum perforata* (St John's wort) (used in depression) induces CYP3A4 and can reduce levels of statins cleared by this mechanism; *Gingko biloba* (used for Alzheimer's disease and intermittent claudication) reduces platelet aggregation and can potentiate other medications that affect bleeding; psyllium can retard the absorption of some drugs and minerals.

For a more detailed discussion of CAM and diabetes, see the review by Yeh and colleagues (62).

RECOMMENDATIONS

1. At this time, CAM is not recommended for glycemic control for individuals with diabetes, as there is not sufficient evidence regarding safety and efficacy *[Grade D, Consensus]*.

2. Individuals with diabetes should be routinely asked if they are using CAM *[Grade D, Consensus]*.

REFERENCES

1. Eisenberg DM, Davis RB, Ettner SL, et al. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. *JAMA*. 1998;280:1569-1575.

2. Ryan EA, Pick ME, Marceau C. Use of alternative medicines in diabetes mellitus. *Diabet Med*. 2001;18:242-245.

3. Angell M, Kassirer JP. Alternative medicine – the risks of untested and unregulated remedies. *N Engl J Med*. 1998;339:839-841.

4. Ezzo J, Berman BM, Vickers AJ, et al. Complementary medicine and the Cochrane Collaboration. *JAMA*. 1998;280:1628-1630.

5. Saper RB, Kales SN, Paquin J, et al. Heavy metal content of ayurvedic herbal medicine products. *JAMA*. 2004;292:2868-2873.

6. Bunyapraphatsara N, Yongchaiyudha S, Rungpitarangsi V. Antidiabetic activity of *Aloe vera* L. juice II. Clinical trial in diabetes mellitus patients in combination with glibenclamide. *Phytomedicine*. 1996;3:245-248.

7. Yongchaiyudha S, Rungpitarangsi V, Bunyapraphatsara N, et al. Antidiabetic activity of *Aloe vera* L. juice I. Clinical trial in new cases of diabetes mellitus. *Phytomedicine*. 1996;3:241-243.

8. Ludvik B, Neuffer B, Pacini G. Efficacy of Ipomoea batatas (Caiapo) on diabetes control in type 2 diabetic subjects treated with diet. *Diabetes Care*. 2004;27:436-440.

9. Azad Khan AK, Akhtar S, Mahtab H. *Coccinia indica* in the treatment of patients with diabetes mellitus. *Bangladesh Med Res Counc Bull*. 1979;5:60-66.

10. Gao YH, Lan J, Dai XH, et al. A phase I/II study of Ling Zhi mushroom *Ganoderma lucidum* (W.Curt.:Fr.) Lloyd (Aphyllophoromycetidae) extract in patients with type 2 diabetes. *Int J Med Mushr*. 2004;6:33-39.

11. Baskaran K, Kizar Ahamath B, Radha Shanmugasundaram K, et al. Antidiabetic effect of a leaf extract from *Gymnema sylvestre* in non-insulin-dependent diabetes mellitus patients. *J Ethnopharmacol*. 1990;30:295-300.

12. Agrawal P, Rai V, Singh RB. Randomized placebo-controlled, single blind trial of holy basil leaves in patients with non-insulin-dependent diabetes mellitus. *Int J Clin Pharmacol Ther*. 1996;34:406-409.

13. Jayawardena MH, de Alwis NM, Hettigoda V, et al. A double blind randomised placebo controlled cross over study of a herbal preparation containing *Salacia reticulata* in the treatment of type 2 diabetes. *J Ethnopharmacol*. 2005;97:215-218.

14. Kim JI, Kim JC, Kang MJ, et al. Effects of pinitol isolated from soybeans on glycaemic control and cardiovascular risk factors in Korean patients with type II diabetes mellitus: a randomized controlled study. *Eur J Clin Nutr*. 2005;59:456-458.

15. Fujita H, Yamagami T, Ohshima K. Long-term ingestion of a fermented soybean-derived Touchi-extract with alpha-glucosidase inhibitory activity is safe and effective in humans with borderline and mild type-2 diabetes. *J Nutr*. 2001;131:2105-2108.

16. Hariharan RS, Venkataraman S, Sunitha P, et al. Efficacy of vijayasar (*Pterocarpus marsupium*) in the treatment of newly diagnosed patients with type 2 diabetes mellitus: a flexible dose double-blind multicenter randomized controlled trial. *Diabetologia Croatica*. 2005;34:13-20.

17. Teixeira CC, Fuchs FD, Weinert LS, et al. The efficacy of folk medicines in the management of type 2 diabetes mellitus: results of a randomized controlled trial of *Syzygium cumini* (L.) Skeels. *J Clin Pharm Ther*. 2006;31:1-5.

18. Sangsuwan C, Udompanthurak S, Vannasaeng S, et al. Randomized controlled trial of *Tinospora crispa* for additional therapy in patients with type 2 diabetes mellitus. *J Med Assoc Thai*. 2004;87:543-546.

19. Liu X, Wei J, Tan F, et al. Antidiabetic effect of Pycnogenol French maritime pine bark extract in patients with diabetes type II. *Life Sci*. 2004;75:2505-2513.

20. Sitprija S, Plengvidhya C, Kangkaya V, et al. Garlic and diabetes mellitus phase II clinical trial. *J Med Assoc Thai*. 1987;70(suppl 2):223-227.

21. Jayagopal V, Albertazzi P, Kilpatrick ES, et al. Beneficial effects of soy phytoestrogen intake in postmenopausal women with type 2 diabetes. *Diabetes Care*. 2002;25:1709-1714.

22. Eriksson JG, Forsén TJ, Mortensen SA, et al. The effect of coenzyme Q10 administration on metabolic control in patients with type 2 diabetes mellitus. *Biofactors*. 1999;9:315-318.

23. Lonn E, Yusuf S, Hoogwerf B, et al. Effects of vitamin E on cardiovascular and microvascular outcomes in high-risk patients with diabetes: results of the HOPE study and MICRO-HOPE substudy. *Diabetes Care*. 2002;25:1919-1927.

24. Boshtam M, Rafiei M, Golshadi ID, et al. Long term effects of oral vitamin E supplement in type II diabetic patients. *Int J Vitam Nutr Res*. 2005;75:341-346.

25. Ble-Castillo JL, Carmona-Díaz E, Méndez JD, et al. Effect of alpha-tocopherol on the metabolic control and oxidative stress in female type 2 diabetics. *Biomed Pharmacother*. 2005;59:290-295.

26. Nazaimoon WW, Sakinah O, Gapor A, et al. Effects of palm olein tocopherol and tocotrienol on lipid peroxidation, lipid profiles and glycemic control in non-insulin diabetes mellitus patients. *Nutr Res.* 1996;16:1901-1911.

27. Scroggie DA, Albright A, Harris MD. The effect of glucosamine-chondroitin supplementation on glycosylated hemoglobin levels in patients with type 2 diabetes mellitus: a placebo-controlled, double-blinded, randomized clinical trial. *Arch Intern Med.* 2003;163:1587-1590.

28. Khan A, Safdar M, Ali Khan MM, et al. Cinnamon improves glucose and lipids of people with type 2 diabetes. *Diabetes Care.* 2003;26:3215-3218.

29. Vanschoonbeek K, Thomassen BJ, Senden JM, et al. Cinnamon supplementation does not improve glycemic control in postmenopausal type 2 diabetes patients. *J Nutr.* 2006;136:977-980.

30. Mang B, Wolters M, Schmitt B, et al. Effects of a cinnamon extract on plasma glucose, HbA, and serum lipids in diabetes mellitus type 2. *Eur J Clin Invest.* 2006;36:340-344.

31. Blevins SM, Leyva MJ, Brown J, et al. Effect of cinnamon on glucose and lipid levels in noninsulin-dependent type 2 diabetes. *Diabetes Care.* 2007;30:2236-2237.

32. Rosales RF, Fernando RE. An inquiry to the hypoglycemic action of *Momodica charantia* among type 2 diabetic patients. *Phil J Intern Med.* 2001;39:213-216.

33. John AJ, Cherian R, Subhash HS, et al. Evaluation of the efficacy of bitter gourd (*momordica charantia*) as an oral hypoglycemic agent – a randomized controlled clinical trial. *Indian J Physiol Pharmacol.* 2003;47:363-365.

34. Bordia A, Verma SK, Srivastava KC. Effect of ginger (*Zingiber officinale Rosc.*) and fenugreek (*Trigonella foenumgraecum L.*) on blood lipids, blood sugar and platelet aggregation in patients with coronary artery disease. *Prostaglandins Leukot Essent Fatty Acids.* 1997;56:379-384.

35. Gupta A, Gupta R, Lal B. Effect of *Trigonella foenum-graecum* (fenugreek) seeds on glycaemic control and insulin resistance in type 2 diabetes mellitus: a double blind placebo controlled study. *J Assoc Physicians India.* 2001;49:1057-1061.

36. Sotaniemi EA, Haapakoski E, Rautio A. Ginseng therapy in non-insulin-dependent diabetic patients. *Diabetes Care.* 1995; 18:1373-1375.

37. Vuksan V, Sung MK, Sievenpiper JL, et al. Korean red ginseng (*Panax ginseng*) improves glucose and insulin regulation in well-controlled, type 2 diabetes: results of a randomized, double-blind, placebo-controlled study of efficacy and safety. *Nutr Metab Cardiovasc Dis.* 2008;18:46-56.

38. Althuis MD, Jordan NE, Ludington EA, et al. Glucose and insulin responses to dietary chromium supplements: a meta-analysis. *Am J Clin Nutr.* 2002;76:148-155.

39. Martin J, Wang ZQ, Zhang XH, et al. Chromium picolinate supplementation attenuates body weight gain and increases insulin sensitivity in subjects with type 2 diabetes. *Diabetes Care.* 2006;29:1826-1832.

40. Kleefstra N, Houweling ST, Jansman FG, et al. Chromium treatment has no effect in patients with poorly controlled, insulin-treated type 2 diabetes in an obese Western population: a randomized, double-blind, placebo-controlled trial. *Diabetes Care.* 2006;29:521-525.

41. Ghosh D, Bhattacharya B, Mukherjee B, et al. Role of chromium supplementation in Indians with type 2 diabetes mellitus. *J Nutr Biochem.* 2002;13:690-697.

42. Anderson RA, Roussel AM, Zouari N, et al. Potential antioxidant effects of zinc and chromium supplementation in people with type 2 diabetes mellitus. *J Am Coll Nutr.* 2001;20:212-218.

43. Anderson RA, Cheng N, Bryden NA, et al. Elevated intakes of supplemental chromium improve glucose and insulin variables in individuals with type 2 diabetes. *Diabetes.* 1997;46:1786-1791.

44. Bahijiri SM, Mira SA, Mufti AM, et al. The effects of inorganic chromium and brewer's yeast supplementation on glucose tolerance, serum lipids and drug dosage in individuals with type 2 diabetes. *Saudi Med J.* 2000;21:831-837.

45. Kleefstra N, Houweling ST, Bakker SJ, et al. Chromium treatment has no effect in patients with type 2 diabetes in a Western population: a randomized, double-blind, placebo-controlled trial. *Diabetes Care.* 2007;30:1092-1096.

46. Balk EM, Tatsioni A, Lichtenstein AH, et al. Effect of chromium supplementation on glucose metabolism and lipids: a systematic review of randomized controlled trials. *Diabetes Care.* 2007;30:2154-2163.

47. Goldfine AB, Patti ME, Zuberi L, et al. Metabolic effects of vanadyl sulfate in humans with non-insulin-dependent diabetes mellitus: in vivo and in vitro studies. *Metabolism.* 2000;49:400-410.

48. de Lordes Lima M, Cruz T, Pousada JC, et al. The effect of magnesium supplementation in increasing doses on the control of type 2 diabetes. *Diabetes Care.* 1998;21:682-686.

49. Rodríguez-Morán M, Guerrero-Romero F. Oral magnesium supplementation improves insulin sensitivity and metabolic control in type 2 diabetic subjects: a randomized double-blind controlled trial. *Diabetes Care.* 2003;26:1147-1152.

50. de Valk HW, Verkaaik R, van Rijn HJ, et al. Oral magnesium supplementation in insulin-requiring type 2 diabetic patients. *Diabet Med.* 1998;15:503-507.

51. Eibl NL, Kopp HP, Nowak HR, et al. Hypomagnesemia in type II diabetes: effect of a 3-month replacement therapy. *Diabetes Care.* 1995;18:188-192.

52. Eriksson J, Kohvakka A. Magnesium and ascorbic acid supplementation in diabetes mellitus. *Ann Nutr Metab.* 1995;39:217-223.

53. Jacob S, Ruus P, Hermann R, et al. Oral administration of RAC-alpha-lipoic acid modulates insulin sensitivity in patients with type-2 diabetes mellitus: a placebo-controlled pilot trial. *Free Radic Biol Med.* 1999;27:309-314.

54. Chen H, Karne RJ, Hall G, et al. High-dose oral vitamin C partially replenishes vitamin C levels in patients with type 2 diabetes and low vitamin C levels but does not improve endothelial dysfunction or insulin resistance. *Am J Physiol Heart*

Circ Physiol. 2006;290:H137-H145.

55. Derosa G, Cicero AF, Gaddi A, et al. The effect of L-carnitine on plasma lipoprotein(a) levels in hypercholesterolemic patients with type 2 diabetes mellitus. *Clin Ther.* 2003;25: 1429-1439.

56. Rahbar AR, Shakerhosseini R, Saadat N, et al. Effect of L-carnitine on plasma glycemic and lipidemic profile in patients with type II diabetes mellitus. *Eur J Clin Nutr.* 2005;59:592-596.

57. Namdul T, Sood A, Ramakrishnan L, et al. Efficacy of Tibetan medicine as an adjunct in the treatment of type 2 diabetes. *Diabetes Care.* 2001;24:175-176.

58. Liu JP, Zhang M, Wang WY, et al. Chinese herbal medicines for type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2004;(3): CD003642.

59. Vray M, Attali JR. Randomized study of glibenclamide versus traditional Chinese treatment in type 2 diabetic patients. Chinese-French Scientific Committee for the Study of Diabetes. *Diabete Metab.* 1995;21:433-439.

60. Hsia SH, Bazargan M, Davidson MB. Effect of Pancreas Tonic (an ayurvedic herbal supplement) in type 2 diabetes mellitus. *Metabolism.* 2004;53:1166-1173.

61. Krawinkel MB, Keding GB. Bitter gourd (*Momordica charantia*): a dietary approach to hyperglycemia. *Nutr Rev.* 2006;64:331-337.

62. Yeh GY, Eisenberg DM, Kaptchuk TJ, et al. Systematic review of herbs and dietary supplements for glycemic control in diabetes. *Diabetes Care.* 2003;26:1277-1294.

Identification of Individuals at High Risk of Coronary Events

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by David Fitchett MD FRCPC, Lawrence A. Leiter MD FRCPC FACP and Guy Tremblay MD FRCPC

KEY MESSAGES

- Diabetes increases the prevalence of coronary artery disease (CAD) approximately 2- to 3-fold compared to individuals without diabetes. People with diabetes develop CAD 10 to 12 years earlier than individuals without diabetes. When a person with diabetes has an acute coronary event, the short- and long-term outcomes are considerably worse than for the person without diabetes.

- People with diabetes should be considered to have a high 10-year risk of CAD events if ≥45 years and male, or ≥50 years and female. For the younger person (male <45 years or female <50 years) with diabetes, the risk of developing CAD may be assessed from the evaluation of risk factors for CAD (both classical and diabetes-related).

- When assessing the need for pharmacologic measures to reduce risk in the younger person with diabetes, it is important to consider his or her high lifetime risk of developing CAD.

INTRODUCTION

Diabetes increases the prevalence of coronary artery disease (CAD) approximately 2- to 3-fold compared to individuals without diabetes (1-3). Coronary and cerebrovascular events are responsible for >75% of the deaths in people with diabetes, and are 40 times more likely to occur than the serious consequences of microvascular disease such as end-stage renal failure (4). When a person with diabetes has an acute coronary event, the short- and long-term outcomes are considerably worse than for the person without diabetes (5,6).

Individuals at high risk of cardiovascular (CV) morbidity and mortality should receive pharmacologic vascular protective measures such as statin and angiotensin-converting enzyme (ACE) inhibitor or angiotensin II antagonist (ARB) therapy and acetylsalicylic acid (ASA) therapy. The "high-risk" threshold for dyslipidemia treatment in the general population is defined as the level of risk for hard CAD events observed in people with established CAD – a mean 20% 10-year risk of cardiac death or nonfatal myocardial infarction (MI) (7,8). Although a high proportion of people with diabetes are at high risk for CAD (9) over a 10-year period, it is recognized that some do not have a risk equivalent to a person with established CAD (10,11). The definitions of

"high risk" established in this section are those used in the present guidelines for dyslipidemia treatment and ACE inhibitor or ARB therapy and ASA therapy.

RISK FACTORS

Age is the most powerful overall predictor of CAD risk. In the general population, the average male will reach a 20% 10-year risk of a CAD event by age 60, the average female by age 65. Diabetes confers a risk that is equivalent to aging approximately 15 years, with a transition from intermediate risk to high risk in men at age 47.9 years, and in women almost 7 years later at age 54.3 years (2). It is therefore recommended that people with diabetes be considered at high risk if ≥45 years and male, or ≥50 years and female. For the younger person (male <45 years or female <50 years) with diabetes, the risk of developing CAD may be assessed from the evaluation of risk factors for CAD (both classical and diabetes-related).

Classical risk factors for CAD, such as smoking, hypertension and hyperlipidemia (elevated low-density lipoprotein cholesterol [LDL-C] and low high-density lipoprotein cholesterol), add to the risk conferred by diabetes alone (12). Diabetes-related risk factors such as duration of diabetes >15 years (13) and hyperglycemia (as determined by glycated hemoglobin [A1C] levels [14]), as well as the presence of microvascular disease (micro- or macroalbuminuria [15], impaired renal function [16] or retinopathy [17]) and features of metabolic syndrome (18), add to the risk of premature CAD events.

Type 1 diabetes is an independent risk factor for premature CVD and mortality in young adults (20 to 39 years) (19). The presence of CAD in people with type 1 diabetes is related to age, duration of diabetes, presence of retinopathy, higher A1C levels and higher albumin excretion rates, as well as to traditional CAD risk factors such as elevated total cholesterol and LDL-C cholesterol, smoking and excess body weight (20). A recent study (21) showed that for all age groups, the majority of people with type 1 diabetes had at least 1 CV risk factor. Even if an individual with type 1 diabetes has a low short-term risk of a CV event (i.e. younger and shorter duration of diabetes), his/her long-term risk is very high. In the absence of firm data on risk, individuals are classified as high-risk if >30 years old with a duration of diabetes of >15 years.

Subclinical vascular disease is common in people with diabetes (22), and the detection of unrecognized disease will immediately place a person at a high risk for CAD events. A history of chest discomfort, unexplained dyspnea, exertional leg pain (23) or erectile dysfunction (24-26) may indicate CAD or peripheral arterial disease. The presence of a carotid or femoral bruit or a low ankle brachial index (27) suggests vascular disease, and a duplex ultrasound study should be considered to establish the presence of atherosclerotic disease. Measurement of the carotid intima thickness (28) and detection of coronary calcification (29-31) and silent myocardial ischemia (32) are additional tests that can be considered in the person at risk. However, their role in the routine screening of the younger person with diabetes for risk stratification is not yet established.

RISK TABLES

Risk tables and equations such as the UKPDS allow the calculation of the absolute global risk of a coronary or CV event for an individual with type 2 diabetes with no prior history of MI or stroke (33). In the future, the SCORE risk engine (34) may be valuable in helping clinicians establish absolute vascular risk for a Canadian population. Other available risk tables, such as PROCAM (35), the CV Life Expectancy Model (36) and the Strong Heart Study (37), have limitations that may reduce their accuracy to predict outcomes, especially in a younger population with diabetes.

RISK MANAGEMENT OF PATIENTS WITH DIABETES WITHOUT CVD

Strategies to reduce CV events by initiating pharmacologic vascular protective measures could include the following: 1) a population health strategy of treating all patients with diabetes; 2) a baseline risk strategy of treating only patients at moderate to high risk; 3) an individual risk-factor strategy of treating only patients with LDL-C above a certain threshold; and 4) an age cutoff strategy of treating patients above an age when the average risk crosses from intermediate to high risk (i.e. a combination of strategies 1 and 2). An analysis of these 4 strategies (38) showed that the fourth strategy, based on the age cutoff, was a good compromise between high effectiveness and high efficiency in reducing CV events. The age transition from intermediate to high risk for CAD events of 47.9 years for men and 54.3 years for women is based on Canadian observations (2) and provides the basis for the recommendations for vascular protection.

OTHER RELEVANT GUIDELINES

RECOMMENDATIONS

1. Assessment for CAD risk should be performed periodically in people with diabetes and should include *[Grade D, Consensus]*:
   - CV history (dyspnea, chest discomfort)
   - Lifestyle (smoking, sedentary lifestyle, poor eating habits)
   - Duration of diabetes
   - Sexual function history
   - Abdominal obesity
   - Lipid profile
   - Blood pressure
   - Reduced pulses or bruits
   - Glycemic control
   - Presence of retinopathy
   - Estimated glomerular filtration rate and random albumin to creatinine ratio
   - Periodic electrocardiograms as indicated (see "Screening for the Presence of Coronary Artery Disease," p. S99).

2. The following individuals with diabetes should be considered at high risk for CV events:
   - Men aged ≥45 years, women aged ≥50 years *[Grade B, Level 2 (2)]*.
   - Men <45 years and women <50 years with ≥1 of the following *[Grade D, Consensus]*:
     - Macrovascular disease (e.g. silent myocardial infarction or ischemia, evidence of peripheral arterial disease, carotid arterial disease or cerebrovascular disease)
     - Microvascular disease (especially nephropathy and retinopathy)
     - Multiple additional risk factors, especially with a family history of premature coronary or cerebrovascular disease in a first-degree relative
     - Extreme level of a single risk factor (e.g. LDL-C >5.0 mmol/L, systolic BP >180 mm Hg)
     - Duration of diabetes >15 years with age >30 years.

REFERENCES

1. Lee WL, Cheung AM, Cape D, et al. Impact of diabetes on coronary artery disease in women and men: a meta-analysis of prospective studies. *Diabetes Care.* 2000;23:962-968.

2. Booth GL, Kapral MK, Fung K, et al. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. *Lancet.* 2006;368:29-36.

3. Lloyd-Jones DM, Leip EP, Larson MG, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. *Circulation.* 2006;113:791-798.

4. Gerstein HC. Reduction of cardiovascular events and microvascular complications in diabetes with ACE inhibitor treatment: HOPE and MICRO-HOPE. *Diabetes Metab Res Rev.* 2002;18(suppl 3):S82-S85.

5. Malmberg K, Ryden L. Myocardial infarction in patients with diabetes mellitus. *Eur Heart J.* 1988;9:259-264.

6. Malmberg K, Yusuf S, Gerstein HC, et al. Impact of diabetes on long-term prognosis in patients with unstable angina and non-Q-wave myocardial infarction: results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry. *Circulation*. 2000;102:1014-1019.

7. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106:3143-3421.

8. McPherson R, Frohlich J, Fodor G, et al. Canadian Cardiovascular Society position statement—recommendations for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease. *Can J Cardiol.* 2006;22:913-927.

9. Haffner SM, Lehto S, Ronnemaa T, et al. Mortality for coronary heart disease in subjects with type 2 diabetes and in non-diabetic subjects with and without prior myocardial infarction. *N Engl J Med*. 1998;339:229-234.

10. Evans JMM, Wang J, Morris AD. Comparison of cardiovascular risk between patients with type 2 diabetes and those who had had a myocardial infarction: cross sectional and cohort studies. *BMJ*. 2002;324:939-942.

11. Wannamethee SG, Shaper AG, Lennon L. Cardiovascular disease incidence and mortality in older men with diabetes and in men with coronary heart disease. *Heart*. 2004;90:1398-1403.

12. Turner RC, Millns H, Neil HA, et al. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). *BMJ*. 1998;316:823-828.

13. Fox CS, Sullivan L, D'Agostino RB Sr, et al. The significant effect of diabetes duration on coronary heart disease mortality: the Framingham Heart Study. *Diabetes Care*. 2004;27:704-708.

14. Selvin E, Marinopoulos S, Berkenblit G, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med*. 2004;141:421-431.

15. Dinneen SF, Gerstein HC. The association of microalbuminuria and mortality in non-insulin-dependent diabetes mellitus. A systemic overview of the literature. *Arch Intern Med*. 1997; 157:1413-1418.

16. Mann JF, Gerstein HC, Pogue J, et al. Cardiovascular risk in patients with early renal insufficiency: implications for the use of ACE inhibitors. *Am J Cardiovasc Drugs.* 2002;2:157-162.

17. Faglia E, Favales F, Calia P, et al. Cardiac events in 735 type 2 diabetic patients who underwent screening for unknown asymptomatic coronary heart disease: 5-year follow-up report from the Milan Study on Atherosclerosis and Diabetes (MiSAD). *Diabetes Care*. 2002;25:2032-2036.

18. Alexander CM, Landsman PB, Teutsch SM, et al; Third National Health and Nutrition Examination Survey (NHANES III); National Cholesterol Education Program (NCEP). NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. *Diabetes*. 2003;52:1210-1214.

19. Laing SP, Swerdlow AJ, Slater SD, et al. The British Diabetic Association Cohort Study, II: cause-specific mortality in patients with insulin-treated diabetes mellitus. *Diabet Med*. 1999;16:466-471.

20. Nathan DM, Cleary PA, Backlund JY, et al; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med*. 2005;353:2643-2653.

21. Schwab KO, Doerfer J, Hecker W, et al; DPV Initiative of the German Working Group for Pediatric Diabetology. Spectrum and prevalence of atherogenic risk factors in 27,358 children, adolescents, and young adults with type 1 diabetes. Cross-sectional data from the German diabetes documentation and quality management system (DPV). *Diabetes Care*. 2006;29:218-225.

22. Barzilay JI, Spiekerman CF, Kuller LH, et al; Cardiovascular Health Study. Prevalence of clinical and isolated subclinical cardiovascular disease in older adults with glucose disorders: the Cardiovascular Health Study. *Diabetes Care*. 2001;24:1233-1239.

23. Brand FN, Abbott RD, Kannel WB. Diabetes, intermittent claudication, and risk of cardiovascular events. The Framingham Study. *Diabetes*. 1989;38:504-509.

24. Gazzaruso C, Giordanetti S, De Amici E, et al. Relationship between erectile dysfunction and silent myocardial ischemia in apparently uncomplicated type 2 diabetic patients. *Circulation*. 2004;110:22-26.

25. Min JK, Williams KA, Okwuosa TM, et al. Prediction of coronary heart disease by erectile dysfunction in men referred for nuclear stress testing. *Arch Intern Med*. 2006;166:201-206.

26. Chiurlia E, D'Amico R, Ratti C, et al. Subclinical coronary artery atherosclerosis in patients with erectile dysfunction. *J Am Coll Cardiol*. 2005;46:1503-1506.

27. Rutter MK, Wahid ST, McComb JM, et al. Significance of silent ischemia and microalbuminuria in predicting coronary events in asymptomatic patients with type 2 diabetes. *J Am Coll Cardiol*. 2002;40:56-61.

28. Chambless LE, Heiss G, Folsom AR, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987-1993. *Am J Epidemiol*. 1997; 146:483-494.

29. Raggi P, Shaw LJ, Berman DS, et al. Prognostic value of coronary artery calcium screening in subjects with and without diabetes. *J Am Coll Cardiol*. 2004;43:1663-1669.

30. Anand DV, Lim E, Hopkins D, et al. Risk stratification in uncomplicated type 2 diabetes: prospective evaluation of the combined use of coronary artery calcium imaging and selective myocardial perfusion scintigraphy. *Eur Heart J*. 2006;27: 713-721.

31. Scholte AJ, Bax JJ, Wackers FJ. Screening of asymptomatic patients with type 2 diabetes mellitus for silent coronary artery disease: combined use of stress myocardial perfusion

imaging and coronary calcium scoring. *J Nucl Cardiol*. 2006; 13:11-18.

32. Wackers FJ, Young LH, Inzucchi SE, et al; Detection of Ischemia in Asymptomatic Diabetics Investigators. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. *Diabetes Care*. 2004;27:1954-1961.

33. Diabetes Trials Unit, Oxford Centre for Diabetes, Endocrinology & Metabolism. *UKPDS Risk Engine*. Diabetes Trials Unit, University of Oxford website. Available at: http://www.dtu.ox.ac.uk/riskengine/. Accessed September 1, 2008.

34. Conroy RM, Pyorale K, FitzGerald AP, et al; SCORE project group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J*. 2003;24:987-1003.

35. Assmann G, Cullen P, Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Munster (PROCAM) study. *Circulation*. 2002;105:310-315.

36. Grover SA, Paquet S, Levinton C, et al. Estimating the benefits of modifying risk factors of cardiovascular disease: a comparison of primary vs. secondary prevention. *Arch Intern Med*. 1998;158:655-662.

37. Lee ET, Howard BV, Wang W, et al Prediction of coronary heart disease in a population with high prevalence of diabetes and albuminuria: the Strong Heart Study. *Circulation*. 2006;113: 2897-2905.

38. Siyambalapitiya S, Bulugahapitiya U, Sithole J, et al. Combining population health and baseline risk strategy by determining an age cut off for initiating statins in patients with diabetes: a population-based study. *Diabetes Care*. 2007;30: 2025-2059.

Screening for the Presence of Coronary Artery Disease

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee
The initial draft of this chapter was prepared by Paul Poirier MD PhD FRCPC FACC FAHA

KEY MESSAGES

- Compared to people without diabetes, people with diabetes (especially women) are at higher risk of developing heart disease, and at an earlier age. Unfortunately, a large proportion will have no symptoms before either a fatal or nonfatal myocardial infarction (MI). Hence, it is desirable to identify patients at high risk for vascular events, especially patients with established severe coronary artery disease (CAD).

- In individuals at high risk of CAD (based on age, gender, description of chest pain, history of prior MI and the presence of several other risk factors), exercise stress testing is useful for the assessment of prognosis.

- Exercise capacity is frequently impaired in people with diabetes due to the high prevalence of obesity, sedentary lifestyle, peripheral neuropathy (both sensory and motor) and vascular disease. For those unable to perform an exercise test, pharmacologic or nuclear stress imaging may be required.

INTRODUCTION

The majority (65 to 80%) of people with diabetes will die from heart disease (1,2). Compared to people without diabetes, people with diabetes (especially women) are at higher risk of developing heart disease, and at an earlier age. A high proportion of deaths occur in patients with no prior signs or symptoms of cardiovascular disease (CVD). Furthermore, people with diabetes have a high prevalence of silent myocardial ischemia, and almost one-third of myocardial infarctions (MIs) occur without recognized or typical symptoms (silent MIs) (3). The goals of screening are to improve life expectancy and quality of life by preventing MI and heart failure through the early detection of coronary artery disease (CAD).

STRESS TESTING

Exercise stress testing is useful in patients at high risk of CAD for the assessment of prognosis and the identification of individuals who may benefit from coronary artery revascularization to improve long-term survival. The most predictive clinical observation for CAD in the person with or without diabetes is a history of chest pain or discomfort, but these features will be absent in a significant number (20 to 50%) of people with diabetes (4-10). Clinical findings such as dyspnea on exertion, resting electrocardiogram (ECG) abnormalities

or multiple risk factors for atherosclerosis may also indicate the presence of CAD. Recognition of such features is of clinical importance, as the outcome of CAD events is worse in people with diabetes when shortness of breath is the primary symptom (4).

The presence of CAD risk factors and resting ECG abnormalities identify patients with diabetes at increased risk of important CAD and abnormal stress ECG or perfusion imaging results (11). A resting ECG at the time of diagnosis of diabetes also provides a baseline to which future ECGs can be compared. In patients considered to be at high risk for CAD, a repeat resting ECG may detect changes that result from silent MI and lead to earlier detection of critical CAD. There is evidence that early screening and intervention in people with diabetes and with silent ischemia is beneficial and may improve long-term survival (7,12). Screening with exercise ECG stress testing will find 3-vessel CAD in 13 to 15% of those with abnormal stress test findings (10,13) and lead to angiography with revascularization in 1 to 3% of asymptomatic individuals (10,13-15). The Definition of Ischemia in Asymptomatic Diabetes (DIAD) study (11) is prospectively investigating the value of routine adenosine stress myocardial perfusion scanning in asymptomatic patients with type 2 diabetes ≥55 years for the prevention of coronary events. The baseline study showed either perfusion defects or stress-induced ECG abnormalities in 22% of patients and large defects in 6%. In this study, multiple risk factors for CAD did not help to predict the patients with positive screening tests for CAD. Yet, a randomized pilot study on the impact of stress testing to screen for CAD in asymptomatic subjects with diabetes suggested a significant reduction in cardiac death and MI (16). Larger and adequately powered studies are necessary to support this provocative observation before clinical practice is changed. However, it is important to keep in mind that the goals of screening for CAD are to improve life expectancy and quality of life by preventing MI and heart failure through early detection.

The choice of initial stress test should be based on evaluation of the resting ECG, the individual's ability to exercise, and local expertise and technology. ECG abnormalities that limit the diagnostic accuracy of a stress ECG include resting ST depression (≥1 mm), left bundle branch block (LBBB) or right bundle branch block, an intraventricular conduction defect with a QRS duration >120 ms, ventricular paced

rhythm or pre-excitation. Individuals with these resting ECG findings should have a stress test with an imaging modality such as scintigraphic myocardial perfusion imaging or echocardiography.

The strongest and most consistent prognostic marker identified during exercise ECG stress testing is the person's maximum exercise capacity (4). Although exercise capacity is decreased in individuals with diabetes (17,18), it is still of prognostic importance (4). Silent ischemia is most likely to occur in individuals with diabetes who are older (mean age 65 years) and have elevated total cholesterol and proteinuria (14). An ECG with ST-T abnormalities at rest has been shown to be most predictive for silent ischemia (OR 9.27, 95% CI, 4.44-19.38) and the only significant predictor of silent ischemia in women (14). The relevance of ST-T abnormalities as a predictive factor for silent ischemia emphasizes the importance of recording a resting ECG in most individuals with type 2 diabetes. An abnormal ECG may indicate the need for further investigations and result in the earlier detection and treatment of CAD (14). An abnormal exercise ECG is associated with an annual CAD event rate of 2.1%, compared with 0.97% in subjects with normal exercise ECG (15). Myocardial ischemia (whether silent or symptomatic) detected during exercise stress testing in individuals with diabetes is associated with poorer long-term survival compared to individuals without diabetes (7). Silent MI is common (40%) in older asymptomatic people with type 2 diabetes, but is more frequent (65%) in those with diabetes who also have microalbuminuria (19). People with diabetes and silent ischemia have an annual event rate for CAD of 6.2% (50% of events were new-onset angina and 50% cardiac death or MIs) (20). Thus, silent MI is a prelude not only to symptomatic ischemia, but also to potentially fatal events. Also, it has been shown in a randomized trial in patients with silent ischemia (the vast majority of whom did not have diabetes) that long-term anti-ischemic drug therapy (~11 years follow-up) reduces cardiac events (cardiac death, nonfatal MI, acute coronary syndrome or revascularization) with preservation of ejection fraction (21).

Exercise capacity is frequently impaired in people with diabetes due to the high prevalence of obesity, sedentary lifestyle, peripheral neuropathy (both sensory and motor) and vascular disease in this population. Individuals who cannot adequately exercise on a stress test have a poorer prognosis than those who can, regardless of the reason for this incapacity. Perfusion imaging also provides important prognostic information. Myocardial perfusion imaging has similar predictive value for cardiac death and nonfatal MI in individuals with diabetes as in those without diabetes (22). For those unable to perform an exercise ECG stress test, pharmacologic stress imaging using dipyridamole, adenosine or dobutamine testing is required. Stress echocardiography and stress nuclear imaging have similar values for cardiac events in the general population (23), but no comparative data are available for the person with diabetes. In a meta-analysis of perfusion imaging, an abnormal scan was predictive of future CAD events in subjects with and without diabetes. However, the cardiac event rate in individuals with diabetes was significantly greater than in those without diabetes (22). The choice of the optimal imaging modality to detect stress-induced MI is best determined by local availability and expertise. The utility of newer CAD diagnostic modalities such as computed tomography angiography, coronary artery calcium scoring and cardiac magnetic resonance imaging is currently unknown in terms of guiding management decisions in patients with type 2 diabetes (24).

RECOMMENDATIONS

1. In the following individuals, in addition to CAD risk assessment, a baseline resting ECG should be performed *[Grade D, Consensus]* in:
   - All individuals >40 years of age
   - All individuals with duration of diabetes >15 years
   - All individuals (regardless of age) with hypertension, proteinuria, reduced pulses or vascular bruits

   A repeat resting ECG should be performed every 2 years in people considered at high risk for CV events *[Grade D, Consensus]*.

2. Persons with diabetes should undergo investigation for CAD by exercise ECG stress testing as the initial test *[Grade D, Consensus]* in the presence of the following:
   - Typical or atypical cardiac symptoms (e.g. unexplained dyspnea, chest discomfort) *[Grade C, Level 3 (4)]*
   - Resting abnormalities on ECG (e.g. Q waves) *[Grade D, Consensus]*
   - Peripheral arterial disease (abnormal ankle-brachial ratio) *[Grade D, Level 4 (9)]*
   - Carotid bruits *[Grade D, Consensus]*
   - Transient ischemic attack *[Grade D, Consensus]*
   - Stroke *[Grade D, Consensus]*

3. Pharmacologic stress echocardiography or nuclear imaging should be used in individuals with diabetes in whom resting ECG abnormalities preclude the use of exercise ECG stress testing (e.g. LBBB or ST-T abnormalities) *[Grade D, Consensus]*. In addition, individuals who require stress testing and are unable to exercise should undergo pharmacologic stress echocardiography or nuclear imaging *[Grade C, Level 3 (22)]*.

4. Individuals with diabetes who demonstrate ischemia at low exercise capacity (<5 metabolic equivalents [METs]) on stress testing should be referred to a cardiac specialist *[Grade D, Consensus]*.

OTHER RELEVANT GUIDELINES

REFERENCES

1. Lee WL, Cheung AM, Cape D, et al. Impact of diabetes on coronary artery disease in women and men: a meta-analysis of prospective studies. *Diabetes Care.* 2000;23:962-968.

2. Booth GL, Kapral MK, Fung K, et al. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. *Lancet.* 2006;368:29-36.

3. Cohn PF, Fox KM, Daly C. Silent myocardial ischemia. *Circulation.* 2003;108:1263-1277.

4. Zellweger MJ, Hachamovitch R, Kang X, et al. Prognostic relevance of symptoms versus objective evidence of coronary artery disease in diabetic patients. *Eur Heart J.* 2004;25:543-550.

5. Rajagopalan N, Miller TD, Hodge DO, et al. Identifying high-risk asymptomatic diabetic patients who are candidates for screening stress single-photon emission computed tomography imaging. *J Am Coll Cardiol.* 2005;45:43-49.

6. Weiner DA, Ryan TJ, Parsons L, et al. Significance of silent myocardial ischemia during exercise testing in patients with diabetes mellitus: a report from the Coronary Artery Surgery Study (CASS) Registry. *Am J Cardiol.* 1991;68:729-734.

7. Inoguchi T, Yamashita T, Umeda F, et al. High incidence of silent myocardial ischemia in elderly patients with non insulin-dependent diabetes mellitus. *Diabetes Res Clin Pract.* 2000;47:37-44.

8. Nesto RW, Phillips RT, Kett KG, et al. Angina and exertional myocardial ischemia in diabetic and nondiabetic patients: assessment by exercise thallium scintigraphy. *Ann Intern Med.* 1988;108:170-175.

9. Bacci S, Villella M, Villella A, et al. Screening for silent myocardial ischaemia in type 2 diabetic patients with additional atherogenic risk factors: applicability and accuracy of the exercise stress test. *Eur J Endocrinol.* 2002;147:649-654.

10. Wackers FJ, Young LH, Inzucchi SE, et al; Detection of Ischemia in Asymptomatic Diabetics Investigators. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. *Diabetes Care.* 2004;27:1954-1961.

11. Myers J, Prakash M, Froelicher V, et al. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med.* 2002;346:793-801.

12. Sorajja P, Chareonthaitawee P, Rajagopalan N, et al. Improved survival in asymptomatic diabetic patients with high-risk SPECT imaging treated with coronary artery bypass grafting. *Circulation.* 2005;112(9 suppl):I311-I316.

13. Paillole C, Ruiz J, Juliard JM, et al. Detection of coronary artery disease in diabetic patients. *Diabetologia.* 1995;38:726-731.

14. Prevalence of unrecognized silent myocardial ischemia and its association with atherosclerotic risk factors in noninsulin-dependent diabetes mellitus. Milan Study on Atherosclerosis and Diabetes (MiSAD) Group. *Am J Cardiol.* 1997;79:134-139.

15. Faglia E, Favales F, Calia P, et al; Milan Study on Atherosclerosis and Diabetes (MiSAD). Cardiac events in 735 type 2 diabetic patients who underwent screening for unknown asymptomatic coronary heart disease: 5-year follow-up report from the Milan Study on Atherosclerosis and Diabetes (MiSAD). *Diabetes Care.* 2002;25:2032-2036.

16. Faglia E, Manuela M, Antonella Q, et al. Risk reduction of cardiac events by screening of unknown asymptomatic coronary artery disease in subjects with type 2 diabetes mellitus at high cardiovascular risk: an open-label randomized pilot study. *Am Heart J.* 2005;149:e1-e6.

17. Poirier P, Garneau C, Bogaty P, et al. Impact of left ventricular diastolic dysfunction on maximal treadmill performance in normotensive subjects with well-controlled type 2 diabetes mellitus. *Am J Cardiol.* 2000;85:473-477.

18. Poirier P, Bogaty P, Garneau C, et al. Diastolic dysfunction in normotensive men with well-controlled type 2 diabetes: importance of maneuvers in echocardiographic screening for preclinical diabetic cardiomyopathy. *Diabetes Care.* 2001;24:5-10.

19. Rutter MK, McComb JM, Brady S, et al. Silent myocardial ischemia and microalbuminuria in asymptomatic subjects with non-insulin-dependent diabetes mellitus. *Am J Cardiol.* 1999;83:27-31.

20. Rutter MK, Wahid ST, McComb JM, et al. Significance of silent ischemia and microalbuminuria in predicting coronary events in asymptomatic patients with type 2 diabetes. *J Am Coll Cardiol.* 2002;40:56-61.

21. Erne P, Schoenenberger AW, Zuber M, et al, Effects of anti-ischaemic drug therapy in silent myocardial ischaemia type 1: the Swiss Interventional Study on Silent Ischaemia type 1 (SWISSI I): a randomized, controlled pilot study. *Eur Heart J* 2007;28:2110-2117.

22. Shaw LJ, Iskandrian AE. Prognostic value of gated myocardial perfusion SPECT. *J Nucl Cardiol.* 2004;11:171-185.

23. Schinkel AF, Bax JJ, Elhendy A, et al. Long-term prognostic value of dobutamine stress echocardiography compared with myocardial perfusion scanning in patients unable to perform exercise tests. *Am J Med.* 2004;117:1-9.

24. Bax JJ, Young LH, Frye RL, et al. Screening for coronary artery disease in patients with diabetes. *Diabetes Care.* 2007;30:2729-2736.

COMPLICATIONS AND COMORBIDITIES

Vascular Protection in People With Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee
The initial draft of this chapter was prepared by David Fitchett MD FRCPC and Maria Kraw MD FRCPC

KEY MESSAGES

- The first priority in the prevention of macrovascular complications should be reduction of cardiovascular (CV) risk through a comprehensive, multifaceted approach, integrating both lifestyle and pharmacologic measures.

- Treatment with angiotensin-converting enzyme (ACE) inhibitors has been shown to result in better outcomes for people with atherosclerotic vascular disease, recent myocardial infarction, left ventricular impairment and heart failure. In a similar population, angiotensin II receptor antagonists have been shown to be noninferior to ACE inhibitors for vascular protection.

- Low-dose acetylsalicylic acid therapy may be considered in people with stable CVD. The decision to prescribe antiplatelet therapy for primary prevention of CV events, however, should be based on individual clinical judgment.

VASCULAR PROTECTION

In order to reduce the excessive cardiovascular disease (CVD) risk associated with diabetes, all coronary risk factors must be addressed and treated aggressively. The Steno-2 studies (1,2) demonstrated that a target-driven, comprehensive, multifaceted approach to risk factor management applied to high-risk patients with type 2 diabetes and microalbuminuria over a period of 7 years resulted in a >50% reduction of CVD (HR 0.47, 95% CI, 0.24–0.73)

and microvascular events (nephropathy HR 0.39, 95% CI, 0.17–0.87; retinopathy HR 0.42, 95% CI, 0.21–0.86). It is likely that similar relative benefits would be achieved by applying a comprehensive, multifaceted approach to risk factor control in high-risk patients with diabetes who do not have microalbuminuria.

Patients at the highest risk for CV events include those who have diabetes and atherosclerotic vascular disease that includes either clinically recognized disease (e.g. coronary artery disease [CAD], peripheral arterial disease [PAD] and cerebrovascular disease) or clinically silent disease (e.g. silent myocardial ischemia or infarction, and PAD identified by the presence of bruits or abnormal ultrasound or ankle-brachial index). Other patients at high risk include those with microvascular disease and multiple risk factors or extreme levels of a single risk factor (Table 1) (see also "Identification of Individuals at High Risk of Coronary Events," p. S95).

When deciding on appropriate treatment strategies, it is important to prioritize treatment goals. Since some of the available treatments, such as angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists (ARBs), have potential uses in controlling blood pressure (BP) as well as reducing the risks for CVD and nephropathy, it can be challenging to integrate the data to make recommendations for one application over another. Table 2 summarizes the priorities for vascular and renal protection, while Table 3 summarizes recommended interventions for vascular protection.

Table 1. People with diabetes considered at high risk of a CV event*

- Men aged ≥45 years, women aged ≥50 years
- Men <45 years and women <50 years with ≥1 of the following:
  - Macrovascular disease (MI or ischemia, CAD, PAD, stroke, transient ischemic attack, cerebrovascular disease, evidence of silent MI or ischemia or PAD)
  - Microvascular disease (especially nephropathy or retinopathy)
  - Multiple additional risk factors, especially with a family history of premature coronary or cerebrovascular disease in a first-degree relative
  - Extreme level of a single risk factor (e.g. LDL-C >5.0 mmol/L, systolic BP >180 mm Hg)
  - Duration of diabetes >15 years with age >30 years

*See also "Identification of Individuals at High Risk of Coronary Events," p. S95

BP = blood pressure
CAD = coronary artery disease
CV = cardiovascular

LDL-C = low-density lipoprotein cholesterol
MI = myocardial infarction
PAD = peripheral arterial disease

Table 2. Priorities for vascular and renal protection

Clinical strategy	Target population
Step 1: Initiate vascular protection	All people with diabetes (see Table 3)
Step 2: Treat elevated BP	All people with diabetes whose BP remains ≥130/80 mm Hg after applying vascular protective measures (see "Treatment of Hypertension," p. S115)
Step 3: Initiate renal protection	All people with diabetes who have proteinuria after applying vascular measures and after achieving BP <130/80 mm Hg (See "Chronic Kidney Disease in Diabetes," p. S126)

BP = blood pressure

Table 3. Interventions for vascular protection

Population	Interventions (in alphabetical order)

All people with diabetes	• Lifestyle modifications
	  • Achievement and maintenance of a healthy body weight (see "Management of Obesity in Diabetes," p. S77)
	  • Healthy diet (see "Nutrition Therapy," p. S40)
	  • Regular physical activity (see "Physical Activity and Diabetes," p. S37)
	  • Smoking cessation
	• Optimize BP control (see "Treatment of Hypertension," p. S115)
	• Optimize glycemic control (see "Targets for Glycemic Control," p. S29)

People with diabetes considered at high risk of a CV event (see Table 1)	• ACE inhibitor or ARB therapy (see Recommendation #2) • Antiplatelet therapy (see Recommendation #3) • Lipid-lowering medication (primarily statins) (see "Dyslipidemia," p. S107)

ACE = angiotensin converting enzyme
ARB = angiotension II receptor antagonist
BP = blood pressure
CV = cardiovascular

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM INHIBITION

The renin-angiotensin-aldosterone system (RAAS) plays a central role in the pathophysiology of vascular and cardiac disease, especially in people with diabetes. Interruption of the RAAS with ACE inhibitors has been shown to result in better outcomes for people with atherosclerotic vascular disease, recent myocardial infarction (MI), left ventricular (LV) impairment and heart failure.

The Heart Outcomes Prevention Evaluation (HOPE) study (3) examined the hypothesis that ACE inhibitors would reduce the incidence of acute vascular events (CV mortality, nonfatal MI and stroke) in individuals at high risk. Subjects included in the HOPE trial were >55 years of age and had proven coronary disease, cerebrovascular disease or PAD, or diabetes plus ≥1 additional risk factor for vascular disease. In the overall population, ramipril 10 mg daily reduced the primary endpoint by 22% (p<0.001), with a significant reduction of each of its components (CV death 26% [p<0.001], nonfatal MI 20% [p<0.001] and stroke 32% [p<0.001]). The MICRO-HOPE analysis (4) of the 38% of subjects in the HOPE study with diabetes (n=3577) showed an enhanced benefit from ramipril in this population. CV death was reduced by 37% (p<0.0001), MI by 22% (p<0.01) and stroke by 33% (p<0.0074). The subgroup of 2458 subjects with diabetes and CVD had a significant reduction of the primary outcome. In the subgroup of 1119 subjects with diabetes and no established CVD, the reduction of the primary endpoint did not achieve significance. Other benefits observed in the MICRO-HOPE trial included a reduced progression of nephropathy and reduced development of heart failure.

The European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA) study (5) included 12 218 subjects with CAD (prior MI, history of revascularization, angiographically proven coronary disease with >70% stenosis and chest pain with abnormal stress testing). Treatment with perindopril 8 mg daily resulted in a significant 20% reduction of the primary composite endpoint of CV mortality, resuscitated cardiac arrest and nonfatal MI (p<0.0003). In the 1502 subjects with diabetes enrolled in the EUROPA study (6), the benefits from perindopril were similar to those observed in the overall group; however, the sample size was too small to show a statistically significant benefit in this subgroup.

The Prevention of Events with Angiotensin Converting Enzyme inhibition (PEACE) study (7) randomized 8290 subjects with stable CAD and normal or mildly impaired LV function to receive either trandolapril 4 mg daily or placebo. A modified primary endpoint of CV death, nonfatal MI and coronary revascularization was not significantly reduced (HR 0.96, 95% CI, 0.88–1.06) during the median follow-up period of 4.8 years. The majority of endpoints were due to coronary revascularization, which was not modified by ACE inhibition.

A combined analysis (8) of the 3 trials (HOPE, EUROPA and PEACE) showed that all-cause mortality, CV mortality, nonfatal MI, all stroke, congestive heart failure and revascularization by coronary bypass surgery, but not percutaneous coronary intervention, were reduced by ACE inhibition treatment. The combined endpoint of CV death, nonfatal MI and stroke was reduced by 18% (OR 0.82, 95% CI, 0.76–0.88). A meta-analysis (9) of 7 studies of ACE inhibition in people with CAD or diabetes plus 1 additional risk factor treated for

at least 2 years showed decreased overall mortality (OR 0.86, 95% CI, 0.79–0.93), CV mortality (OR 0.81, 95% CI, 0.73–0.90), MI (OR 0.82, 95% CI, 0.75–0.89) and stroke (OR 0.77, 95% CI, 0.66–0.88).

Whether the benefits of ACE inhibition result from a reduction of BP remains controversial. The benefits of ACE inhibition in both the HOPE and EUROPA trials were observed in individuals with or without a history of hypertension, and in those with higher and lower BP readings (4,5). Furthermore, recent analyses of BP trials have indicated a benefit of ACE inhibition beyond that of BP lowering (10). Also, trials of other agents such as calcium channel blockers, which lower BP in normotensive individuals with CAD, have failed to reduce coronary events other than those related to a reduction of angina (11).

The HOPE and EUROPA studies confirmed the benefit of ACE inhibition in people with diabetes and established vascular disease (4,5). The HOPE study is the only study that has included individuals with diabetes and no evident vascular disease. In this relatively small subgroup, the point estimate of benefit was of similar magnitude to the overall group, yet did not achieve significant benefit. Hence, the level of evidence and the recommendation are less robust for this population than for people with both diabetes and CVD.

ARBs have been shown to be noninferior to ACE inhibition for the prevention of events in patients with heart failure and in those with reduced LV ejection fraction after MI. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) study (12) compared the vascular protective properties of the ACE inhibitor ramipril with the ARB telmisartan and the combination of the ACE and the ARB in patients at high risk for vascular events. Of the 25 620 patients entered in the study, 9632 had diabetes. Of these patients, 7406 had diabetes and vascular disease, and 2226 had "high-risk diabetes." The ONTARGET patients with "high-risk diabetes" (defined as diabetes with non-macrovascular end-organ damage [i.e. with diabetic nephropathy or retinopathy]) were different from the HOPE patients (diabetes with ≥1 CV risk factors). In the overall study, telmisartan 80 mg daily was noninferior to ramipril 10 mg daily for the primary endpoint of death, MI, stroke and admission to hospital with heart failure, when administered for a median period of 56 months (RR 1.01, 95% CI, 0.94–1.09). The telmisartan-treated patients had less cough and angioedema, but more hypotensive episodes. The combination of ramipril and telmisartan was not superior to ramipril alone, and hypotensive adverse effects, including syncope were more frequent in the dual-treatment arm. For patients with diabetes, the primary end-point relative risk point estimate was close to 1 and similar to the group without diabetes, both for those receiving telmisartan compared to ramipril, as well as for those receiving the combination of telmisartan and ramipril compared to ramipril alone. For patients with diabetes and nonvascular end-organ dam-

age, the point estimate was also close to 1, however due to the small sample size the confidence intervals were wide. In summary, for patients with diabetes with vascular disease, the ARB telmisartan was not inferior to ramipril to prevent vascular events, however no confidence intervals or noninferiority margins for this population have yet been published. For patients with diabetes and nonvascular end-organ damage the sample size is too small to make any conclusive recommendation.

ANTIPLATELET THERAPY

In addition to traditional risk factors for CVD such as smoking, hypertension, hyperglycemia and dyslipidemia, atherosclerosis in people with diabetes can be accelerated by a procoagulant state. Individuals with diabetes have a variety of alterations in platelet function that can predispose them to increased platelet activation and thrombosis, including increased turnover (13), enhanced aggregation (14) and increased thromboxane synthesis (15). The efficacy of antiplatelet agents in people with diabetes also appears to be reduced, particularly in those with poor metabolic control (16,17).

Acetylsalicylic acid (ASA) is the antiplatelet agent most commonly studied in the prevention of CV events in people with diabetes. A number of primary, mixed primary/secondary, and secondary CV event prevention trials have studied the effect of ASA in diabetes with varied results. The US Physicians Health Study (18) was a primary prevention trial with a subgroup of 533 male physicians with diabetes treated with 325 mg ASA every 2 days. ASA use reduced the risk of MI by 60%, although the results were not significant due to the small number of events (11/275 in the ASA group vs. 26/258 in the placebo group, p=0.22). The Primary Prevention Project (PPP) trial (19) studied the effect of low-dose ASA (100 mg/day) in over 1000 people with diabetes and found a marginal decrease in major CV events (RR 0.90, 95% CI, 0.50–1.62) with a nonsignificant 23% increase in CV deaths. This result is in contrast to the significant 41% reduction in major CV events seen in individuals without diabetes. The Hypertension Optimal Treatment (HOT) (20) trial studied the effect of 75 mg ASA daily in a subset of 1501 high-risk subjects with diabetes and hypertension. Fewer than 10% of subjects had clinical evidence of previous MI, stroke or other CAD. In the whole HOT population, ASA reduced the risk of pooled CV events by 15% and the risk of MI by 36%. Specific data on the diabetes subgroup were not included, but the subjects with diabetes and CVD were reported to have had similar outcomes to the overall HOT population.

The Antithrombotic Trialists (21) reported a meta-analysis of 195 randomized trials of antiplatelet therapy published up to 1997, including 9 trials with almost 5000 people with diabetes. Compared to a 22% reduction in the risk of major CV events among all 140 000 high-risk subjects on antiplatelet therapy, subjects with diabetes showed no significant benefit

(7±8% risk reduction). Within this meta-analysis, the Early Treatment Diabetic Retinopathy Study (ETDRS) (22) was the only trial specifically designed to examine the effect of high-dose ASA in high-risk subjects with diabetes and retinopathy. The reduction in serious vascular events (vascular death, non-fatal MI, nonfatal stoke) was nonsignificant (RR 0.91, 99% CI, 0.75–1.11), although a larger reduction (although still nonsignificant) was noted for fatal and nonfatal MI (RR 0.83, 99% CI, 0.66–1.04).

Taken together, these studies suggest that ASA therapy may confer less benefit for CV event reduction in individuals with diabetes than in those without diabetes. This may be due to increased ASA resistance in people with diabetes, as well as ASA-insensitive mechanisms of platelet activation and thrombus formation. Given the known benefit of ASA in secondary prevention of vascular events in the general population (21) and a trend toward MI reduction in people with diabetes and CAD (22), it is reasonable to consider prescribing ASA for people with diabetes and CAD. The decision to prescribe ASA for primary prevention of CV events should be based on individual clinical judgment given the lack of evidence for benefit and the side effects of long-term use.

If an antiplatelet agent is to be used, ASA appears to be as effective as other antiplatelet agents (20) and may be the best choice given that it is the most widely studied and the most economical. Patients who cannot tolerate ASA should substitute an alternate antiplatelet agent, such as clopidogrel. Clopidogrel is an inhibitor of adenosine diphosphate-induced platelet aggregation that is effective for secondary prevention in people with diabetes. In the posthoc analysis of the diabetic subgroup (1914 patients) of the Clopidogrel Versus Aspirin in Patients with Risk of Ischemic Events (CAPRIE) trial, the composite vascular endpoint (ischemic stroke, MI or vascular death) occurred in 15.6% of those randomized to daily treatment with 75 mg clopidogrel vs. 17.7% of those on 325 mg of ASA (p=0.42) (23). The addition of clopidogrel to low-dose ASA was not shown to be of benefit in high-risk subjects with diabetes in the Clopidogrel and Aspirin Versus Aspirin Alone for the Prevention of Atherothrombotic Events (CHARISMA) trial (24).

The effective dose of ASA in people with diabetes remains controversial. It has been suggested that due to the increase in platelet turnover and thromboxane synthesis in diabetes, higher doses or multiple daily dosing of ASA may be preferred (16). Clinical trials in subjects without diabetes suggest no differences in daily ASA dosages in terms of reducing CV risk. Similar results were seen in both the ETDRS and the PPP trials, despite the use of 650 mg per day in the former and 100 mg per day in the latter. There have been no clinical trials on whether multiple daily dosing would improve CV outcomes. Low-dose ASA (75–325 mg daily) is often recommended to limit both gastrointestinal (GI) toxicity and the potential adverse effects of prostaglandin inhibition on renal function or BP control.

ASA therapy does not increase the risk of vitreous hemorrhage in people with diabetic retinopathy (17), nor does it increase stroke or fatal bleeds in those with adequately controlled hypertension (18). Antiplatelet agents should not be used in people with inherited or acquired bleeding disorders, recent GI bleeding or serious hepatic failure. ASA should not be used in individuals <21 years of age because of the risk of Reye syndrome.

RECOMMENDATIONS

1. The first priority in the prevention of diabetes complications should be the reduction of CV risk by vascular protection through a comprehensive, multifaceted approach *[Grade D, Consensus, for all people with diabetes; Grade A, Level 1A (1), for people with type 2 diabetes age >40 years with microalbuminuria]* as follows:
   - For *all* people with diabetes (in alphabetical order):
     - Lifestyle modification
       - Achievement and maintenance of a healthy body weight
       - Healthy diet
       - Regular physical activity
       - Smoking cessation
     - Optimize BP control
     - Optimize glycemic control
   - For all people with diabetes considered at *high risk* of a CV event (in alphabetical order):
     - ACE inhibitor or ARB therapy
     - Antiplatelet therapy (as recommended)
     - Lipid-lowering medication (primarily statins)

2. Individuals with diabetes at high risk for CV events should receive an ACE inhibitor or ARB at doses that have demonstrated vascular protection *[Grade A, Level 1A, for people with vascular disease (4,12); Grade B, Level 1A, for other high-risk groups (4,12)]*.

3. Low-dose ASA therapy (81–325 mg) may be considered in people with stable CVD *[Grade D, Consensus]*. Clopidogrel (75 mg) may be considered in people unable to tolerate ASA *[Grade D, Consensus]*. The decision to prescribe antiplatelet therapy for primary prevention of CV events, however, should be based on individual clinical judgment *[Grade D, Consensus]*.

OTHER RELEVANT GUIDELINES

Management of Acute Coronary Syndromes, p. S119
Treatment of Diabetes in People With Heart Failure, p. S123

REFERENCES

1. Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med*. 2003;348:383-393.

2. Gaede P, Lund-Andersen H, Parving H, et al. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med*. 2008;358:580-591.

3. Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med*. 2000;342:145-153.

4. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet*. 2000;355:253-259.

5. Fox KM; EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet*. 2003;362:782-788.

6. Daly CA, Fox KM, Remme WJ, et al; EUROPA Investigators. The effect of perindopril on cardiovascular morbidity and mortality in patients with diabetes in the EUROPA study: results from the PERSUADE substudy. *Eur Heart J*. 2005;26:1369-1378.

7. Braunwald E, Domanski W, Fowler SE, et al; PEACE Investigators. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med*. 2004;351:2058-2068.

8. Dagenais GR, Pogue J, Fox K, et al. Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. *Lancet*. 2006;368:581-588.

9. Danchin N, Cucherat M, Thuillez C, et al. Angiotensin-converting enzyme inhibitors in patients with coronary artery disease and absence of heart failure or left ventricular systolic dysfunction: an overview of long-term randomized controlled trials. *Arch Intern Med*. 2006;166:787-796.

10. Verdecchia P, Reboldi G, Angeli F, et al. Angiotensin-converting enzyme inhibitors and calcium channel blockers for coronary heart disease and stroke prevention. *Hypertension*. 2005;46:386-392.

11. Poole-Wilson PA, Lubsen J, Kirwan BA, et al; A Coronary disease Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system investigators. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial. *Lancet*. 2004;364:849-857.

12. The ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;385;15:1547-1559.

13. DiMinno G, Silver MJ, Cerbone AM, et al. Trial of repeated low-dose aspirin in diabetic angiopathy. *Blood*. 1986;68:886-891.

14. Halushka PV, Rogers RC, Loadholt CB, et al. Increased platelet thromboxane synthesis in diabetes mellitus. *J Lab Clin Med*. 1981;97:87-96.

15. Davi G, Catalano I, Averna M, et al. Thromboxane biosynthesis and platelet function in type II diabetes mellitus. *N Engl J Med*. 1990;322:1769-1774.

16. Watala C, Golanski J, Pluta J, et al. Reduced sensitivity of platelets from type 2 diabetic patients to acetylsalicylic acid (aspirin) — its relation to metabolic control. *Thromb Res*. 2004;113:101-113.

17. Friend M, Vucenik I, Miller M. Platelet responsiveness to aspirin in patients with hyperlipidaemia. *BMJ*. 2003;326:82-83.

18. Final report on the aspirin component of the ongoing Physicians' Health Study. Steering Committee of the Physicians' Health Study Research Group. *N Engl J Med*. 1989;321:129-135.

19. Sacco M, Pellegrini F, Roncaglioni MC, et al; PPP Collaborative Group. Primary prevention of cardiovascular events with low-dose aspirin and vitamin E in type 2 diabetic patients: results of the Primary Prevention Project (PPP) trial. *Diabetes Care*. 2003;26:3264-3272.

20. Hansson L, Zanchetti Al, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. HOT Study Group. *Lancet*. 1998;351:1755-1762.

21. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction and stroke in high risk patients. *BMJ*. 2002;324:71-86.

22. Aspirin effects on mortality and morbidity in patients with diabetes mellitus. Early Treatment Diabetic Retinopathy Study report 14. ETDRS Investigators. *JAMA*. 1992;268:1292-1300.

23. Bhatt D, Marso S, Hirsch A, et al. Amplified benefit of clopidogrel versus aspirin in patients with diabetes mellitus. *Am J Cardiol*. 2002;90:625-628.

24. CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med*. 2006;354;16.

Dyslipidemia

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Lawrence A. Leiter MD FRCPC FACP, Jacques Genest MD FRCPC, Stewart B. Harris MD MPH FCFP FACPM, Gary Lewis MD FRCPC, Ruth McPherson MD PhD FRCPC, George Steiner MD FRCPC and Vincent Woo MD FRCPC

KEY MESSAGES

- The beneficial effects of lowering low-density lipoprotein (LDL-C) with statin therapy apply equally well to people with diabetes as to those without.

- The primary target for most people with diabetes is an LDL-C of ≤2.0 mmol/L, which is generally achievable with statin monotherapy.

- The secondary goal is a total cholesterol/high-density lipoprotein cholesterol ratio of <4.0. This is often more difficult to achieve than the primary LDL-C target, and may require improved glycemic control, intensification of lifestyle changes (weight loss, physical activity, smoking cessation) and, if necessary, pharmacologic interventions.

DYSLIPIDEMIA IN DIABETES

Diabetes is associated with a high risk of vascular disease (2- to 4-fold greater than that of individuals without diabetes), with cardiovascular disease (CVD) being the primary cause of death among people with type 1 or type 2 diabetes (1-3). Aggressive management of all CV risk factors, including dyslipidemia, is therefore generally necessary (4). The most common lipid pattern in people with type 2 diabetes consists of hypertriglyceridemia (hyper-TG), low high-density lipoprotein cholesterol (HDL-C) and normal plasma concentrations of low-density lipoprotein cholesterol (LDL-C). However, in the presence of even mild hyper-TG, LDL-C particles are typically small and dense and may be more susceptible to oxidation. In addition, chronic hyperglycemia promotes the glycation of LDL-C, and both these processes are believed to increase the atherogenicity of LDL-C. In those with type 1 diabetes, plasma lipid and lipoprotein concentrations may be normal, but there may be oxidation and glycation of the lipoproteins, which may impair their function and/or enhance their atherogenicity.

RISK ASSESSMENT OF INDIVIDUALS WITH DIABETES

People with diabetes should be assessed to determine their short- and long-term risks for CVD. Most individuals with established diabetes are at high risk for vascular events and should be treated accordingly. Clinical assessment can identify those with diabetes whose risk level might be considered

lower, but even in this group, it is important to consider that the average person with newly diagnosed type 2 diabetes may have had the disease for some time prior to diagnosis. In addition, all people with diabetes have an extremely high lifetime risk of CVD; thus, even if the short-term risk is lower, early intervention to improve the lipid profile may be warranted. Physicians must also use their clinical judgement and carefully weigh diabetes-specific as well as traditional CVD risk factors in their decisions about when and how to implement risk-reduction strategies in a given individual (see "Identification of Individuals at High Risk of Coronary Events," p. S95).

SCREENING

The burden of dyslipidemia is high in people with diabetes. A national cross-sectional chart audit study of 2473 Canadians with type 2 diabetes revealed that 55% of those with a diagnosis of diabetes of ≤2 years had dyslipidemia. This proportion rose to 66% in those with diabetes for ≥15 years (5). A fasting lipid profile (total cholesterol [TC], HDL-C, TG and calculated LDL-C) should therefore be conducted at the time of diagnosis of diabetes, and then every 1 to 3 years, as clinically indicated. More frequent testing should be conducted if treatment for dyslipidemia is initiated. A fast of >8 hours may be inappropriate for individuals with diabetes, especially if they are using a long-acting insulin. For screening in children and adolescents, please refer to the diabetes in children sections, pages S150 and S162.

LIFESTYLE MODIFICATION

Lifestyle interventions remain a key component of CVD prevention strategies and diabetes management in general. Individuals with type 2 diabetes are frequently overweight and sedentary. In those with a body mass index (BMI) ≥25 kg/m² and/or abdominal obesity (6), weight reduction should be strongly recommended. Even a modest weight loss of 5 to 10% of initial body weight can be associated with an improvement in the lipid profile of individuals with dyslipidemia and diabetes (7). As well, an energy-restricted, well-balanced diet that is low in dietary cholesterol, saturated fats, trans fatty acids and refined carbohydrates is essential. In short-term studies, a combination of various dietary interventions (increased intake of viscous fibres, plant sterols, nuts and soy proteins) was shown to lower LDL-C by 30% in

highly motivated individuals with hypercholesterolemia but without diabetes (8). However, in a "real-world" setting, only one-third of individuals were able to adhere to this diet over a 1-year period of time (9). Regular aerobic exercise helps individuals lose weight and maintain this weight reduction over time (10), and may be associated with reductions in TG and elevations in HDL-C. Regular exercise can also improve glycemic control in people with type 2 diabetes (11) and is associated with substantial reductions in CV morbidity and mortality in both type 1 (12) and type 2 diabetes (13-15). Indeed, a steep inverse relationship between fitness and mortality was observed in a cohort of men with diabetes, and this association was independent of BMI (16). Smoking cessation should be encouraged and supported. While lifestyle modification should be encouraged in all people with dyslipidemia, most will be unable to achieve recommended lipid targets without pharmacologic intervention. Accordingly, for most people with diabetes, lifestyle interventions should be seen as an important adjunct to, but not a substitute for, pharmacologic treatment.

LDL-C

A number of studies have shown that the degree of LDL-C lowering with statins and the beneficial effects of lowering LDL-C apply equally well to people with and without diabetes (17-24). Large, recently published trials have demonstrated the benefits of statin therapy in both the primary and secondary prevention of vascular disease, and subgroup analyses of these studies have shown similar benefits in subsets of participants with diabetes (17-19). While statin therapy across all subgroups has shown the same relative risk reduction in terms of outcomes, the absolute benefit depends on absolute risk, which is increased in people with diabetes. Subgroup analyses from statin trials have also shown similar benefits of LDL-C lowering, regardless of baseline LDL-C (20,22). Therefore, statin use should be considered for any person with diabetes at high risk of a vascular event. In the very small group of lower-risk individuals with type 2 diabetes, the relative reduction in CVD risk with statin therapy is likely to be similar to those at higher global risk for CVD, but the absolute benefit from statin therapy is predicted to be small. However, such individuals' global CVD risk will increase with age and in the presence of additional risk factors for CVD. Therefore, repeated monitoring of the individual's clinical condition and lipid screening every 1 to 3 years, as outlined in the Screening section above, are recommended.

The results of the Heart Protection Study (HPS) provide considerable insight into the importance of LDL-C lowering (21). In this large study involving >20 000 subjects, a similar benefit in terms of risk ratio reduction was observed in subjects with baseline LDL-C >3.5 mmol/L, 3.0 to 3.5 mmol/L and <3.0 mmol/L. All randomized subjects were included in this analysis. In the cohort with diabetes (n=5963, including

615 people with type 1 diabetes), treatment with 40 mg simvastatin daily resulted in a 27% reduction in CV events and a 25% reduction in stroke relative to treatment with placebo. The risk reduction was similar in the cohorts with and without diabetes, and the treatment benefit was independent of baseline HDL-C and LDL-C levels (LDL-C <3.0 mmol/L or ≥3.0 mmol/L), sex, vascular disease, type of diabetes (type 1 vs. type 2) and glycated hemoglobin (A1C) (20). These results confirmed that whatever the existing serum LDL-C level, lowering it further with the use of a statin is beneficial. However, the HPS did not demonstrate the effect of treating LDL-C to any particular preset targets. In a post-hoc analysis of the entire study sample, the investigators found similar event reductions in individuals with baseline LDL-C values <2.6 mmol/L, but this analysis was not performed in the subset of people with diabetes who had baseline LDL-C values <2.6 mmol/L because of insufficient power.

In the Collaborative Atorvastatin Diabetes Study (CARDS) (22), the first completed statin trial to be conducted exclusively in people with type 2 diabetes without known vascular disease, mean baseline LDL-C was 3.1 mmol/L, and all subjects had at least 1 additional CV risk factor (i.e. in addition to known diabetes). CARDS demonstrated that treatment with atorvastatin 10 mg daily was safe and highly efficacious in reducing the risk of first CVD events, including stroke. Treatment resulted in a mean LDL-C of 2.0 mmol/L and was associated with a 37% reduced risk for CV events and a 48% reduced risk for stroke. The study provided important new evidence to support the value of treating even so-called "normal" LDL-C levels in people with type 2 diabetes and no known vascular disease. CARDS subjects all had at least 1 additional CV risk factor – a profile that would also apply to an estimated 70 (25) to 80% (22) of people with type 2 diabetes; analysis of the United States (US) Third National Health and Nutrition Examination Survey (NHANES III) data indicates that 82% of people with diabetes and no clinically evident coronary artery disease (CAD) have at least 1 of the CARDS entry criteria risk factors (22). The authors of CARDS conclude that the data "challenge the use of a particular threshold level of LDL-C as the sole arbiter of which individuals with type 2 diabetes should receive statin therapy … The absolute risk, determined by other risk factors in addition to LDL-C, should drive the target levels." Indeed, the authors question whether any individuals with type 2 diabetes can be considered at sufficiently low risk for statin therapy to be withheld (22). A recently published subanalysis of the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA) revealed similar benefits of atorvastatin 10 mg vs. placebo in people with type 2 diabetes, hypertension and at least 3 additional risk factors (26).

The Atorvastatin Study for the Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN) (27) assessed the effect of 10 mg atorvastatin vs. placebo on CVD prevention in 2410 people with

type 2 diabetes. Although originally designed as a secondary prevention trial, the protocol underwent several changes, including the addition of subjects without known CAD, and the eventual switch of all patients with known CAD to open-label lipid-lowering medication. Mean LDL-C reduction over 4 years in the atorvastatin group was 29% vs. placebo (p <0.0001). The composite primary endpoint was reduced by a nonsignificant 13.7%, which is generally believed to be related to the methodological limitations of the study design and the protocol changes.

In the diabetic subset (n=1051) of the Treating to New Targets (TNT) trial (24) conducted in individuals with stable CAD, those subjects treated with atorvastatin 80 mg daily who achieved a group mean LDL-C of 2.0 mmol/L had 25% fewer major CV events than those treated with atorvastatin 10 mg daily who achieved a mean LDL-C of 2.5 mmol/L (p=0.026). Intensive therapy with atorvastatin 80 mg vs. therapy with 10 mg also reduced the rate of all CV and cerebrovascular events. Notably, an increased event rate for all primary and secondary efficacy outcomes was noted for the diabetes subgroup compared with the overall study population, reinforcing the evidence that people with diabetes and CAD have an extremely high risk of subsequent CV events.

A recent meta-analysis of >90 000 statin-treated subjects indicated that for every 1.0 mmol/L reduction in LDL-C there was an approximately 20% reduction in CVD events, regardless of baseline LDL-C. The proportional reductions were very similar in all subgroups, including those with diabetes without pre-existing vascular disease (28). Although this linear relationship between the proportional CVD risk reduction and LDL-C lowering would suggest that there is no lower limit of LDL-C or specified LDL-C target (as the authors suggest), the clinical trial evidence summarized above would suggest that a target LDL-C of ≤2.0 mmol/L is currently the most appropriate target for high-risk individuals. This target is achievable in the vast majority of people with either a statin alone or a statin in combination with a second agent, such as a cholesterol absorption inhibitor. For those with an on-treatment LDL-C of 2.0 to 2.5 mmol/L, the physician should use clinical judgement as to whether additional LDL-C lowering is required.

Table 1 summarizes recommended treatment targets. Tables 2A and 2B summarize considerations that should guide the choice of pharmacologic agent(s) to treat dyslipidemia.

People with impaired glucose tolerance (IGT) (particularly in the context of the metabolic syndrome) are at significant risk for the development of CVD. Indeed, some studies suggest that their vascular risk is almost as high as individuals with type 2 diabetes (29). No clinical trial of lipid-lowering agents has been conducted exclusively in people with IGT; however, given their increased CV risk, one can consider treating this population to the same targets as people with diabetes (30). To reduce the CV morbidity

COMPLICATIONS AND COMORBIDITIES

Table 1. Lipid targets for individuals with diabetes at high risk for CVD

Index	Target value
Primary target: LDL-C	≤2.0 mmol/L*
Secondary target: TC/HDL-C ratio	<4.0

*Clinical judgement should be used to decide whether additional LDL-C lowering is required for individuals with an on-treatment LDL-C of 2.0 to 2.5 mmol/L

CVD = cardiovascular disease
HDL-C = high-density lipoprotein cholesterol
LDL-C = low-density lipoprotein cholesterol
TC = total cholesterol

Table 2A. First-line therapy to achieve primary lipid target of LDL-C ≤2.0 mmol/L

Statins*

Generic name[†]	Trade name	Considerations
atorvastatin	Lipitor	Drugs of choice to lower LDL-C. At higher doses, modest TG-lowering effects and HDL-C–raising effects
fluvastatin	Lescol	
lovastatin	Mevacor and generic	
pravastatin	Pravachol and generic	
rosuvastatin	Crestor	
simvastatin	Zocor and generic	

*Prevention of statin-induced myopathy requires attention to factors that increase risk, such as age >80 years (especially women); small body frame and frailty; higher dose of statin; multisystem diseases (e.g. chronic renal insufficiency due to diabetes); multiple medications; hypothyroidism; perioperative periods; alcohol abuse; excessive grapefruit juice consumption; and specific concomitant medications such as fibrates (especially gemfibrozil) (refer to specific statin package inserts for others) (47)
[†]Listed in alphabetical order

HDL-C = high-density lipoprotein cholesterol
LDL-C = low-density lipoprotein cholesterol
TG = triglyceride

Note: Physicians should refer to the most current edition of *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association, Ottawa, Ontario, Canada) for product monographs and complete prescribing information.

Table 2B. Other lipid-modifying medications		
Drug class* **Generic name* (trade name)**	*Principal effects*	*Other considerations*
Bile acid sequestrants • cholestyramine resin (Questran, Questran Light and generic) • colestipol HCl (Colestid)	• Lower LDL-C	• GI intolerability, which worsens with increasing doses • May elevate TG
Cholesterol absorption inhibitor • ezetimibe (Ezetrol)	• Lower LDL-C	• Less effective than statins as monotherapy • Effective when used in combination with a statin to further lower LDL-C
Fibrates • bezafibrate (Bezalip and generic) • fenofibrate (micronized/microcoated) (Lipidil Micro/Lipidil Supra, Lipidil EZ and generic) • gemfibrozil (Lopid and generic)	• Lower TG • Variable effect on LDL-C • Highly variable effect on HDL-C (more effective at raising HDL-C when baseline TG is high)	• May also increase creatinine and homocysteine levels • Do not use gemfibrozil in combination with a statin due to increased risk of myopathy and rhabdomyolysis[†]
Nicotinic acid • Extended-release niacin (Niaspan) • Immediate-release niacin (generic, non-prescription) • Long-acting (e.g. "no-flush") niacin (generic, nonprescription) **Not recommended**	• Raise HDL-C • Lower TG • Lower LDL-C	• Can cause dose-related deterioration of glycemic control • Extended-release niacin has similar efficacy and better tolerability than immediate-release niacin • Long-acting niacin should **not** be used due to increased hepatotoxicity and decreased efficacy (52)

*Listed in alphabetical order
[†]See footnote to Table 2A regarding prevention of myopathy

HDL-C = high-density lipoprotein cholesterol
LDL-C = low-density lipoprotein cholesterol
TG = triglyceride

Note: Physicians should refer to the most current edition of *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association, Ottawa, Ontario, Canada) for product monographs and complete prescribing information.

and mortality associated with prediabetes and metabolic syndrome, an aggressive approach aimed at associated CV risk factors, including dyslipidemia, is warranted. Lifestyle interventions aimed at reducing the risk of developing both type 2 diabetes and coronary disease are essential.

TC/HDL-C RATIO, HDL-C, TG

The TC/HDL-C ratio is a sensitive and specific index of CV risk (31). This simple lipid ratio is recommended as a secondary goal of therapy. Once the LDL-C goal of ≤2.0 mmol/L has been reached, one can consider lowering the TC/HDL-C ratio to the recommended goal of <4.0 (Table 1). This is typically more difficult to achieve than the primary LDL-C target, requires ongoing reinforcement of lifestyle modification and frequently requires combination therapy. Even with such aggressive measures, this secondary target is frequently not achieved.

An elevated TC/HDL-C ratio in the face of an optimal LDL-C of ≤2.0 mmol/L is usually associated with a low HDL-C and/or elevated TG. This form of dyslipidemia is more amenable to lifestyle modification (increase in physical activity and weight reduction) and improvement in glycemic control than an isolated LDL-C elevation. Initially, treatment should consist of intensification of lifestyle modification and improvement of glycemic control, using glucose-lowering therapies as needed. If the ratio remains elevated after a 4- to 6-month trial of these measures, and once glycemic control and LDL-C have been optimized, adjuvant lipid-modifying therapy may be used in conjunction with statin therapy.

If low HDL-C is the major cause of a persistently elevated TC/HDL-C ratio (in those whose LDL-C is already opti-

mally controlled with a statin), niacin (immediate-release or extended-release formulation) is the adjuvant agent of choice. Combination lipid-lowering therapy with niacin is generally safe (32-35). Niacin can cause deterioration of glycemic control (32) (although there is now evidence that the adverse effects of niacin on glycemia may have been overemphasized [33]).

In the placebo-controlled HDL Atherosclerosis Treatment Study (HATS) (34), combined low-dose simvastatin (10 to 20 mg/day) and high-dose niacin (2 to 4 g/day) stabilized coronary atherosclerosis with an associated ≥13% absolute risk reduction (up to 90% relative risk reduction) for CV outcomes, although the number of subjects with diabetes was small. In the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2 trial, 1 g extended-release niacin added to existing statin therapy significantly improved HDL-C (21%), TG and non-HDL-C, and likely contributed to observed reduction of carotid intima-media thickness in subjects also treated with a statin (35).

Specific targets for TG are not provided in these guidelines because there are very few clinical trial data to support recommendations based on specific TG target levels. Nonetheless, a TG level of <1.5 mmol/L is considered optimal, since below this level of hyper-TG there are fewer associated metabolic abnormalities such as low HDL-C, small dense LDL particles and postprandial lipemia (36,37). Recognizing the atherogenicity of small, dense LDL particles and remnant lipoproteins and the important antiatherogenic role of HDL particles, it is important to improve these metabolic parameters by lifestyle modification, improvement in glycemic control and pharmacotherapy when indicated. The atherogenic impact of LDL-C particle size will be minimized and reductions in TC/HDL-C ratio will occur if very low plasma concentrations of LDL-C are achieved.

To reduce the risk of pancreatitis, a fibrate is recommended for individuals with fasting TG levels >10.0 mmol/L who do not respond to other measures such as tight glycemic control, weight loss and restriction of refined carbohydrates and alcohol. For those with moderate hyper-TG (4.5 to 10.0 mmol/L), either a statin or a fibrate can be attempted as first-line therapy, with the addition of a second lipid-lowering agent of a different class if target lipid levels are not achieved after 4 to 6 months on monotherapy. While several studies have shown that CVD prevention is associated with fibrate treatment (38-42), there is much less evidence for CVD risk reduction with fibrates relative to statins in people with diabetes. In some studies, no statistically significant reduction in the primary endpoint was demonstrated with fibrate therapy (43,44). Combination therapy with fenofibrate (45,46) or bezafibrate plus a statin appears to be relatively safe if appropriate precautions are taken (Tables 2A and 2B), but the efficacy of these approaches with regard to outcomes has yet to be established. Because of an increased risk

of myopathy and rhabdomyolysis, statins should not be used in combination with gemfibrozil (47).

Although monotherapy with niacin or fibrates has been shown to prevent CVD events, there is currently insufficient evidence for statin plus niacin and no evidence for fibrate plus niacin combinations to reduce CV risk in people with diabetes. However, adequately powered, event-reduction, prospective, randomized, controlled clinical trials are currently underway with various classes of agents to examine whether the addition of other therapies in individuals already treated with statins further reduces CV events and/or prolongs survival (Action to Control Cardiovascular Risk in Diabetes [ACCORD] for statin plus fibrate; Atherothrombosis Intervention in Metabolic Syndrome with Low HDL-C/High Triglyceride and Impact on Global Health Outcomes [AIM HIGH] for statin plus extended-release niacin). Until the results of these clinical trials become available, for high-risk individuals who have a persistent elevation of TC/HDL-C despite achieving the primary LDL-C target of ≤2.0 mmol/L, niacin or fibrates can be added to statin therapy at the physician's discretion.

ADDITIONAL LIPID MARKERS OF CVD RISK
Apo B, Apo B/Apo A1 ratio
There is 1 apolipoprotein B molecule (apo B) per LDL, very low-density lipoprotein and intermediate-density lipoprotein particle (all of which are atherogenic). Apo B has repeatedly been shown to be a better risk marker for CVD events than LDL-C; consequently, the measurement of apo B and its monitoring in response to lipid-lowering therapy has been advocated by some (48). The measurement of apo B is most clinically useful in the individual with hyper-TG, since it provides an indication of the total number of atherogenic lipoprotein particles in the circulation. In such cases, knowledge of the apo B level may guide the aggressiveness with which lipid-lowering therapy is pursued (i.e. more aggressive therapy in individuals in whom the apo B level is elevated). An optimal level of apo B in high-risk individuals has not yet been precisely determined, but based on available evidence can be considered to be ~<0.9 g/L (49).

Apo A1 is a surrogate marker of the number of HDL particles in the circulation (there may be 2 to 4 apo A1 molecules per HDL particle). The apo B/apo A1 ratio was recently found to be the best predictor of CVD risk, accounting for 50% of population-attributable events in a population without diabetes (although its comparison to the TC/HDL-C ratio as a risk predictor was not reported in that study) (50).

There are, however, some limitations to the use of these measures in guiding clinical decision-making. While both apo B and the apo B/apo A1 ratio have been shown to predict CVD events, there is no clinical trial evidence for specific targets for these indices in individuals with or without diabetes. In addition, although standardized, the measurement of apo B and apo A1 is currently not widely available in Canada.

RECOMMENDATIONS

1. People with type 1 or type 2 diabetes should be encouraged to adopt a healthy lifestyle to lower their risk of CVD. This entails adopting healthy eating habits, achieving and maintaining a healthy weight, engaging in regular physical activity and smoking cessation *[Grade D, Consensus]*.

2. Fasting lipid levels (TC, HDL-C, TG and calculated LDL-C) should be measured at the time of diagnosis of diabetes and then every 1 to 3 years as clinically indicated. More frequent testing should be performed if treatment for dyslipidemia is initiated *[Grade D, Consensus]*.

3. Individuals at high risk of a vascular event should be treated with a statin to achieve an LDL-C ≤2.0 mmol/L *[Grade A, Level 1 (20,22), Level 2 (24)]*. Clinical judgement should be used as to whether additional LDL-C lowering is required for those with an on-treatment LDL-C of 2.0 to 2.5 mmol/L *[Grade D, Consensus]*.

4. The primary target of therapy is LDL-C *[Grade A, Level 1(20,22), Level 2 (24)]*; the secondary target is TC/HDL-C ratio *[Grade D, Consensus]*.

5. If the TC/HDL-C ratio is ≥4.0, consider strategies to achieve a TC/HDL-C ratio <4.0 *[Grade D, Consensus]*, such as improved glycemic control, intensification of lifestyle modifications (weight loss, physical activity, smoking cessation) and, if necessary, pharmacologic interventions *[Grade D, Consensus]*.

6. If serum TG is >10.0 mmol/L despite best efforts at optimal glycemic control and other lifestyle interventions (e.g. weight loss, restriction of refined carbohydrates and alcohol), a fibrate should be prescribed to reduce the risk of pancreatitis *[Grade D, Consensus]*. For those with moderate hyper-TG (4.5 to 10.0 mmol/L), either a statin or a fibrate can be attempted as first-line therapy, with the addition of a second lipid-lowering agent of a different class if target lipid levels are not achieved after 4 to 6 months on monotherapy *[Grade D, Consensus]*.

7. For individuals not at target(s) despite optimally dosed first-line therapy as described above, combination therapy can be considered. Although there are as yet no completed trials demonstrating clinical outcomes in subjects receiving combination therapy, pharmacologic treatment options include (listed in alphabetical order):
   • Statin plus ezetimibe *[Grade B, Level 2 (51)]*.
   • Statin plus fibrate *[Grade B, Level 2 (46), Level 3 (45)]*.
   • Statin plus niacin *[Grade B, Level 2 (33)]*.

8. Plasma apo B can be measured, at the physician's discretion, in addition to LDL-C and TC/HDL-C ratio, to monitor adequacy of lipid-lowering therapy in the high-risk individual *[Grade D, Consensus]*. Target apo B should be <0.9 g/L *[Grade D, Consensus]*.

OTHER RELEVANT GUIDELINES

Definition, Classification and Diagnosis of Diabetes and Other Dysglycemic Categories, p. S10
Physical Activity and Diabetes, p. S37
Nutrition Therapy, p. S40
Management of Obesity in Diabetes, p. S77
Identification of Individuals at High Risk of Coronary Events, p. S95
Screening for the Presence of Coronary Artery Disease, p. S99
Vascular Protection in People With Diabetes, p. S102
Treatment of Hypertension, p. S115
Management of Acute Coronary Syndromes, p. S119
Treatment of Diabetes in People With Heart Failure, p. S123
Type 1 Diabetes in Children and Adolescents, p. S150
Type 2 Diabetes in Children and Adolescents, p. S162

REFERENCES

1. Roglic G, Unwin N, Bennett PH, et al. The burden of mortality attributable to diabetes: realistic estimates for the year 2000. *Diabetes Care*. 2005;28:2130-2135.

2. Morrish NJ, Wang SL, Stevens LK, et al. Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetologia*. 2001;44(suppl 2):S14-S21.

3. Booth GL, Rothwell D, Fung K, et al. Diabetes and cardiac disease. In: Hux JE, Booth G, Laupacis A, eds. *Diabetes in Ontario: An ICES Practice Atlas*. 2002:5.95-5.127.

4. Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med*. 2003;348:383-393.

5. Harris SB, Ekoé JM, Zdanowicz Y, et al. Glycemic control and morbidity in the Canadian primary care setting (results of the diabetes in Canada evaluation study). *Diabetes Res Clin Pract*. 2005;70:90-97.

6. International Diabetes Federation. The IDF consensus worldwide definition of the metabolic syndrome. International Diabetes Federation website. Available at: http://www.idf.org/webdata/docs/MetSyndrome_FINAL.pdf. Accessed September 1, 2008.

7. Dattilo AM, Kris-Etherton PM. Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. *Am J Clin Nutr*. 1992;56:320-328.

8. Jenkins DJ, Kendall CW, Marchie A, et al. A dietary portfolio: maximal reduction of low-density lipoprotein cholesterol with diet. *Curr Atheroscler Rep*. 2004;6:492-498.

9. Kendall CW, Jenkins DJ. Assessment of the longer-term effects of a dietary portfolio of cholesterol-lowering foods in hypercholesterolemia. *Am J Clin Nutr*. 2006;83:582-591.

10. Wing RR. Weight loss in the management of type 2 diabetes. In: Gerstein HC, Haynes RB, eds. *Evidence-based Diabetes Care*. Hamilton, ON: BC Decker Inc.; 2001:252-276.

11. Boulé NG, Haddad E, Kenny GP, et al. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. *JAMA*. 2001;286:1218-1227.

12. Moy CS, Songer TJ, LaPorte RE, et al. Insulin-dependent diabetes mellitus, physical activity, and death. *Am J Epidemiol.* 1993;137:74-81.

13. Hu FB, Stampfer MJ, Solomon CG, et al. The impact of diabetes mellitus on mortality from all causes and coronary heart disease in women: 20 years of follow-up. *Arch Intern Med.* 2001;161:1717-1723.

14. Wei M, Gibbons LW, Kampert JB, et al. Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with type 2 diabetes. *Ann Intern Med.* 2000;132:605-611.

15. Warburton DE, Nichol CW, Bredin SS. Health benefits of physical activity: the evidence. *CMAJ.* 2006;174:801-809.

16. Church TS, Cheng YJ, Earnest CP, et al. Exercise capacity and body composition as predictors of mortality among men with diabetes. *Diabetes Care.* 2004;27:83-88.

17. Pyörälä K, Pedersen TR, Kjekshus J, et al. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). *Diabetes Care.* 1997;20:614-620.

18. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med.* 1996;335:1001-1009.

19. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Engl J Med.* 1998;339:1349-1357.

20. Collins R, Armitage J, Parish S, et al; Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet.* 2003;361:2005-2016.

21. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet.* 2002;360:7-22.

22. Colhoun HM, Betteridge DJ, Durrington PN, et al; CARDS Investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet.* 2004;364:685-696.

23. LaRosa JC, Grundy SM, Waters DD, et al; Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med.* 2005;352:1425-1435.

24. Shepherd J, Barter P, Carmena R, et al. Effect of lowering LDL cholesterol substantially below currently recommended levels in patients with coronary heart disease and diabetes: the Treating to New Targets (TNT) study. *Diabetes Care.* 2006;29:1220-1226.

25. Evans JM, Wang J, Morris AD. Comparison of cardiovascular risk between patients with type 2 diabetes and those who had had a myocardial infarction: cross sectional and cohort studies. *BMJ.* 2002;324:939-942.

26. Sever PS, Poulter NR, Dalhof B, et al. Reduction in cardiovascular events with atorvastatin in 2532 patients with type 2 diabetes. Anglo-Scandinavian Cardiac Outcomes Trial–lipid-lowering arm (ASCOT-LLA). *Diabetes Care.* 2005;28:1151-1157.

27. Knopp RH, D'emden M, Smilde SJ, et al. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN). *Diabetes Care.* 2006;29:1478-1485.

28. Baigent C, Keech A, Kearney PM, et al; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet.* 2005;366:1267-1278.

29. Tominaga M, Eguchi H, Manaka H, et al. Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose. *Diabetes Care.* 1999;22:920-924.

30. Girman CJ, Rhodes T, Mercuri M, et al; 4S Group and the AFCAPS/TexCAPS Research Group. The metabolic syndrome and risk of major coronary events in the Scandinavian Simvastatin Survival Study (4S) and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). *Am J Cardiol.* 2004;93:136-141.

31. Genest J, Frohlich J, Fodor G, et al; Working Group on Hypercholesterolemia and Other Dyslipidemias. Recommendations for the management of dyslipidemia and the prevention of cardiovascular disease: summary of the 2003 update. *CMAJ.* 2003;169:921-924.

32. Elam MB, Hunninghake DB, Davis KB, et al. Effect of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral arterial disease: the ADMIT study: a randomized trial. Arterial Disease Multiple Intervention Trial. *JAMA.* 2000;284:1263-1270.

33. Grundy SM, Vega GL, McGovern ME, et al; Diabetes Multicenter Research Group. Efficacy, safety, and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes: results of the assessment of diabetes control and evaluation of the efficacy of niaspan trial. *Arch Intern Med.* 2002;162:1568-1576.

34. Brown BG, Zhao XQ, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med.* 2001;345:1583-1592.

35. Taylor AJ, Sullenburger LE, Lee HJ, et al. Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2: a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. *Circulation.* 2004;110:3512-3517.

36. Griffin BA, Freeman DJ, Tait GW, et al. Role of plasma triglyceride in the regulation of plasma low density lipoprotein (LDL) subfractions: relative contribution of small, dense LDL to coronary heart disease risk. *Atherosclerosis.* 1994;106:241-253.

37. Packard CJ, Shepherd J. Lipoprotein heterogeneity and apolipoprotein B metabolism. *Arterioscler Thromb Vasc Biol.* 1997;17:3542-3556.

38. Elkeles RS, Diamond JR, Poulter C, et al. Cardiovascular outcomes in type 2 diabetes. A double-blind placebo-controlled study of bezafibrate: the St. Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention (SENDCAP) Study. *Diabetes Care.* 1998;21:641-648.

39. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med.* 1999;341:410-418.

40. Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomised study. *Lancet.* 2001;357:905-910.

41. Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med.* 1987; 317:1237-1245.

42. Robins SJ, Rubins HB, Faas FH, et al; Veterans Affairs HDL Intervention Trial (VA-HIT). Insulin resistance and cardiovascular events with low HDL cholesterol: the Veterans Affairs HDL Intervention Trial (VA-HIT). *Diabetes Care.* 2003;26: 1513-1517.

43. Keech A, Simes RJ, Barter P, et al; FIELD Study Investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet.* 2005;366:1849-1861.

44. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease: the Bezafibrate Infarction Prevention (BIP) Study. *Circulation.* 2000; 102:21-27.

45. Durrington PN, Tuomilehto J, Hamann A, et al. Rosuvastatin and fenofibrate alone and in combination in type 2 diabetes patients with combined hyperlipidaemia. *Diabetes Res Clin Pract.* 2004;64:137-151.

46. Athyros VG, Papageorgiou AA, Athyrou VV, et al. Atorvastatin and micronized fenofibrate alone and in combination in type 2 diabetes with combined hyperlipidemia. *Diabetes Care.* 2002; 25:1198-1202.

47. Pasternak RC, Smith SC Jr, Bairey-Merz C, et al; American Heart Association; National Heart, Lung and Blood Institute. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol.* 2002;40;567-572.

48. Barter PJ, Ballantyne CM, Carmena R, et al. Apo B versus cholesterol in estimating cardiovascular risk and in guiding therapy: report of the thirty-person ten-country panel. *J Intern Med.* 2006;259:247-258.

49. Walldius G, Jungner I, Holme I, et al. High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. *Lancet.* 2001;358:2026-2033.

50. Yusuf S, Hawken S, Ounpuu S, et al; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART Study): case-control study. *Lancet.* 2004;364:937-952.

51. Simons L, Tonkon M, Masana L, et al. Effects of ezetimibe added to on-going statin therapy on the lipid profile of hypercholesterolemic patients with diabetes or metabolic syndrome. *Curr Med Res Opin.* 2004;20:1437-1445.

52. McKenney J. New perspectives on the use of niacin in the treatment of lipid disorders. *Arch Intern Med.* 2004;164:697-705.

Treatment of Hypertension

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Bruce Culleton MD FRCPC, Denis Drouin MD FRCPC, Pierre LaRochelle MD PhD FRCPC, Lawrence A. Leiter MD FRCPC FACP, Philip McFarlane MD FRCPC and Sheldon Tobe MD FRCPC

KEY MESSAGES

- In the prevention of diabetes-related complications, vascular protection (using a multifaceted, comprehensive approach to risk reduction) is the first priority, followed by control of hypertension in those whose blood pressure (BP) levels remain above target, then nephroprotection for those with proteinuria despite the above measures.

- People with diabetes and elevated BP should be aggressively treated to achieve a target BP of <130/80 mm Hg to reduce the risk of both micro- and macrovascular complications.

- Most people with diabetes will require multiple BP-lowering medications to achieve BP targets.

INTRODUCTION

Most people with diabetes will develop hypertension (1), which is a major determinant of both microvascular and cardiovascular (CV) complications. In the United Kingdom Prospective Diabetes Study (UKPDS), the risk of microvascular disease rose 13% for each 10 mm Hg rise in systolic blood pressure (BP) (2). CV risk is 2 to 7 times higher in people with diabetes (3-5), and up to 75% of this risk may be attributable to the presence of hypertension (6,7). In the UKPDS, the risk of both myocardial infarction (MI) and death rose by 12% for every 10 mm Hg increase in systolic BP (2).

Hypertension is a treatable risk factor. Recent studies suggest that a delay in the recognition and management of hypertension, particularly in high-risk individuals, increases their risk of CV morbidity and mortality (8-10). Therefore, people with diabetes should be regularly screened (i.e. at every diabetes-related clinic visit) for the presence of hypertension, and those with elevated BP should be aggressively treated to achieve target BP values in order to reduce the risk of both the micro- and macrovascular complications of diabetes.

In the prevention of diabetes-related complications, vascular protection (using a multifaceted, comprehensive approach to risk reduction) is the first priority, followed by control of hypertension in those whose BP levels remain above target, then nephroprotection for those with proteinuria despite the above measures (See "Vascular Protection in People With Diabetes," p. S102).

BP TARGETS

The recommended BP targets are <130/80 mm Hg and apply regardless of whether nephropathy is present or not. The Hypertension Optimal Treatment (HOT) Trial (11) and UKPDS (12) provide level 2 evidence for a diastolic BP target of <80 mm Hg. In both trials, subjects with diabetes were randomized to treatments that yielded different mean diastolic BP values (HOT: 85, 83 and 81 mm Hg; UKPDS: 87 and 82 mm Hg). Clinically important reductions in micro- and macrovascular complications (11,12), CV death (11) and diabetes-related death (12) were seen in the lowest BP groups.

The evidence for a systolic target of 130 mm Hg is weaker and includes 2 prospective cohort studies (2,13) and the normotensive Appropriate Blood Pressure Control in Diabetes (ABCD) randomized controlled trial (RCT) (14). In these studies, direct relationships were seen between higher systolic BP levels and death, coronary artery disease (CAD), nephropathy and proliferative retinopathy (2,13). The Pittsburgh Epidemiology of Diabetes Complications Study (13), a prospective cohort study of subjects with type 1 diabetes, reported statistically significant associations between CV complications and mortality as systolic BP rose above 115 mm Hg and as diastolic BP rose above 80 mm Hg. Although this relationship extended to systolic BP values <130 mm Hg, the current evidence lacked the strength to identify and recommend a systolic target lower than 130 mm Hg.

Results from the normotensive ABCD trial, in which persons with diabetes were randomized to either a moderate treatment strategy (achieved mean BP of 137/81 mm Hg) or an intensive treatment strategy (achieved mean BP of 128/75 mm Hg) also support a systolic target of 130 mm Hg (14). Although no difference was seen between the 2 groups in the prespecified primary outcome (creatinine clearance), statistically significant reductions in risks for other complications, including selected measures of nephropathy, retinopathy and stroke, occurred in the intensively treated subjects. However, because a large number of secondary endpoints were tested for significance without adjustment for multiple comparisons, and because estimates of treatment effects for some secondary outcomes were based on small numbers (e.g. strokes) and were therefore unstable, the ABCD Trial findings have not been accorded level 1 status. Stronger evidence for an optimal systolic BP awaits completion of the Action to Control Cardiovascular Risk in Diabetes

RECOMMENDATIONS

1. Blood pressure should be measured at every diabetes clinic visit for the assessment of hypertension [Grade D, Consensus].

2. Hypertension should be diagnosed in people with diabetes according to national hypertension guidelines (http://www.hypertension.ca/chep) [Grade D, Consensus].

3. Persons with diabetes and hypertension should be treated to attain systolic BP <130 mm Hg [Grade C, Level 3 (2,13,14)] and diastolic BP <80 mm Hg [Grade B, Level 2 (11,12)]. These target BP levels are the same as the BP treatment thresholds [Grade D, Consensus].

4. Lifestyle interventions to reduce BP should be considered, including achieving and maintaining a healthy weight and limiting sodium and alcohol intake [Grade D, Consensus]. Lifestyle recommendations should be initiated concurrently with pharmacological intervention to reduce BP [Grade D, Consensus].

5. For persons with diabetes and normal urinary albumin excretion and without chronic kidney disease, with BP ≥130/80 mm Hg, despite lifestyle interventions:
   • Any of the following medications (listed in alphabetical order) is recommended, with special consideration to ACE inhibitors and ARBs given their additional renal benefits [Grade D, Consensus, for the special consideration to ACE inhibitors and ARBs]:
      • ACE inhibitor [Grade A, Level 1A (19)]
      • ARB [Grade A, Level 1A (20); Grade B, Level 2, for non-left ventricular hypertrophy (20)]
      • DHP CCB [Grade B, Level 2 (22)]
      • Thiazide-like diuretic [Grade A, Level 1A (22)]
   • If the above drugs are contraindicated or cannot be tolerated, a cardioselective beta blocker [Grade B, Level 2 (21)] or non-DHP CCB [Grade B, Level 2 (23)] can be substituted.
   • Additional antihypertensive drugs should be used if target BP levels are not achieved with standard-dose monotherapy [Grade C, Level 3 (12,22)].
   • Add-on drugs should be chosen from the first-line choices listed above [Grade D, Consensus].

6. For people with diabetes and albuminuria (persistent albumin to creatinine ratio [ACR] ≥2.0 mg/mmol in men and ≥2.8 mg/mmol in women), an ACE inhibitor or an ARB is recommended as initial therapy [Grade A, Level 1A (15-18)]. If BP remains ≥130/80 mm Hg despite lifestyle interventions and the use of an ACE inhibitor or ARB, additional antihypertensive drugs should be used to obtain target BP [Grade D, Consensus].

7. For persons with diabetes and a normal urinary albumin excretion rate, with no chronic kidney disease and with isolated systolic hypertension, a long-acting DHP CCB [Grade C, Level 3 (26)] is an alternative initial choice to an ACE inhibitor [Grade B, Level 2 (19)], an ARB [Grade B, Level 2 (20)] or a thiazide-like diuretic [Grade B, Level 2 (22,25)].

8. Alpha-blockers are not recommended as first-line agents for the treatment of hypertension in persons with diabetes [Grade A, Level 1A (27)].

(ACCORD) trial, in which thousands of people with diabetes are being randomized to systolic BP targets of <120 or <140 mm Hg.

Note that the recommended BP targets are based on office determinations. Although the concept of home BP monitoring and 24-hour continuous ambulatory BP monitoring to guide treatment in people with diabetes is attractive, the role of such techniques remains unclear.

TREATMENT OF HYPERTENSION

Concurrent with lifestyle modification, an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) is recommended as initial therapy. This is based, in part, on several randomized trials that have established the capacity of both drug classes to prevent major renal outcomes in subjects with diabetic nephropathy (15-18). The recommendations are also founded on the diabetic substudy of the Heart Outcomes Prevention Evaluation (MICRO-HOPE) (ramipril vs. placebo) (19) and the Losartan Intervention for Endpoint Reduction (LIFE) study (losartan vs. atenolol) (20). In these trials, people with diabetes were clearly identified as a subgroup of a priori interest, and large reductions in major prespecified outcomes, including all-cause mortality (19,20), CV mortality (19,20) and nonfatal CV events (19,20), were seen in subjects given an ACE inhibitor or an ARB. The use of atenolol as an active comparator in LIFE does not weaken conclusions about the benefits of ARBs, because atenolol had previously been shown to reduce major CV outcomes in individuals with diabetes and hypertension (12,21).

Recommendations for the use of dihydropyridine (DHP) calcium channel blockers (CCBs) and thiazide-like diuretics are based on the results of the clinical outcomes in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) substudy (22) in people with diabetes. This study in 13 101 subjects with hypertension and diabetes was prespecified in the protocol and showed no significant differences in the incidence of the primary outcome (fatal coronary heart disease and nonfatal MI) for those assigned to a thiazide-like diuretic compared to an ACE inhibitor or a DHP CCB as first-line therapy.

The antihypertensive drugs recommended as second-line therapy are supported by several generally less definitive studies. For example, the apparent equivalence of captopril and atenolol in the UKPDS (which was insufficiently powered to detect a difference) warrants a grade B recommendation for cardioselective beta blockers (21). The International Verapamil-Trandolapril Study (INVEST), an RCT of 22 576 patients with CAD and hypertension, compared atenolol- to verapamil-based treatment with the addition of an ACE inhibitor in 80 and 75% of cases, respectively. A prespecified analysis of subjects with diabetes found no differences in the first occurrence of the primary outcomes of death and fatal and nonfatal strokes (23).

Add-on therapy consists of combinations of first-line therapies. The results of a large RCT, the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) trial, which assessed the fixed combination of an ACE inhibitor (perindopril) plus a thiazide-like diuretic (indapamide) vs. placebo in 11 140 individuals with type 2 diabetes, were recently published (24). Mean entry BP was 145±22 / 81±11 mm Hg, and 75% of the patients were receiving BP-lowering medication prior to the addition of the combination or placebo. A mean systolic BP reduction of 5.6 mm Hg (95% CI, 5.2–6.0) and a mean diastolic BP reduction of 2.2 mm Hg (95% CI, 2.0–2.4) were associated with a reduction in total and CV mortality. No other trials have specifically compared various second-line medications in hypertensive patients with diabetes.

The key objective in the management of hypertension is to obtain systolic and diastolic BP targets, and multiple drugs will often be needed to meet such targets. Specifically, direct relationships have been seen between the size of the incremental BP reduction and the subsequent reduction in hypertension-related complications (2,13,24). For example, in the UKPDS, 29% of subjects randomized to tight BP control required ≥3 antihypertensive drugs by the trial's end (12). In ALLHAT (22), the mean number of medications was >2, and up to one-third of subjects required >3 medications. Thus, any BP reduction was associated with a lower risk of complications, but larger BP reductions were associated with larger reductions in risk and required multiple medications.

Two studies have looked post hoc at the effects of thiazide-like diuretics (Systolic Hypertension in the Elderly Program [SHEP]) (25) and long-acting DHP CCBs (Systolic Hypertension in Europe [Syst-Eur] Trial) (26) in subjects with isolated systolic hypertension and diabetes. In both cases, there were statistically significant reductions in CV events.

The recommendation to avoid alpha-blockers as monotherapy or as add-on therapy ahead of other antihypertensive classes is based on ALLHAT, in which the alpha-blocker arm of the trial was stopped early because of a significantly higher risk for stroke and combined CV events compared to subjects randomized to diuretic therapy (27).

OTHER RELEVANT GUIDELINES

Physical Activity and Diabetes, p. S37
Nutrition Therapy, p. S40
Identification of Individuals at High Risk of Coronary
 Events, p. S95
Screening for the Presence of Coronary Artery Disease, p. S99
Vascular Protection in People With Diabetes, p. S102
Chronic Kidney Disease in Diabetes, p. S126

RELATED WEBSITES

Canadian Hypertension Education Program. Available at: http://www.hypertension.ca/chep. Accessed September 1, 2008.

REFERENCES

1. Geiss LS, Rolka DB, Engelgau MM. Elevated blood pressure among U.S. adults with diabetes, 1988-1994. *Am J Prev Med*. 2002;22:42-48.

2. Adler AI, Stratton IM, Neil HA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *BMJ*. 2000;321:412-419.

3. Booth GL, Rothwell DM, Fung K, et al. Diabetes and cardiac disease. In: Hux J, Booth G, Slaughter P, et al. *Diabetes in Ontario: An ICES Practice Atlas*. Toronto, ON: Institute for Clinical Evaluative Sciences; 2003:5.95-5.112.

4. Hanefeld M, Schmechel H, Schwanebeck U, et al. Predictors of coronary heart disease and death in NIDDM: the Diabetes Intervention Study experience. *Diabetologia*. 1997;40(suppl 2): S123-S124.

5. Hanefeld M, Fischer S, Julius U, et al. Risk factors for myocardial infarction and death in newly detected NIDDM: the Diabetes Intervention Study, 11-year follow-up. *Diabetologia*. 1996;39:1577-1583.

6. Sowers JR, Epstein M, Frohlich ED. Diabetes, hypertension, and cardiovascular disease: an update. *Hypertension*. 2001;37: 1053-1059.

7. Sowers JR, Epstein M. Diabetes mellitus and associated hypertension, vascular disease, and nephropathy. An update. *Hypertension*. 1995;26(6 Pt 1):869-879.

8. Hansson L, Lindholm LH, Niskanen L, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet*. 1999;353:611-616.

9. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002;288:2981-2997.

10. Julius S, Kjeldsen SE, Weber M, et al; VALUE trial group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet*. 2004;363:2022-2031.

11. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet*. 1998;351:1755-1762.

12. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ*. 1998;317:703-713.

13. Orchard TJ, Forrest KY, Kuller LH, et al; Pittsburgh Epidemiology of Diabetes Complications Study. Lipid and blood pressure treatment goals for type 1 diabetes: 10-year incidence data from the Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetes Care*. 2001;24:1053-1059.

14. Schrier RW, Estacio RO, Esler A, et al. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. *Kidney Int.* 2002;61:1086-1097.

15. Lewis EJ, Hunsicker LG, Bain RP, et al. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med.* 1993;329:1456-1462.

16. Lewis EJ, Hunsicker LG, Clarke WR, et al; Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med.* 2001;345:851-860.

17. Brenner BM, Cooper ME, de Zeeuw D, et al; RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med.* 2001;345:861-869.

18. The ACE Inhibitors in Diabetic Nephropathy Trialist Group. Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta-analysis of individual patient data. *Ann Intern Med.* 2001;134:370-379.

19. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet.* 2000;355:253-259.

20. Lindholm LH, Ibsen H, Dahlof B, et al; LIFE Study Group. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet.* 2002;359:1004-1010.

21. UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. *BMJ.* 1998;317:713-720.

22. Whelton PK, Barzilay J, Cushman WC, et al; ALLHAT Collaborative Research Group. Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med.* 2005;165:1401-1409.

23. Bakris GL, Gaxiola E, Messerli FH, et al; INVEST Investigators. Clinical outcomes in the diabetes cohort of the INternational VErapamil SR-Trandolapril study. *Hypertension.* 2004;44:637-642.

24. Patel A, ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomized controlled trial. *Lancet.* 2007;370:829-840.

25. Curb JD, Pressel SL, Cutler JA, et al. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. Systolic Hypertension in the Elderly Program Cooperative Research Group. *JAMA.* 1996;276:1886-1892.

26. Tuomilehto J, Rastenyte D, Birkenhager WH, et al. Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *N Engl J Med.* 1999;340:677-684.

27. ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *JAMA.* 2000;283:1967-1975.

Management of Acute Coronary Syndromes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee
The initial draft of this chapter was prepared by David Fitchett MD FRCPC

KEY MESSAGES

- Diabetes is an independent predictor of increased short- and long-term mortality, recurrent myocardial infarction (MI) and the development of heart failure in patients with acute MI (AMI).

- Patients with an AMI and hyperglycemia should receive insulin-glucose infusion therapy to maintain blood glucose between 7.0 and 10.0 mmol/L for at least 24 hours, followed by multidose subcutaneous insulin for at least 3 months.

- People with diabetes are less likely to receive recommended treatment such as revascularization, thrombolysis, beta blockers or acetylsalicylic acid (ASA) than people without diabetes. Efforts should be directed at promoting adherence to existing proven therapies in the high-risk patient with MI and diabetes.

INTRODUCTION

Acute myocardial infarction (AMI) is responsible for about 11% of deaths in Canada each year. This represents about half of all deaths attributable to coronary artery disease (1). Approximately 30% of hospital admissions for AMI are in patients with diabetes (2-6). The hospital admission rates for AMI, corrected for age and sex differences, are over 3-fold higher in patients with diabetes (7). Diabetes is an independent predictor of increased short- and long-term mortality, recurrent MI and the development of heart failure in patients with AMI (8-10). Predictors of 1-year mortality in the person with diabetes and AMI include blood glucose (BG) level at hospital admission, age, blood pressure (BP), prior MI, duration of diabetes, insulin therapy and urine albumin level (11,12).

THERAPEUTIC STRATEGIES IN ACUTE CORONARY SYNDROMES

Guidelines for the management of patients with acute coronary syndromes (ACS) have been developed by the American College of Cardiology/American Heart Association (13-15) and the European Society of Cardiology (16). In most situations, there are no clinical trials that specifically address management of the patient with diabetes and ACS. However, subgroup analyses in patients with diabetes and ACS show either a similar or enhanced benefit from treatment compared to the overall group for a) reperfusion with fibrinoly-sis (17) or primary angioplasty (18,19) for ST-segment elevation ACS; and b) high-risk non-ST-segment elevation ACS with an early invasive strategy (20), the use of dual antiplatelet therapy with acetylsalicylic acid (ASA) and clopidogrel (21), and glycoprotein IIb/IIIa inhibitors in patients with non-ST segment elevation ACS (22).

ISSUES IN THE MANAGEMENT OF THE PATIENT WITH DIABETES AND ACS

Thrombolysis and ocular hemorrhage

There is concern that the risk of ocular hemorrhage is increased in the person with diabetes. In the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO 1) trial, there was no intra-ocular hemorrhage in the more than 6000 patients with diabetes who received thrombolytic therapy (23). Intra-ocular hemorrhage is an extremely rare complication of diabetes; consequently, diabetic retinopathy should not be considered a contraindication to fibrinolysis in patients with ST-segment elevation MI (STEMI) and diabetes (23).

Glycemic control

Hyperglycemia in the early hours after presentation is associated with increased in-hospital and 6-month mortality, independent of the presence of diabetes (24-26), and admission BG is an independent predictor of survival after AMI (25). The Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI 1) study (27-32) indicated that tight glycemic control with the use of intravenous insulin in the early hours after presentation, followed by multidose subcutaneous insulin treatment over the subsequent months, resulted in a 30% reduction in 1-year mortality. The DIGAMI 2 study (33) failed to achieve the study goals, both in the number of patients recruited and in glycemic control, but despite these limitations, it did demonstrate that outcomes were closely related to glycemic control, however achieved. Studies have shown that glucose-insulin-potassium infusion in patients with AMI do not improve outcomes. However, these protocols often resulted in increased BG levels, and therefore cannot be used as evidence for outcomes associated with glycemic control. In the Hyperglycemia: Intensive Insulin Infusion in Infarction (HI-5) study (34) of glucose and insulin in patients with AMI, patients with BG maintained <8.0 mmol/L had lower mortality than subjects with higher levels.

Long-term management

The discharge prescription for a patient with ACS includes dual antiplatelet therapy with ASA and clopidogrel, a beta-adrenergic blocker, an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II antagonist (ARB) and a statin.

An ACE inhibitor should be given within the first 24 hours to patients with anterior AMI, pulmonary congestion or left ventricular ejection fraction (LVEF) <40%. Benefits from ACE inhibition are observed in patients with diabetes (35,36) who have a LVEF <40% or heart failure during hospitalization. An ARB may be used for patients who cannot tolerate an ACE inhibitor and have either clinical or radiologic signs of heart failure or LVEF <40% (37). Most patients with diabetes and ACS will benefit from ACE inhibitor or ARB therapy to prevent recurrent vascular events (see "Vascular Protection in People With Diabetes," p. S102).

Long-term beta blockade provides similar long-term benefit for the patient with or without diabetes (38,39). Mortality is reduced 23% (95% CI, 15–31%), and 42 patients treated for 2 years will result in 1 life saved (37). Beta blockers are used less often in patients with diabetes following ACS, despite a greater absolute benefit (40). Part of this care gap may result from concern that beta blockade could both prolong an episode of hypoglycemia and/or mask hypoglycemic symptoms. However, the treatment benefits outweigh this relatively small risk. Use of a beta-1 selective beta blocker (e.g. metoprolol or bisoprolol) may reduce the risk of hypoglycemia.

Treatment gap

Despite their significantly higher risk of death and recurrent vascular events, people with diabetes are less likely to be followed by a cardiologist (41) or to receive recommended evidence-based treatment such as revascularization, thrombolysis, beta blockers or ASA than people without diabetes (42-47). The treatment gap may be 1 reason for the poorer outcomes seen in the patient with diabetes. Efforts should be directed at promoting adherence to existing proven therapies in the high-risk patient with MI and diabetes. Strategies such as quality assurance assessment and structured order sheets should be developed to promote improved application of evidence-based proven therapy in the patient with MI.

OTHER RELEVANT GUIDELINES

Insulin Therapy in Type 1 Diabetes, p. S46
Pharmacologic Management of Type 2 Diabetes, p. S53
In-hospital Management of Diabetes, p. S71
Screening for the Presence of Coronary Artery
 Disease, p. S99
Vascular Protection in People With Diabetes, p. S102

RECOMMENDATIONS

1. In patients with diabetes and acute STEMI, the presence of retinopathy should not be a contraindication to fibrinolysis [Grade B, Level 2 (23)].

2. All patients with AMI, regardless of whether or not they have a prior diagnosis of diabetes, should have their BG level measured on admission [Grade D, Consensus]. Those with BG >12.0 mmol/L should receive insulin-glucose infusion therapy to maintain BG between 7.0 and 10.0 mmol/L for at least 24 hours, followed by multidose subcutaneous insulin for at least 3 months [Grade A, Level 1A (29,32)]. An appropriate protocol should be developed and staff trained to ensure the safe and effective implementation of this therapy and to minimize the likelihood of hypoglycemia [Grade D, Consensus].

3. As beta blockers provide similar or enhanced survival benefit in patients with diabetes and MI compared to patients without diabetes, they should be prescribed and not withheld because of concern about the risks associated with hypoglycemia [Grade D, Consensus].

REFERENCES

1. Healthy Ontario.com. Available at: http://www.healthyontario.com/ConditionDetails.aspx?disease_id=163. Accessed September 1, 2008.

2. Hochman JS, McCabe CH, Stone PH, et al, for the TIMI Investigators. Outcome and profile of women and men presenting with acute coronary syndromes: a report from TIMI IIIB. Thrombolysis in Myocardial Infarction. *J Am Coll Cardiol.* 1997;30:141-148.

3. Malmberg K, Ryden L. Myocardial infarction in patients with diabetes mellitus. *Eur Heart J.* 1988;9:259-264.

4. Bittl JA, Strony J, Brinker JA, et al, for the Hirulog Angioplasty Study Investigators. Treatment with bivalirudin (Hirulog) as compared with heparin during coronary angioplasty for unstable or postinfarction angina. *N Engl J Med.* 1995;333:764-769.

5. Topol EJ, Fuster V, Harrington RA, et al. Recombinant hirudin for unstable angina pectoris. A multicenter, randomized angiographic trial. *Circulation.* 1994;89:1557-1566.

6. Stone PH, Thompson B, Anderson HV, et al. Influence of race, sex, and age on management of unstable angina and non-Q-wave myocardial infarction: the TIMI III registry. *JAMA.* 1996; 275:1104-1112.

7. Booth GL, Rothwell DM, Fung K, et al. Diabetes and cardiac disease. In: Hux J, Booth G, Slaughter P, et al. *Diabetes in Ontario: An ICES Practice Atlas.* Toronto, ON: Institute for Clinical Evaluative Sciences; 2003:5.95-5.112.

8. Haffner SM, Lehto S, Ronnemaa T, et al. Mortality for coronary heart disease in subjects with type 2 diabetes and in non-diabetic subjects with and without prior myocardial infarction. *N Engl J Med.* 1998;339:229-234.

9. Sprafka JM, Burke GL, Folsom AR, et al. Trends in prevalence

of diabetes mellitus in patients with myocardial infarction and effect of diabetes on survival. The Minnesota Heart Survey. *Diabetes Care*. 1991;14:537-543.

10. Fuller JH, Stevens LK, Wang SL. Risk factors for cardiovascular mortality and morbidity: the WHO Mutinational Study of Vascular Disease in Diabetes. *Diabetologia*. 2001;44(suppl 2): S54-S64.

11. Malmberg K, Ryden L, Hamsten A, et al. Mortality prediction in diabetic patients with myocardial infarction: experiences from the DIGAMI study. *Cardiovasc Res*. 1997;34:248-253.

12. Stevens RJ, Coleman RL, Adler AI, et al. Risk factors for myocardial infarction case fatality and stroke case fatality in type 2 diabetes: UKPDS 66. *Diabetes Care*. 2004;27:201-207.

13. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST elevation myocardial infarction — executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *Circulation*. 2004;110:588-636.

14. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction— summary article: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee on the Management of Patients with Unstable Angina). *J Am Coll Cardiol*. 2002;40:1366-1374.

15. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). *J Am Coll Cardiol*. 2000;36:970-1062.

16. Bertrand ME, Simmoons ML, Fox KA, et al. Management of acute coronary syndromes: acute coronary syndromes without persistent ST segment elevation. Recommendations of the Task Force of the European Society of Cardiology. *Eur Heart J*. 2000; 21:1406-1432.

17. Fibrinolytic Therapy Trialists (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomized trials of more than 1000 patients. *Lancet*. 1994;343:311-322.

18. Grines C, Patel A, Zijlstra F, et al; PCAT Collaborators. Percutaneous transluminal coronary angioplasty. Primary coronary angioplasty compared with intravenous thrombolytic therapy for acute myocardial infarction: six-month follow up and analysis of individual patient data from randomized trials. *Am Heart J*. 2003;145:47-57.

19. Bonnefoy E, Steg PG, Chabaud S, et al. Is primary angioplasty more effective than prehospital fibrinolysis in diabetics with acute myocardial infarction? Data from the CAPTIM randomized clinical trial. *Eur Heart J*. 2005;26:1712-1718.

20. Cannon CP, Weintraub WS, Demopoulos LA et al; TACTICS (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy) — Thrombolysis in Myocardial Infarction 18 Invest. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med*. 2001;344:1879-1887.

21. Yusuf S, Zhao F, Mehta SR, et al; Clopidogrel in Unstable Angina to Prevent recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;345:494-502.

22. Roffi M, Chew DP, Mukherjee D, et al. Platelet glycoprotein IIb/IIIa inhibitors reduce mortality in diabetic patients with non-ST-segment-elevation acute coronary syndromes. *Circulation*. 2001;104:2767-2771.

23. Mahaffey KW, Granger CB, Toth CA, et al. Diabetic retinopathy should not be a contraindication to thrombolytic therapy for acute myocardial infarction: a review of ocular hemorrhage incidence and location in the GUSTO-I trial. Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries. *J Am Coll Cardiol*. 1997;30:1606-1610.

24. Ishihara M, Kojima S, Sakamoto T, et al. Acute hyperglycemia is associated with adverse outcome after acute myocardial infarction in the coronary intervention era. *Am Heart J*. 2005; 150:814-820.

25. Hadjadj S, Coisne D, Mauco G, et al. Prognostic value of admission plasma glucose and HbA in acute myocardial infarction. *Diabet Med*. 2004;21:305-310.

26. Ainla T, Baburin A, Teesalu R, et al. The association between hyperglycaemia on admission and 180-day mortality in acute myocardial infarction patients with and without diabetes. *Diabet Med*. 2005;22:1321-1325.

27. Almbrand B, Johannesson M, Sjostrand B, et al. Cost-effectiveness of intense insulin treatment after acute myocardial infarction in patients with diabetes mellitus; results from the DIGAMI study. *Eur Heart J*. 2000;21:733-739.

28. Davies MJ, Lawrence IG. DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction): theory and practice. *Diabetes Obes Metab*. 2002;4:289-295.

29. Malmberg K. Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group. *BMJ*. 1997;314:1512-1515.

30. Malmberg K, Ryden L, Hamsten A, et al. Effects of insulin treatment on cause-specific one-year mortality and morbidity in diabetic patients with acute myocardial infarction. DIGAMI Study Group. Diabetes Insulin-Glucose in Acute Myocardial Infarction. *Eur Heart J*. 1996;17:1337-1344.

31. Malmberg KA, Efendic S, Ryden LE. Feasibility of insulin-glucose infusion in diabetic patients with acute myocardial infarction. A report from the multicenter trial: DIGAMI. *Diabetes Care*. 1994;17:1007-1014.

32. Malmberg K, Ryden L, Efendic S, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol.* 1995;26:57-65.

33. Malmberg K, Ryden L, Wedel H, et al; DIGAMI Investigators. Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on mortality and morbidity. *Eur Heart J.* 2005;26:650-661.

34. Cheung NW, Wong VW, McLean M. The Hyperglycemia: Intensive Insulin Infusion in Infarction (HI-5) study: a randomized controlled trial of insulin infusion therapy for myocardial infarction. *Diabetes Care.* 2006;29:765-770.

35. Gustafsson I, Torp-Pedersen C, Kober L, et al. Effect of the angiotensin-converting enzyme inhibitor trandolapril on mortality and morbidity in diabetic patients with left ventricular dysfunction after acute myocardial infarction. Trace Study Group. *J Am Coll Cardiol.* 1999;34:83-89.

36. Borghi C, Bacchelli S, Esposti DD, et al; SMILE Study. Effects of the early ACE inhibition in diabetic nonthrombolyzed patients with anterior acute myocardial infarction. *Diabetes Care.* 2003;26:1862-1868.

37. Freemantle N, Cleland J, Young P, et al. Beta blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ.* 1999;318:1730-1737.

38. Kjekshus J, Gilpin E, Cali G, et al. Diabetic patients and beta-blockers after myocardial infarction. *Eur Heart J.* 1990;11:43-50.

39. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet.* 2001;357:1385-1390.

40. Younis N, Burnham P, Patwala A, et al. Beta blocker prescribing differences in patients with and without diabetes following a first myocardial infarction. *Diabet Med.* 2001;18:159-161.

41. Alter DA, Khaykin Y, Austin PC, et al. Processes and outcomes of care for diabetic acute myocardial infarction patients in Ontario: do physicians undertreat? *Diabetes Care.* 2003;26:1427-1434.

42. Franklin K, Goldberg RJ, Spencer F, et al. Implications of diabetes in patients with acute coronary syndromes. The Global Registry of Acute Coronary Events. *Arch Intern Med.* 2004;164:1457-1463.

43. Eagle KA, Goodman SG, Avezum A, et al. Practice variation and missed opportunities for reperfusion in ST-segment-elevation myocardial infarction: findings from the Global Registry of Acute Coronary Events (GRACE). *Lancet.* 2002;359:373-377.

44. Ohman EM, Roe MT, Smith SC Jr., et al; CRUSADE Investigators. Care of non-ST-segment elevation patients: insights from the CRUSADE national quality improvement initiative. *Am Heart J.* 2004;148(5 suppl):S34-S39.

45. Norhammar A, Malmberg K, Ryden L, et al. Under utilisation of evidence-based treatment partially explains for the unfavourable prognosis in diabetic patients with acute myocardial infarction. *Eur Heart J.* 2003;24:838-844.

46. Yan RT, Yan AT, Tan M, et al; Canadian Acute Coronary Syndrome Registry Investigators. Underuse of evidence-based treatment partly explains the worse clinical outcomes in diabetic patients with acute coronary syndromes. *Am Heart J.* 2006;152:676-683.

47. Brogan GX Jr., Peterson ED, Mulgund J, et al. Treatment disparities in the care of patients with and without diabetes presenting with non-ST-segment elevation acute coronary syndromes. *Diabetes Care.* 2006;29:9-14.

Treatment of Diabetes in People With Heart Failure

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was written by Malcolm Arnold MD FRCPC FRCP FACC

KEY MESSAGES

- Heart failure is still underrecognized and misdiagnosed. This has significant clinical implications, as the prognosis of untreated or undertreated heart failure is poor, yet very effective proven therapies are widely available to most physicians.

- Diabetes can cause heart failure independently of ischemic heart disease by causing a diabetic cardiomyopathy. The incidence of heart failure is 2- to 4-fold higher in people with diabetes compared to those without.

- Generally, heart failure in people with diabetes should be treated similarly to heart failure in those without diabetes, although comorbidities such as renal dysfunction may be more prevalent in people with diabetes and may influence heart failure drug doses and monitoring of therapy.

INTRODUCTION

Type 2 diabetes often occurs in association with other cardiovascular risk factors such as hypertension, dyslipidemia, smoking and obesity, which together are strongly associated with atherosclerosis, ischemic heart disease and left ventricular (LV) dysfunction. LV dysfunction can be clinically silent or associated with the typical clinical signs and symptoms of heart failure (e.g. peripheral edema, shortness of breath and fatigue), although the elderly may have atypical symptoms (1). These symptoms need to be differentiated from other conditions that may have similar presentations, such as chronic obstructive pulmonary disease, pneumonia, anemia, varicose veins, depression etc.

HEART FAILURE IN PEOPLE WITH DIABETES

The diagnosis of heart failure is made by association of typical clinical signs and symptoms with objective evidence such as that obtained from a chest X-ray, an echocardiogram or plasma natriuretic peptide testing (brain natriuretic peptide [BNP] and prohormone of BNP [NT-pro-BNP]) (1). Documentation of systolic and diastolic myocardial function is recommended at the time of diagnosis of heart failure or with a significant change in clinical stability. Heart failure can occur over the entire range of LV ejection fractions (LVEFs), from <10% to >60%. The measurement of plasma BNP and NT-pro-BNP, which are acutely released by ventricular myocytes when the myocardium is stretched due to increased filling pressures, may help make an accurate diagnosis where clinical uncertainty exists (2). However, the practising physician may still underrecognize and misdiagnose heart failure. This has significant clinical implications, as the prognosis of untreated or undertreated heart failure is poor, yet very effective proven therapies are widely available to most physicians.

Diabetes is associated with increased prevalence of heart failure, both systolic (commonly defined as an LVEF <40%) and diastolic (commonly defined as an LVEF >50%, but also referred to as preserved systolic function or preserved ejection fraction). However, the overlap between systolic and diastolic heart failure is considerable, and many people have a combination of systolic and diastolic dysfunction, although one is often reported to be predominant. Current tests such as echocardiography do usually fully characterize all aspects of systolic and diastolic dysfunction in individuals.

It is recognized that diabetes can cause heart failure independently of ischemic heart disease by causing a diabetic cardiomyopathy (3). Epidemiological studies have shown that the incidence of heart failure is 2- to 4-fold higher in people with diabetes compared to those without diabetes (4,5). While an increase in glycated hemoglobin among individuals with diabetes is a recognized risk factor for heart failure (6-10), no study to date has demonstrated that improved glycemic control significantly reduces the incidence of heart failure (11). Microalbuminuria is also an independent risk factor for heart failure, especially in people with diabetes. In individuals with and without diabetes, increasing urinary albumin to creatinine ratio is associated with a stepwise increase (2- to 4-fold) in the risk of heart failure development (8,12). Angiotensin-converting enzyme (ACE) inhibitors significantly reduce urinary albumin excretion, and in large clinical trials of subjects with cardiovascular disease or diabetes they have been shown to lower the risk of new-onset heart failure (13-15).

TREATMENT OF INDIVIDUALS WITH BOTH DIABETES AND HEART FAILURE

In most heart failure clinical trials, diabetes is present in over one-third of subjects. In the large landmark clinical trials of heart failure, there is no evidence to suggest that treatment choices for heart failure should be different in subjects with diabetes compared to those without diabetes. No large, prospective trials of heart failure have tested different heart failure drugs or doses in subjects with diabetes vs. those with-

out diabetes. Generally, heart failure in people with diabetes should be treated similarly to those without diabetes, although comorbidities such as renal dysfunction may be more prevalent in people with diabetes and may influence heart failure drug doses and monitoring of therapy. Treatment choices for diabetes (i.e. dietary and/or pharmacologic therapy) each have advantages and disadvantages in heart failure patients.

Metformin

Metformin is an effective oral antihyperglycemic agent but, based on isolated case reports and a biochemical rationale for a risk of lactic acidosis (16-18), it is approved for use under a warning in the setting of several conditions, including heart failure. Two large meta-analyses and a smaller case series have evaluated the occurrence and outcomes of lactic acidosis with the use of metformin or other antihyperglycemic agents in over 40 000 subjects, including those with heart failure. Only subjects with a serum creatinine of up to 150 µmol/L were included in the meta-analyses, and up to 200 µmol/L in the case series. Lactic acidosis was not increased, and cardiovascular outcomes in heart failure patients taking metformin were better than in those taking other antihyperglycemic agents. The current evidence suggests that patients with heart failure fare at least as well, if not better, with metformin than with other antihyperglycemic agents if they have only mild to moderate renal dysfunction (estimated glomerular filtration rate [eGFR] >30 mL/min). As such, metformin should still be considered as first-line therapy in heart failure patients with mild to moderate renal dysfunction (16-18).

Thiazolidinediones

Thiazolidinediones (TZDs) are known to cause fluid retention, although this is generally mild. Recent studies suggest that this is not a direct toxic effect on the myocardium. The Prospective Pioglitazone Clinical Trial In Macrovascular Events (PROACTIVE) study of pioglitazone in individuals at risk of cardiac ischemic events showed that TZDs were associated with fewer cardiac ischemic events, but at the cost of an increase in heart failure hospitalizations (2% absolute excess over 2.8 years, or <1% per year) (19). The recently completed Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication (DREAM) study tested whether development of diabetes could be prevented by rosiglitazone and/or ramipril (2x2 factorial design). In >5000 subjects, a significant reduction of new glucose intolerance and cardiovascular events (0.8% absolute reduction) were seen with rosiglitazone, but a small excess of new-onset heart failure was also observed (0.4% absolute excess) (20). A recently completed randomized trial comparing the efficacy of rosiglitazone, metformin or glyburide monotherapy in people with type 2 diabetes reported a greater treatment failure rate of monotherapy with glyburide or metformin compared to rosiglitazone, but an increase in reported heart failure with rosiglitazone. When only adjudicated events were considered, there was no significant difference in cardiovascular-related or heart failure-related mortality in any arm (21). Recent reports suggest that the fluid retention can be safely managed with careful observation, taking care not to increase diuretic therapy in the absence of either symptoms or signs of central volume overload rather than just peripheral edema (17,18). In an addition to product monographs in November 2007, Health Canada advised that, "Treatment with all rosiglitazone products is now contraindicated in patients with any stage of heart failure, (i.e. NYHA Class I, II, III or IV)." (22) A recent meta-analysis (23) has not confirmed any difference in the risk of congestive heart failure between rosiglitazone and pioglitazone. Glitazones may be used cautiously in patients with stable mild heart failure if close specialist monitoring is available, but should not be used in patients with unstable or severe heart failure.

A detailed discussion of the rationale and evidence for the treatment approach to heart failure patients is available in the Canadian Cardiovascular Society consensus recommendations (http://www.hfcc.ca) (1,24).

RECOMMENDATIONS

1. Individuals with diabetes and heart failure should receive the same heart failure therapies as those identified in the evidence-based Canadian Cardiovascular Society heart failure recommendations (http://www.hfcc.ca) *[Grade D, Consensus]*.

2. Unless contraindicated, metformin may be used in people with type 2 diabetes and heart failure *[Grade C, Level 3 (16,17)]*. Metformin should be temporarily withheld if renal function acutely worsens, and should be discontinued if renal function significantly and chronically worsens *[Grade D, Consensus]*.

3. Physicians should be aware that people taking TZDs are at increased risk of heart failure and may present with symptoms such as increased dyspnea and peripheral edema *[Grade B, Level 2 (19,20)]*.

4. In people with diabetes and heart failure and an eGFR <60 mL/min:
   • Starting doses of ACE inhibitors or angiotensin receptor II antagonists (ARBs) should be halved *[Grade D, Consensus]*.
   • Serum electrolytes and creatinine, blood pressure and body weight, as well as heart failure symptoms and signs, should be monitored more frequently *[Grade D, Consensus]*.
   • Dose uptitration should be more gradual (with monitoring of blood pressure, serum potassium and creatinine) *[Grade D, Consensus]*.
   • The target drug doses should be those identified in the evidence-based Canadian Cardiovascular Society recommendations on heart failure (http://www.hfcc.ca), if well tolerated *[Grade D, Consensus]*.

5. Beta blockers should be prescribed when indicated for systolic heart failure, as they provide similar benefits in people with diabetes compared with people without diabetes *[Grade B, Level 2 (25,26)]*. Where hypoglycemia is a particular concern, a selective beta blocker such as bisoprolol or metoprolol may be preferred *[Grade D, Consensus]*.

OTHER RELEVANT GUIDELINES

Physical Activity and Diabetes, p. S37
Nutrition Therapy, p. S40
Pharmacologic Management of Type 2 Diabetes, p. S53
Screening for the Presence of Coronary Artery Disease, p. S99
Vascular Protection in People With Diabetes, p. S102
Management of Acute Coronary Syndromes, p. S119

REFERENCES

1. Arnold JM, Liu P, Demers C, et al; Canadian Cardiovascular Society. Canadian Cardiovascular Society consensus recommendations on heart failure 2006: diagnosis and management. *Can J Cardiol.* 2006;22:23-45.

2. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic in the emergency diagnosis of heart failure; Breathing Not Properly Multinational Study Investigators. *N Engl J Med.* 2002;347:161-167.

3. Bell DS. Heart failure: the frequent, forgotten, and often fatal complication of diabetes. *Diabetes Care.* 2003;26:2433-2441.

4. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham Study. *Am J Cardiol.* 1974;34:29-34.

5. He J, Ogden LG, Bazzano LA, et al. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. *Arch Intern Med.* 2001;161:996-1002.

6. Johansson S, Wallander MA, Ruigomez A, et al. Incidence of newly diagnosed heart failure in UK general practice. *Eur J Heart Fail.* 2001;3:225-231.

7. Nichols GA, Gullion CM, Koro CE, et al. The incidence of congestive heart failure in type 2 diabetes: an update. *Diabetes Care.* 2004;27:1879-1884.

8. Vaur L, Gueret P, Lievre M, et al; DIABHYCAR Study Group (type 2 DIABetes, HYpertension, CArdiovascular events and Ramipril study). Development of congestive heart failure in type 2 diabetic patients with microalbuminuria or proteinuria: observations from the DIABHYCAR (type 2 DIABetes, HYpertension, CArdiovascular events and Ramipril) study. *Diabetes Care.* 2003;26:855-860.

9. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ.* 2000;321:405-412.

10. Iribarren C, Karter AJ, Go AS, et al. Glycemic control and heart failure among adult patients with diabetes. *Circulation.* 2001;103:2668-2673.

11. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet.* 1998;352:837-853.

12. Gerstein HC, Mann JF, Yi Q, et al; HOPE Study Investigators. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA.* 2001;286:421-426.

13. Arnold JM, Yusuf S, Young J, et al; HOPE Investigators. Prevention of Heart Failure in Patients in the Heart Outcomes Prevention Evaluation (HOPE) Study. *Circulation.* 2003;107:1284-1290.

14. Fox KM; EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) Investigators. Efficacy of perindopril in reduction of cardiovascular patients with stable coronary artery disease: a randomized, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet.* 2003;362:782-788.

15. Braunwald E, Domanski MJ, Fowler SE, et al; PEACE Trial Investigators. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med.* 2004;351:2058-2068.

16. Eurich DT, Majumdar SR, McAlister FA, et al. Improved clinical outcomes associated with metformin in patients with diabetes and heart failure. *Diabetes Care.* 2005;28:2345-2351.

17. Masoudi FA, Inzucchi SE, Wang Y, et al. Thiazolidinediones, metformin, and outcomes in older patients with diabetes and heart failure: an observational study. *Circulation.* 2005;111:583-590.

18. Masoudi FA, Wang Y, Inzucchi SE, et al. Metformin and thiazolidinedione use in Medicare patients with heart failure. *JAMA.* 2003;290:81-85.

19. Dormandy JA, Charbonnel B, Eckland DJ, et al; PROACTIVE Investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet.* 2005;366:1279-1289.

20. DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet.* 2006;368:1096-1105.

21. Kahn SE, Haffner SM, Heise MA, et al; ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med.* 2006;355:2427-2443.

22. GlaxoSmithKline. Health Canada Endorsed Important Safety Information on Avandia®, Avandamet® and Avandaryl®. Cardiac Safety of Avandia® (rosiglitazone maleate). November 6, 2007. Available at: avandia_hpc-cps_5-eng.pdf. Accessed September 1, 2008.

23. Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomized clinical trials. *Lancet.* 2007;370:1129-1136.

24. Arnold JM, Howlett JG, Dorian P, et al. Canadian Cardiovascular Society Consensus Conference recommendations on heart failure update 2007: prevention, management during intercurrent illness or acute decompensation, and use of biomarkers. *Can J Cardiol.* 2007;23:21-45.

25. Bell DS, Lukas MA, Holdbrook FK, et al. The effect of carvedilol on mortality risk in heart failure patients with diabetes: results of a meta-analysis. *Curr Med Res Opin.* 2006;22:287-296.

26. Haas SJ, Vos T, Gilbert RE, et al. Are beta-blockers as efficacious in patients with diabetes mellitus as in patients without diabetes mellitus who have chronic heart failure? A meta-analysis of large-scale clinical trials. *Am Heart J.* 2003;146:848-853.

COMPLICATIONS AND COMORBIDITIES

Chronic Kidney Disease in Diabetes

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee
The initial version of this chapter was written by Philip McFarlane MD FRCPC and Bruce Culleton MD FRCPC

KEY MESSAGES

- Identification of chronic kidney disease (CKD) in diabetes requires screening for proteinuria, as well as an assessment of renal function.

- All individuals with CKD should be considered at high risk for cardiovascular events, and should be treated to reduce these risks.

- The progression of renal damage in diabetes can be slowed through intensive glycemic control and optimization of blood pressure. Progression of diabetic nephropathy can be slowed through the use of medications that disrupt the renin-angiotensin-aldosterone system.

INTRODUCTION

Chronic kidney disease (CKD) is one of the most common and potentially devastating complications of diabetes. Fifty percent of people with diabetes have CKD, and CKD associated with diabetes is the leading cause of kidney failure in Canada (1-4). CKD in diabetes can be due to classic diabetic nephropathy or other forms of kidney damage. Classic diabetic nephropathy progresses from subclinical disease to the earliest clinically detectable stage characterized by persistent proteinuria (2,5,6) (Figure 1). The degree of proteinuria is characterized as either microalbuminuria (urinary albumin 30 to 300 mg/day) or overt nephropathy (urinary albumin >300 mg/day) (Table 1). Typica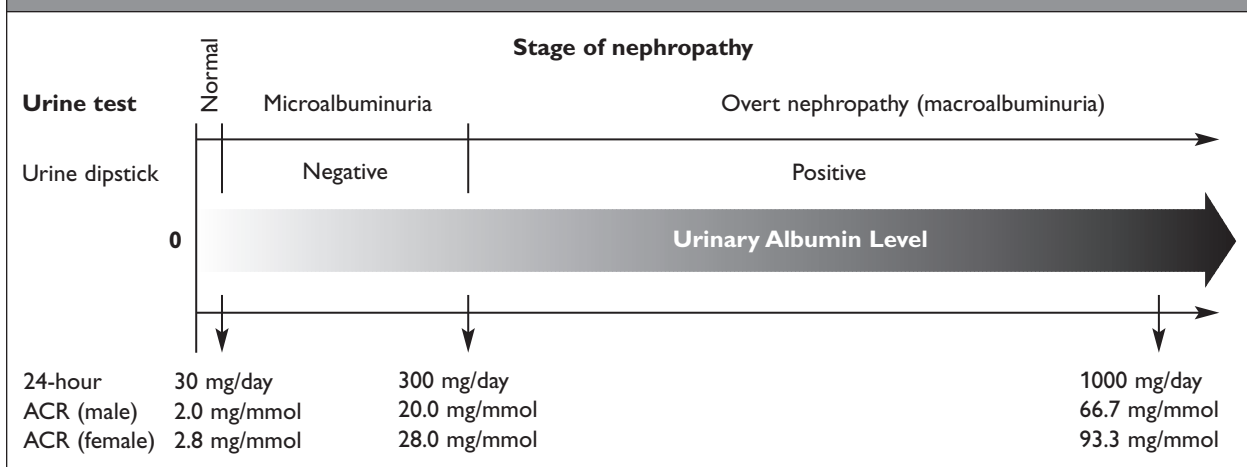lly it takes many years to progress through these stages (2,7,8), and significant renal dysfunction is not usually seen until late in the course (9). Because type 2 diabetes can be unrecognized for a long time prior to diagnosis, it is possible for renal disease, including advanced nephropathy, to be present at the time of diagnosis of type 2 diabetes (10,11).

Although diabetic nephropathy is common, as many as 50% of people with diabetes and significant renal dysfunction have normal urinary albumin levels with renal disease that is not related to classic diabetic nephropathy (12). For example, hypertensive nephrosclerosis and renovascular disease are common causes of CKD in people with diabetes. Table 2 lists indicators that favour the presence of renovascular disease. The risk of end-stage renal disease in diabetes does not appear to vary significantly whether the kidney disease is related to diabetic nephropathy or alternative renal diagnoses (13). Thus, identification of CKD in diabetes requires screening for proteinuria, as well as an assessment of renal function.

Regardless of the cause, the stage of kidney disease can be classified based on the level of renal function (Table 3). In the case of diabetes, the kidney damage associated with stage 1 or 2 CKD manifests as persistent albuminuria (see Screening, p. S127).

It is also important to recognize that people with CKD are among those at highest risk for cardiovascular (CV) morbidity and mortality, and that interventions to lower CV risk remain the most important priority in this population (14,15).

Figure 1. Stage of diabetic nephropathy by level of urinary albumin by various test methods

	Normal	Microalbuminuria	Overt nephropathy (macroalbuminuria)
Urine dipstick		Negative	Positive
	0	Urinary Albumin Level	
24-hour	30 mg/day	300 mg/day	1000 mg/day
ACR (male)	2.0 mg/mmol	20.0 mg/mmol	66.7 mg/mmol
ACR (female)	2.8 mg/mmol	28.0 mg/mmol	93.3 mg/mmol

ACR = albumin to creatinine ratio

Table 1. Stages of classic diabetic nephropathy according to urinary albumin level

Stage of nephropathy	Urine dipstick for protein	Urine ACR (mg/mmol)	24- urine collection for albumin* (mg/day)
Normal	Negative	<2.0 (men) <2.8 (women)	<30
Micro-albuminuria	Negative	2.0–20.0 (men) 2.8–28.0 (women)	30–300
Overt nephropathy (macroalbu-minuria)	Positive	>20.0 (men) >28.0 (women) >66.7 (men) >93.3 (women)	>300 >1000

*Values are for urinary albumin, not total urinary protein, which will be higher than urinary albumin levels. ACR results may be elevated with conditions other than diabetic nephropathy (see text and Table 4)

ACR = albumin to creatinine ratio

Table 2. Factors favouring the presence of renovascular disease

- Severe or refractory hypertension
- Low eGFR with normal or near-normal ACR
- Low or low-normal serum potassium (especially if patient is on an ACE inhibitor or an ARB)
- Flank or abdominal bruits
- >30% rise in serum creatinine following initiation of an ACE inhibitor or an ARB
- Presence of aortic or peripheral arterial disease
- "Flash" pulmonary edema
- Asymmetric renal size on ultrasound
- Advanced hypertensive retinopathy

ACE = angiotensin-converting enzyme
ACR = albumin to creatinine ratio
ARB = angiotensin II receptor antagonist
eGFR = estimated glomerular filtration rate

SCREENING

Identification of CKD in diabetes is usually a clinical diagnosis, requiring a kidney biopsy only when clinical indicators leave doubt as to the diagnosis. A person with diabetes is considered to have CKD if he or she has classic diabetic nephropathy (as evidenced by persistent albuminuria regardless of level of kidney function), or significantly reduced kidney function (as evidenced by an estimated glomerular filtration rate [eGFR] ≤60 mL/min). Table 4 lists indicators that favour the diagnosis of either diabetic or nondiabetic nephropathy (16-19). As kidney damage is often asymptomatic until severe, screening must be performed to

Table 3. Stages of CKD of all types

Stage	Qualitative description	eGFR (mL/min)
1	Kidney damage, normal GFR	≥90
2	Kidney damage, mildly decreased GFR	60–89
3	Moderately decreased GFR	30–59
4	Severely decreased GFR	15–29
5	End-stage renal disease	<15 (or dialysis)

CKD = chronic kidney disease
eGFR = estimated glomerular filtration rate
GFR = glomerular filtration rate

Table 4. Clinical and laboratory factors favouring the diagnosis of clinical diabetic nephropathy or an alternate renal diagnosis

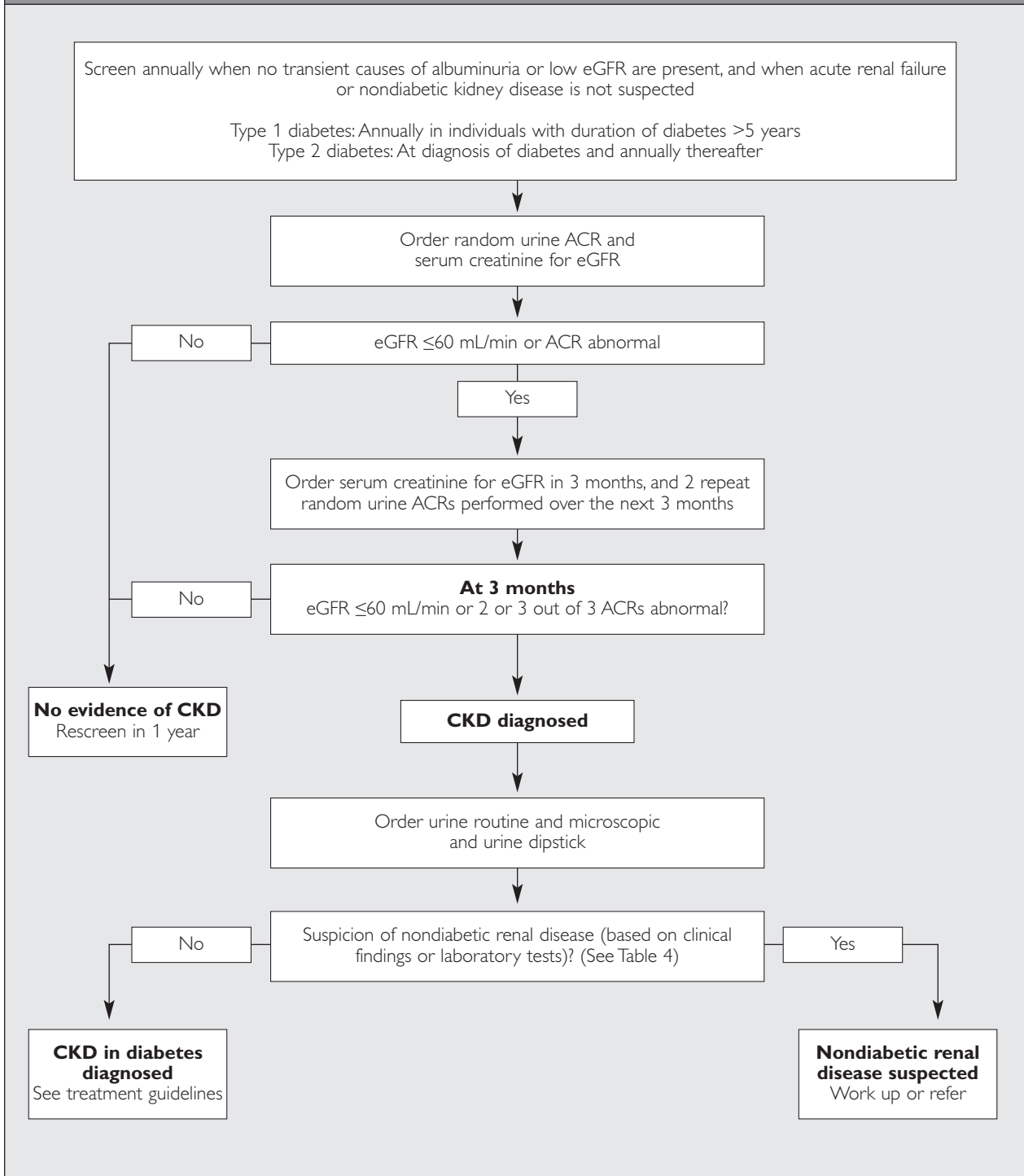| Favours diabetic nephropathy	Favours alternate renal diagnosis
• Persistent albuminuria	• Extreme proteinuria (>6 g/day)
• Bland urine sediment	• Persistent hematuria (microscopic or macroscopic) or active urinary sediment
• Slow progression of disease	• Rapidly falling eGFR
• Low eGFR associated with overt proteinuria	• Low eGFR with little or no proteinuria
• Presence of other complications of diabetes	• Other complications of diabetes not present or relatively not as severe
• Known duration of diabetes >5 years	• Known duration of diabetes ≤5 years
	• Family history of nondiabetic renal disease (e.g. polycystic kidney disease)
	• Signs or symptoms of systemic disease

eGFR = estimated glomerular filtration rate

identify renal damage in order to delay or prevent loss of renal function through early initiation of effective therapies, and to manage complications in those identified with renal disease. In adults, screening is performed by measuring urinary albumin levels and estimating the level of kidney function (Figure 2).

Urine testing

Screening for microalbuminuria should be performed using a random urine test for albumin to creatinine ratio (ACR). As transient microalbuminuria unrelated to diabetic nephropathy can occur, persistent microalbuminuria (at least 2 of 3 ACR tests positive taken at 1- to 8-week intervals) should be demonstrated before the diagnosis of nephropathy is made. Overt nephropathy rarely normalizes without treatment, and repeat ACR testing is not required to make the diagnosis of nephropathy in those with ACR values in the overt nephropathy range. A urine dipstick test should also be performed, either in the laboratory or at the point of care, as a screen for renal disease other than diabetic nephropathy.

Figure 2. Screening for CKD in adults

Screen annually when no transient causes of albuminuria or low eGFR are present, and when acute renal failure or nondiabetic kidney disease is not suspected

Type 1 diabetes: Annually in individuals with duration of diabetes >5 years
Type 2 diabetes: At diagnosis of diabetes and annually thereafter

↓

Order random urine ACR and serum creatinine for eGFR

↓

No ← eGFR ≤60 mL/min or ACR abnormal

Yes ↓

Order serum creatinine for eGFR in 3 months, and 2 repeat random urine ACRs performed over the next 3 months

↓

No ← **At 3 months**
eGFR ≤60 mL/min or 2 or 3 out of 3 ACRs abnormal?

No evidence of CKD
Rescreen in 1 year

CKD diagnosed

↓

Order urine routine and microscopic and urine dipstick

↓

No ← Suspicion of nondiabetic renal disease (based on clinical findings or laboratory tests)? (See Table 4) → Yes

CKD in diabetes diagnosed
See treatment guidelines

Nondiabetic renal disease suspected
Work up or refer

ACR = albumin to creatinine ratio   CKD = chronic kidney disease   eGFR = estimated glomerular filtration rate

Twenty-four-hour urine collections are frequently performed incorrectly, are unpopular with patients and are unnecessary in routine diabetes care (20-24). However, a 24-hour collection can be useful when there is doubt about the accuracy of an eGFR, when screening for nonalbumin urinary proteins (e.g. multiple myeloma) or when estimating daily sodium intake in an individual with refractory edema or hypertension. Individuals should be counselled to discard the first morning urine on the day of collection, and then collect all subsequent urine for a 24-hour period, including the first morning urine of the next day.

Renal function testing
Diabetic nephropathy and damage from other conditions such as hypertension and renovascular disease can lead to a loss of renal function in people with diabetes. An estimate of the kidney's ability to filter toxins from the blood should be made. Serum creatinine is the most commonly used measure of renal function; however, the creatinine may falsely indicate that a person's renal function is normal (25,26). Individuals can lose up to 50% of their renal function before serum creatinine levels rise into the abnormal range (27). The eGFR is a more sensitive method of identifying low kidney function in people with diabetes. In Canada, the eGFR is most often calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) equation, which takes into account the person's serum creatinine, age and sex. Clinicians can further adjust the eGFR for race. Calculation of the MDRD glomerular filtration rate (GFR) is complicated and typically an electronic aid (either a spreadsheet or an Internet-based tool) is used, or the GFR is calculated and reported by the laboratory automatically when a serum creatinine is ordered (28).

Delaying screening for CKD
As the ACR can be elevated with recent major exercise (29), fever (30), urinary tract infection, congestive heart failure (31), menstruation or acute severe elevations of blood pressure (BP) or blood glucose (BG) (32,33), screening for albuminuria should be delayed in the presence of these conditions. Intravascular volume contraction or any acute illness can transiently lower kidney function, and GFR estimation for screening purposes should be delayed until such conditions resolve.

TREATMENT AND FOLLOW-UP
All people with CKD should be considered to be at high risk for CV events and should be treated to reduce these risks. The progression of renal damage in diabetes can be slowed through intensive glycemic control (34) and optimization of BP (35). Progression of diabetic nephropathy can be slowed through the use of medications that disrupt the renin-angiotensin-aldosterone system (RAAS) (36). BP and glycemic targets are the same as for those individuals with diabetes without nephropathy.

In addition to BP control, some antihypertensive have been shown to have additional renal-protective properties. In type 1 diabetes, angiotensin-converting enzyme (ACE) inhibitors have been shown to decrease albuminuria and prevent worsening of nephropathy (37), and angiotensin II receptor antagonists (ARBs) have been shown to reduce proteinuria (38). In type 2 diabetes, ACE inhibitors and ARBs have been shown to decrease albuminuria and prevent worsening of nephropathy, and ARBs have been shown to delay the time to dialysis in those with renal dysfunction at baseline (39-42). In type 2 diabetes, ACE inhibitors have been shown to reduce the chance of developing new nephropathy (39,43). ACE inhibitor plus ARB combination therapy has been shown to lower BP and proteinuria in type 2 diabetes more effectively than monotherapy with either agent (44-46). These renal-protective effects also appear to be present in proteinuric individuals with diabetes and normal or near-normal BP. ACE inhibitors have been shown to reduce progression of diabetic nephropathy in normotensive individuals with type 1 (47-50) or type 2 diabetes (51). In people with diabetes, hypertension and proteinuria, nondihydropyridine calcium channel blockers (non-DHP CCBs) (diltiazem and verapamil) have been shown to decrease albuminuria and are associated with a slower loss of renal function (52-55). However, non-DHP CCBs do not prevent the development of nephropathy (43).

In CKD from causes other than diabetic nephropathy, ACE inhibition has been shown to reduce proteinuria, slow progression of renal disease and delay the need for dialysis (56,57). The issue of whether ARBs and ACE inhibitors are similarly effective in CKD that is not caused by diabetic nephropathy remains controversial (58). Compared to monotherapy with either agent, ACE inhibitor plus ARB combination therapy has been shown to reduce proteinuria (59,60).

In people with CKD and diabetes with or without hypertension, an ACE inhibitor or an ARB would be the preferred initial agent for prevention of renal disease progression. To date, there have been no large-scale hard-endpoint trials for second-line agents in nephropathy (see The Role of Proteinuria Reduction, p. S130).

Treating CKD in diabetes safely
Individuals starting therapy with an ACE inhibitor or an ARB should be monitored within 1 to 2 weeks of initiation or titration of treatment for significant worsening of renal function or the development of significant hyperkalemia. Periodic monitoring should continue in those whose serum creatinine or potassium level increases above normal laboratory limits until these values have stabilized. Serum creatinine typically increases up to 30% above baseline after initiation of an ACE inhibitor or ARB, and usually stabilizes after 2 to 4 weeks of treatment (61). ACE inhibitors and ARBs can be used safely in people with renovascular disease, unless the individual has only a single functioning kid-

RECOMMENDATIONS

1. The best possible glycemic control and, if necessary, intensive diabetes management should be instituted in people with type 1 or type 2 diabetes for the prevention of onset and delay in progression to CKD [Grade A, Level 1A (34,71,72)].

2. In adults, screening for CKD in diabetes should be conducted using a random ACR and a serum creatinine converted into an eGFR [Grade D, Consensus]. Screening should be performed annually in adults with type 1 diabetes of >5 years' duration. Individuals with type 2 diabetes should be screened at diagnosis of diabetes and yearly thereafter. Screening should be delayed when causes of transient albuminuria or low eGFR are present [Grade D, Consensus].

3. People with diabetes and CKD should have a random urine ACR and a serum creatinine converted into an eGFR performed at least every 6 months [Grade D, Consensus].

4. Adults with diabetes and persistent albuminuria (ACR >2.0 mg/mmol in males, >2.8 mg/mmol in females) should receive an ACE inhibitor or an ARB to delay progression of CKD, even in the absence of hypertension [Grade A, Level 1A (37,39-42,47,48,50,51,73), for ACE inhibitor use in type 1 and type 2 diabetes, and for ARB use in type 2 diabetes; Grade D, Consensus, for ARB use in type 1 diabetes].

5. People with diabetes on an ACE inhibitor or an ARB should have their serum creatinine and potassium levels checked within 1 to 2 weeks of initiation or titration of therapy. Potassium and serum creatinine levels should be checked in people with diabetes receiving an ACE inhibitor or ARB during times of acute illness [Grade D, Consensus].

6. The use of thiazide-like diuretics should be considered in individuals with CKD and diabetes for control of sodium and water retention, hypertension or hyperkalemia [Grade D, Consensus]. Alternatively, furosemide can be substituted for or added to thiazide-like diuretics for individuals who fail monotherapy with thiazide-like diuretics or who have severe sodium and water retention or hyperkalemia [Grade D, Consensus].

7. Consideration should be given to stopping ACE inhibitor, ARB and/or diuretic therapy during times of acute illness (e.g. febrile illness, diarrhea), especially when intravascular volume contraction is present or suspected [Grade D, Consensus]. Women should avoid becoming pregnant when receiving ACE inhibitor or ARB therapy, as the use of medications that disrupt the RAAS has been associated with adverse fetal outcomes [Grade D, Consensus].

8. A referral to a nephrologist or internist with an expertise in diabetic nephropathy should be considered if there is a chronic, progressive loss of kidney function, if the eGFR is <30 mL/minute, if the ACR is persistently >60 mg/mmol, or if the individual is unable to achieve BP targets or remain on renal-protective therapies due to adverse effects, such as hyperkalemia or a >30% increase in serum creatinine within 3 months of starting an ACE inhibitor or ARB [Grade D, Consensus].

ney or severe bilateral disease (62,63). However, serum creatinine and potassium levels should be monitored carefully if these medications are used when renovascular disease is suspected (64).

Individuals who develop mild to moderate hyperkalemia should receive nutritional counselling regarding a potassium-restricted diet, and consideration should be given to the use of nonpotassium-sparing diuretics (such as thiazides or furosemide). If an ACE inhibitor or ARB is not tolerated due to severe hyperkalemia, or >30% increase in serum creatinine or allergic reactions, the drug should be withdrawn and other ACE inhibitors or ARBs should not be substituted.

To avoid acute renal failure, ACE inhibitors, ARBs and diuretics should be stopped during acute illnesses associated with intravascular volume contraction. There is no upper limit of the serum creatinine level for initiation of ACE inhibitor or ARB therapy, but if the creatinine clearance is <30 mL/minute, these agents should be started with care or referral for specialized nephrologic care should be considered. As the use during pregnancy of medications that disrupt the RAAS have been associated with congenital malformations (65), women with diabetes of childbearing age should avoid pregnancy if ACE inhibitors or ARBs are required. If a woman with diabetes receiving ACE inhibitor or ARB therapy wishes to become pregnant, consideration should be given to stopping these drugs prior to conception.

Individuals started on a non-DHP CCB should be monitored clinically for development of bradycardia. As all nephroprotective drugs are also antihypertensives, individuals should be monitored for development of hypotension.

The role of proteinuria reduction

The amount of proteinuria correlates with the likelihood of progression of many kidney diseases, including diabetic nephropathy (66-69). Individuals with an antiproteinuric response to an ACE inhibitor or an ARB are less likely to progress to renal failure (66). These findings, in combination with basic science evidence (70), suggest that proteinuria may contribute to kidney damage, and many clinicians now target proteinuria for reduction independent of BP level. However, no large-scale hard-endpoint trials in which proteinuria reduction was the primary intervention have been completed, and the role of proteinuria as a causative factor in renal damage remains controversial. Which populations should be targeted for reduction of proteinuria, the thresholds and targets for antiproteinuric therapies, and the optimal antiproteinuric drug regimens remain topics of active research. While reduction of proteinuria in diabetic nephropathy may be desirable, it is not possible to generate a clinical practice guideline in this area at this time.

Referral

Most people with CKD and diabetes will not require referral to a specialist in renal disease. However, specialist care may be necessary when renal dysfunction is severe, when there are difficulties implementing renal-protective strategies or when there are problems managing the sequelae of renal disease (see Recommendation #8).

OTHER RELEVANT GUIDELINES

Targets for Glycemic Control, p. S29
Identification of Individuals at High Risk of Coronary Events, p. S95
Vascular Protection in People With Diabetes, p. S102
Treatment of Hypertension, p. S115
Type 1 Diabetes in Children and Adolescents, p. S150
Diabetes and Pregnancy, p. S168

RELATED WEBSITES

Canadian Hypertension Society. Available at http://www. hypertension.ca/chs. Accessed September 1, 2008.

Canadian Society of Nephrology. Available at http://www. csnscn.ca. Accessed September 1, 2008.

Nephron Information Center. Available at: http://www. nephron.com. Accessed September 1, 2008.

REFERENCES

1. Canadian Institute for Health Information (CIHI). *Canadian Organ Replacement Registry (CORR): 2001 Annual Report*. Ottawa, ON: CIHI; 2001.

2. Warram JH, Gearin G, Laffel L, et al. Effect of duration of type I diabetes on the prevalence of stages of diabetic nephropathy defined by urinary albumin/creatinine ratio. *J Am Soc Nephrol*. 1996;7:930-937.

3. Reenders K, de Nobel E, van den Hoogen HJ, et al. Diabetes and its long-term complications in general practice: a survey in a well-defined population. *Fam Pract*. 1993;10:169-172.

4. Weir MR. Albuminuria predicting outcome in diabetes: incidence of microalbuminuria in Asia-Pacific Rim. *Kidney Int*. 2004;66(suppl 92):S38-S39.

5. Mathiesen ER, Ronn B, Storm B, et al. The natural course of microalbuminuria in insulin-dependent diabetes: a 10-year prospective study. *Diabet Med*. 1995;12:482-487.

6. Lemley KV, Abdullah I, Myers BD, et al. Evolution of incipient nephropathy in type 2 diabetes mellitus. *Kidney Int*. 2000;58:1228-1237.

7. Gall MA, Nielsen FS, Smidt UM, et al. The course of kidney function in type 2 (non-insulin-dependent) diabetic patients with diabetic nephropathy. *Diabetologia*. 1993;36:1071-1078.

8. Jacobsen P, Rossing K, Tarnow L, et al. Progression of diabetic nephropathy in normotensive type 1 diabetic patients. *Kidney Int*. 1999;71(suppl):S101-S105.

9. Hasslacher C, Ritz E, Wahl P, et al. Similar risks of nephropathy in patients with type I or type II diabetes mellitus. *Nephrol Dial Transplant*. 1989;4:859-863.

10. Ballard DJ, Humphrey LL, Melton LJ, et al. Epidemiology of persistent proteinuria in type II diabetes mellitus. Population-based study in Rochester, Minnesota. *Diabetes*. 1988;37:405-412.

11. Winaver J, Teredesai P, Feldman HA, et al. Diabetic nephropathy as the mode of presentation of diabetes mellitus. *Metabolism*. 1979;28:1023-1030.

12. Middleton RJ, Foley RN, Hegarty J, et al. The unrecognized prevalence of chronic kidney disease in diabetes. *Nephrol Dial Transplant*. 2006;21:88-92.

13. Ruggenenti P, Gambara V, Perna A, et al. The nephropathy of non-insulin-dependent diabetes: predictors of outcome relative to diverse patterns of renal injury. *J Am Soc Nephrol*. 1998;9:2336-2343.

14. Gerstein HC, Mann JF, Yi Q, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and non-diabetic individuals. *JAMA*. 2001;286:421-426.

15. Gaede P, Vedel P, Parving HH, et al. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study. *Lancet*. 1999;353:617-622.

16. VenkataRaman TV, Knickerbocker F, Sheldon CV. Unusual causes of renal failure in diabetics: two case studies. *J Okla State Med Assoc*. 1990;83:164-168.

17. Clinical path conference. Unusual renal complications in diabetes mellitus. *Minn Med*. 1967;50:387-393.

18. Amoah E, Glickman JL, Malchoff CD, et al. Clinical identification of nondiabetic renal disease in diabetic patients with type I and type II disease presenting with renal dysfunction. *Am J Nephrol*. 1988;8:204-211.

19. El-Asrar AM, Al-Rubeaan KA, Al-Amro SA, et al. Retinopathy as a predictor of other diabetic complications. *Int Ophthalmol*. 2001;24:1-11.

20. Ahn CW, Song YD, Kim JH, et al. The validity of random urine specimen albumin measurement as a screening test for diabetic nephropathy. *Yonsei Med J*. 1999;40:40-45.

21. Kouri TT, Viikari JS, Mattila KS, et al. Microalbuminuria. Invalidity of simple concentration-based screening tests for early nephropathy due to urinary volumes of diabetic patients. *Diabetes Care*. 1991;14:591-593.

22. Rodby RA, Rohde RD, Sharon Z, et al. The urine protein to creatinine ratio as a predictor of 24-hour urine protein excretion in type 1 diabetic patients with nephropathy. The Collaborative Study Group. *Am J Kidney Dis*. 1995;26:904-909.

23. Chaiken RL, Khawaja R, Bard M, et al. Utility of untimed urinary albumin measurements in assessing albuminuria in black NIDDM subjects. *Diabetes Care*. 1997;20:709-713.

24. Bakker AJ. Detection of microalbuminuria. Receiver operating characteristic curve analysis favors albumin-to-creatinine ratio over albumin concentration. *Diabetes Care*. 1999;22:307-313.

25. Gault MH, Longerich LL, Harnett JD, et al. Predicting glomerular function from adjusted serum creatinine. *Nephron*. 1992;62:249-256.

26. Bending JJ, Keen H, Viberti GC. Creatinine is a poor marker

of renal failure. *Diabet Med.* 1985;2:65-66.

27. Shemesh O, Golbetz H, Kriss JP, et al. Limitations of creatinine as a filtration marker in glomerulopathic patients. *Kidney Int.* 1985;28:830-838.

28. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med.* 1999;130:461-470.

29. Huttunen NP, Kaar M, Puukka R, et al. Exercise-induced proteinuria in children and adolescents with type 1 (insulin dependent) diabetes. *Diabetologia.* 1981;21:495-497.

30. Solling J, Solling K, Mogensen CE. Patterns of proteinuria and circulating immune complexes in febrile patients. *Acta Med Scand.* 1982;212:167-169.

31. Ritz E. Nephropathy in type 2 diabetes. *J Intern Med.* 1999; 245:111-126.

32. Wiseman M, Viberti G, Mackintosh D, et al. Glycaemia, arterial pressure and micro-albuminuria in type 1 (insulin-dependent) diabetes mellitus. *Diabetologia.* 1984;26:401-405.

33. Ravid M, Savin H, Lang R, et al. Proteinuria, renal impairment, metabolic control, and blood pressure in type 2 diabetes mellitus. A 14-year follow-up report on 195 patients. *Arch Intern Med.* 1992;152:1225-1229.

34. Wang PH, Lau J, Chalmers TC. Meta-analysis of effects of intensive blood-glucose control on late complications of type I diabetes. *Lancet.* 1993;341:1306-1309.

35. Maki DD, Ma JZ, Louis TA, et al. Long-term effects of antihypertensive agents on proteinuria and renal function. *Arch Intern Med.* 1995;155:1073-1080.

36. Kasiske BL, Kalil RS, Ma JZ, et al. Effect of antihypertensive therapy on the kidney in patients with diabetes: a meta-regression analysis. *Ann Intern Med.* 1993;118:129-138.

37. Lewis EJ, Hunsicker LG, Bain RP, et al. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med.* 1993;329:1456-1462.

38. Andersen S, Tarnow L, Rossing P, et al. Renoprotective effects of angiotensin II receptor blockade in type 1 diabetic patients with diabetic nephropathy. *Kidney Int.* 2000;57:601-606.

39. Strippoli GF, Craig MC, Schena FP, et al. Role of blood pressure targets and specific antihypertensive agents used to prevent diabetic nephropathy and delay its progression. *J Am Soc Nephrol.* 2006;17(suppl 2):S153-S155.

40. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med.* 2001;345:851-860.

41. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med.* 2001;345:861-869.

42. Parving HH, Lehnert H, Brochner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med.* 2001; 345:870-878.

43. Ruggenenti P, Fassi A, Ilieva AP, et al. Preventing microalbuminuria in type 2 diabetes. *N Engl J Med.* 2004;351:1941-1951.

44. Wade VL, Gleason BL. Dual blockade of the renin-angiotensin system in diabetic nephropathy. *Ann Pharmacother.* 2004;38: 1278-1282.

45. Mogensen CE, Neldam S, Tikkanen I, et al. Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the Candesartan And Lisinopril Microalbuminuria (CALM) Study. *BMJ.* 2000;321:1440-1444.

46. Igarashi M, Hirata A, Kadomoto Y, et al. Dual blockade of angiotensin II with enalapril and losartan reduces proteinuria in hypertensive patients with type 2 diabetes. *Endocr J.* 2006; 53:493-501.

47. Laffel LM, McGill JB, Gans DJ. The beneficial effect of angiotensin-converting enzyme inhibition with captopril on diabetic nephropathy in normotensive IDDM patients with microalbuminuria. North American Microalbuminuria Study Group. *Am J Med.* 1995;99:497-504.

48. Mathiesen ER, Hommel E, Giese J, et al. Efficacy of captopril in postponing nephropathy in normotensive insulin dependent diabetic patients with microalbuminuria. *BMJ.* 1991;303:81-87.

49. Jerums G, Allen TJ, Campbell DJ, et al. Long-term comparison between perindopril and nifedipine in normotensive patients with type 1 diabetes and microalbuminuria. *Am J Kidney Dis.* 2001;37:890-899.

50. ACE Inhibitors in Diabetic Nephropathy Trialist Group. Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta-analysis of individual patient data. *Ann Intern Med.* 2001;134:370-379.

51. Ravid M, Savin H, Jutrin I, et al. Long-term stabilizing effect of angiotensin-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type II diabetic patients. *Ann Int Med.* 1993;118:577-581.

52. Bakris GL, Copley JB, Vicknair N, et al. Calcium channel blockers versus other antihypertensive therapies on progression of NIDDM associated nephropathy. *Kidney Int.* 1996; 50:1641-1650.

53. Bakris GL, Weir MR, DeQuattro V, et al. Effects of an ACE inhibitor/calcium antagonist combination on proteinuria in diabetic nephropathy. *Kidney Int.* 1998;54:1283-1289.

54. Perez-Maraver M, Carrera MJ, Micalo T, et al. Renoprotective effect of diltiazem in hypertensive type 2 diabetic patients with persistent microalbuminuria despite ACE inhibitor treatment. *Diabetes Res Clin Pract.* 2005;70:13-19.

55. Bakris GL, Weir MR, Secic M, et al. Differential effects of calcium antagonist subclasses on markers of nephropathy progression. *Kidney Int.* 2004;65:1991-2002.

56. Ruggenenti P, Perna A, Gherardi G, et al. Renal function and requirement for dialysis in chronic nephropathy patients on long-term ramipril: REIN follow-up trial. Gruppo Italiano di Studi Epidemiologici in Nefrologia (GISEN). Ramipril

Efficacy in Nephropathy. *Lancet*. 1998;352:1252-1256.

57. Maschio G, Alberti D, Locatelli F, et al. Angiotensin-converting enzyme inhibitors and kidney protection: the AIPRI trial. The ACE Inhibition in Progressive Renal Insufficiency (AIPRI) Study Group. *J Cardiovasc Pharmacol*. 1999;33(suppl 1):S16-S20.

58. Shoda J, Kanno Y, Suzuki H. A five-year comparison of the renal protective effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients with non-diabetic nephropathy. *Intern Med*. 2006;45:193-198.

59. Parving HH, Persson F, Lewis JB, et al. Aliskiren combined with losartan in type 2 diabetes and nephropathy. *N Engl J Med*. 2008;358;23:2433-2446.

60. Minutolo R, Balletta MM, Catapano F, et al. Mesangial hypercellularity predicts antiproteinuric response to dual blockade of RAS in primary glomerulonephritis. *Kidney Int*. 2006; 70:1170-1176.

61. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? *Arch Intern Med*. 2000;160:685-693.

62. Reams GP, Bauer JH, Gaddy P. Use of the converting enzyme inhibitor enalapril in renovascular hypertension. Effect on blood pressure, renal function, and the renin-angiotensin-aldosterone system. *Hypertension*. 1986;8:290-297.

63. Franklin SS, Smith RD. Comparison of effects of enalapril plus hydrochlorothiazide versus standard triple therapy on renal function in renovascular hypertension. *Am J Med*. 1985; 79:14-23.

64. Miyamori I, Yasuhara S, Takeda Y, et al. Effects of converting enzyme inhibition on split renal function in renovascular hypertension. *Hypertension*. 1986;8:415-421.

65. Cooper WO, Hernandez-Diaz S, Arbogast PG, et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. *N Engl J Med*. 2006;354:2443-2451.

66. de Zeeuw D, Remuzzi G, Parving HH, et al. Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: lessons from RENAAL. *Kidney Int*. 2004;65: 2309-2320.

67. de Zeeuw D, Remuzzi G, Parving HH, et al. Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. *Circulation*. 2004;110:921-927.

68. Keane WF, Brenner BM, de Zeeuw D, et al. The risk of developing end-stage renal disease in patients with type 2 diabetes and nephropathy: the RENAAL study. *Kidney Int*. 2003;63: 1499-1507.

69. Forsblom CM, Groop PH, Ekstrand A, et al. Predictive value of microalbuminuria in patients with insulin-dependent diabetes of long duration. *BMJ*. 1992;305:1051-1053.

70. Zoja C, Benigni A, Remuzzi G. Cellular responses to protein overload: key event in renal disease progression. *Curr Opin Nephrol Hypertens*. 2004;13:31-37.

71. The Diabetes Control and Complications (DCCT) Research Group. Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. *Kidney Int*. 1995;47:1703-1720.

72. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352:837-853.

73. Viberti G, Wheeldon NM; MicroAlbuminuria Reduction With VALsartan (MARVAL) Study Investigators. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure-independent effect. *Circulation*. 2002; 106:672-678.

COMPLICATIONS AND COMORBIDITIES

Retinopathy

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee
The initial draft of this chapter was prepared by Shelley R. Boyd MD FRCSC DABO and Filiberto Altomare MD FRCSC

KEY MESSAGES

- Screening is important for early detection of treatable disease. Screening intervals for diabetic retinopathy vary according to the individual's age and type of diabetes.

- Tight glycemic control reduces the onset and progression of sight-threatening diabetic retinopathy.

- Laser therapy reduces the risk of significant visual loss.

INTRODUCTION

Diabetic retinopathy is the most common cause of new cases of legal blindness in people of working age (1). The Eye Diseases Prevalence Research Group determined the crude prevalence rate of retinopathy in the adult diabetic population of the United States to be 40.3%; sight-threatening retinopathy occurred at a rate of 8.2% (2). Previous data showed the prevalence rate of proliferative retinopathy to be 23% in people with type 1 diabetes, 14% in people with type 2 diabetes and on insulin therapy, and 3% in people receiving oral antihyperglycemic therapies (3). Macular edema occurs in 11, 15 and 4% of these groups, respectively (4). First Nations populations in Canada have high rates of diabetes and its complications (5,6). It is estimated that approximately 2 million individuals in Canada (i.e. almost all people with diagnosed diabetes) have some form of diabetic retinopathy (7).

Visual loss is associated with significant morbidity, including increased falls, hip fractures and a 4-fold increase in mortality (8). Among individuals with type 1 diabetes, limb amputation and visual loss due to diabetic retinopathy are the 2 independent predictors of early death (9).

DEFINITION AND PATHOGENESIS

Diabetic retinopathy is clinically exclusively defined, diagnosed and treated based on the extent of retinal vascular disease. Three distinct forms of diabetic retinopathy are described: 1) macular edema, which includes diffuse or focal vascular leakage at the macula; 2) progressive accumulation of blood vessel change that includes microaneurysms, intraretinal hemorrhage, vascular tortuosity and vascular malformation (together known as nonproliferative diabetic retinopathy) that ultimately leads to abnormal vessel growth (proliferative diabetic retinopathy); and 3) retinal capillary closure, a form of vascular change detected by fluorescein angiography, which

is also well recognized as a potentially blinding complication of diabetes, but currently has no treatment options.

SCREENING AND DIAGNOSIS

Since laser therapy for sight-threatening diabetic retinopathy reduces the risk of blindness (10-13), ophthalmic screening strategies are intended to detect treatable disease. Sight-threatening diabetic retinopathy includes severe nonproliferative diabetic retinopathy, proliferative diabetic retinopathy or clinically significant macular edema. Screening programs consider the differences in incidence and prevalence of retinopathy observed in type 1 and type 2 diabetes, and distinguish between children and adults (see Table 1) (14-19).

Diabetic retinopathy rarely develops in children with type 1 diabetes <10 years of age, regardless of the duration of diabetes (18). Among patients <15 years of age, irrespective of age of onset of diabetes, the prevalence of mild nonprolif-

Table 1. Screening for retinopathy

When to initiate screening
- 5 years after diagnosis of type 1 diabetes in all individuals ≥15 years
- In all individuals at diagnosis of type 2 diabetes

Screening methods
- 7-standard field, stereoscopic-colour fundus photography with interpretation by a trained reader (gold standard)
- Direct ophthalmoscopy or indirect slit-lamp fundoscopy through dilated pupil
- Digital fundus photography

If retinopathy is present
- Diagnose retinopathy severity and establish appropriate monitoring intervals (1 year or less)
- Treat sight-threatening retinopathy with laser therapy
- Review glycemic, BP and lipid control, and adjust therapy to reach targets as per guidelines*
- Screen for other diabetes complications

If retinopathy is not present
- Type 1 diabetes: rescreen annually
- Type 2 diabetes: rescreen every 1–2 years
- Review glycemic, BP and lipid control, and adjust therapy to reach targets as per guidelines*
- Screen for other diabetes complications

*See Other Relevant Guidelines, p. S136
BP = blood pressure

erative retinopathy was 2%, and none had sight-threatening diabetic retinopathy (11,18,20). However, the prevalence rate increases sharply after 5 years' duration of diabetes in post-pubertal individuals with type 1 diabetes (18). In the Wisconsin Epidemiology Study of Diabetic Retinopathy 4-year incidence study, no person <17 years of age developed proliferative retinopathy or macular edema (16,21,22). Conversely, in people with type 2 diabetes, retinopathy may be present in 21 to 39% of patients soon after clinical diagnosis, but is sight-threatening in only about 3% (4,17,19,23). In the United Kingdom Prospective Diabetes Study (UKPDS), few patients without retinopathy at diagnosis of diabetes had disease progression to the point of requiring photocoagulation in the following 3 to 6 years (24). More recently, progression rates of diabetic retinopathy were prospectively evaluated (14,15,25). The Liverpool Diabetic Eye Study reported the 1-year cumulative incidence of sight-threatening diabetic retinopathy in individuals with type 1 or type 2 diabetes who at baseline had no diabetic retinopathy, had background retinopathy, or had mild preproliferative retinopathy. In people with type 1 diabetes, the incidence in these groups was 0.3, 3.6 and 13.5%, respectively (14), and in individuals with type 2 diabetes it was 0.3, 5.0 and 15.0%, respectively (15). Although the incidence of sight-threatening diabetic retinopathy in the group without baseline diabetic retinopathy is low (14,15,24,25), there have been no studies comparing various screening intervals in their effectiveness to reduce the risk of vision loss (26).

The gold standard for diagnosing diabetic retinopathy is stereoscopic colour fundus photographs in 7 standard fields (27). However, practical common screening strategies for diabetic retinopathy include clinical examination with ophthalmoscopy with or without diagnostic tools such as fundus photography. The accuracy of direct ophthalmoscopy to assess severity of retinopathy can vary widely (28) and is deemed inadequate through an undilated pupil (29-31). Combining direct ophthalmoscopy with slit-lamp fundus biomicroscopy, diagnostic accuracy was comparable to the gold standard of 7-field stereophotography (32). Optical coherence tomography (OCT) is also currently under investigation for its use in the diagnosis of diabetic macular edema (33,34). Telemedicine programs are widely employed in Canada and internationally for the identification and triage of patients with diabetic retinopathy (35).

PREVENTION OF ONSET AND PROGRESSION

Longer duration of diabetes, elevated glycated hemoglobin (A1C), increased blood pressure (BP), dyslipidemia, low hematocrit, pregnancy (with type 1 diabetes) and severe retinopathy itself are associated with disease progression (16-19,22,36-41).

Glycemic control

In the Diabetes Control and Complications Trial, intensive insulin therapy in people with type 1 diabetes reduced the risk of onset of retinopathy by 76%, and the rate of progression by 54%, compared to conventional therapy (42,43). In type 1 diabetes, rapid improvement of glycemic control may be associated with transient early worsening of retinopathy during the first 12 months, but this effect is offset by long-term gain (44).

The UKPDS demonstrated that in type 2 diabetes, hyperglycemia is an independent risk factor for the incidence and progression of retinopathy (45,46). Tight glycemic control is therefore recommended (45,47).

Anecdotal reports and retrospective analyses of individuals receiving thiazolidinediones (TZDs) suggest a correlation with increased diabetic macular edema (48,49). Individuals who experience changes in vision while on a TZD should be referred to an ophthalmologist for assessment.

BP control

In type 1 and type 2 diabetes, elevated diastolic BP is a significant risk factor for the development of macular edema (22,50), and elevated systolic BP is a risk factor for vision loss (51). In hypertensive individuals, development and progression of retinopathy can be reduced by treatment with antihypertensive agents (52). Further lowering of BP in normotensive people with type 2 diabetes also reduces the progression of retinopathy (53).

Lipid control

Dyslipidemia is an independent risk factor for retinal hard exudates and clinically significant macular edema in type 1 diabetes (54). Similarly, in the Early Treatment Diabetic Retinopathy Study (ETDRS) trial, in which most participants had type 2 diabetes, elevated low-density lipoprotein cholesterol was associated with increased risk of developing hard exudates (38).

TREATMENT

Treatment for diabetic retinopathy includes retinal photocoagulation and vitreoretinal surgery.

Residual vision can often be improved by an accurate spectacle correction and/or magnifying aids, with instructions for use. People with impaired vision should be informed of the services in their community that will assist with retraining for employment, encourage independence and improve their quality of life (55,56).

Laser therapy

As determined in the Diabetic Retinopathy Study (DRS) and the ETDRS, laser therapy by panretinal photocoagulation to the retinal periphery reduces severe visual loss and reduces legal blindness by 90% in people with severe nonproliferative or proliferative retinopathy (11-13). As determined by the ETDRS, focal and/or grid laser treatment to the macula for clinically significant macular edema reduces the incidence

of moderate visual loss by 50% (10). The first study to evaluate the long-term outcome of laser treatment confirmed its benefit (57).

Surgical intervention

The Diabetic Retinopathy Vitrectomy Study (DRVS) Group evaluated the benefit of early vitrectomy (<6 months) in the treatment of severe vitreous hemorrhage (58) and very severe proliferative diabetic retinopathy (59). People with type 1 diabetes of <20 years' duration and severe vitreous hemorrhage were more likely to achieve good vision with early vitrectomy compared to conventional management (58). Similarly, early vitrectomy was associated with a higher chance of visual recovery in people with either type 1 or 2 diabetes with very severe proliferative diabetic retinopathy (59). Surgical advances in vitrectomy since the DRVS trials have demonstrated reduced side effects with more consistent favourable visual outcomes, thus supporting vitrectomy in advanced proliferative diabetic retinopathy (60). Furthermore, these advances have expanded surgical indications to include vitrectomy for diffuse macular edema, resulting in structural and functional improvements (61). It is worth noting that systemic treatment with acetylsalicylic acid (ASA) does not increase the risk or severity of vitreous hemorrhage (62-64). The risk of vitreous hemorrhage or foveola blot hemorrhage associated with warfarin therapy is unknown.

Pharmacologic intervention

Studies investigating local and systemic pharmacologic treatments for diabetic retinopathy are underway, but to date no phase III clinical trial has been successful in achieving its primary endpoint. Nonetheless, earlier phase studies strongly suggested that intra-ocular delivery of anti-vascular endothelial growth factor (anti-VEGF) agents or steroid could be effective in reducing diabetic macular edema or retinal neovascularization. In particular, pegaptanib, an anti-VEGF aptamer approved for the treatment of "wet" age-related macular degeneration, has been shown, in a phase II trial (65) and a pilot study (66), to reduce diabetic macular edema and improve visuals outcomes compared to control interventions. A retrospective review of patients treated for edema demonstrated a reduction in neovascularization (67). Similarly, a meta-analysis by the Cochrane Collaboration (68) supports the intravitreal injection of the steroid triamcinolone acetate (69-71), or the use of implanted intra-ocular devices that release fluocinalone acetonide (72,73) or dexamethasone (74). Finally, 3 phase III clinical trials that are evaluating the effects of renin-angiotensin-aldosterone system blockade are nearing completion, and are of particular note. These are the Diabetic Retinopathy Candesartan Trial (DIRECT) (75), the retinal measurement substudy (AdRem) of the Action in Diabetes in Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial (76) and the Renin Angiotensin System Study (RASS) (77). These studies are based upon data from the EURODIAB Controlled Trial of Lisinopril in Insulin Dependent Diabetes Mellitus (EUCLID) (78) and the United Kingdom Prospective Diabetes Study (UKPDS) (79). The EUCLID study, designed to evaluate renal disease, demonstrated that the odds ratio for risk of progression of diabetic retinopathy was 0.5 in patients treated with angiotensin-converting enzyme (ACE) inhibitors compared to those treated with placebo. However, this study was underpowered for ophthalmic outcomes. Similarly, the UKPDS suggested a reduction in the need for laser therapy in patients with type 2 diabetes who received an angiotensin II receptor blocker. Taken together, better understanding of the mechanisms of diabetic retinopathy and recent development of pharmacologic therapies for other indications suggest that new therapies are on the horizon.

RECOMMENDATIONS

1. In individuals ≥15 years of age with type 1 diabetes, screening and evaluation for retinopathy by an expert professional should be performed annually starting 5 years after the onset of diabetes *[Grade A, Level 1 (16,18)]*.

2. In individuals with type 2 diabetes, screening and evaluation for diabetic retinopathy by an expert professional should be performed at the time of diagnosis of diabetes *[Grade A, Level 1 (17,21)]*. The interval for follow-up assessments should be tailored to the severity of the retinopathy. In those with no or minimal retinopathy, the recommended interval is 1 to 2 years *[Grade A, Level 1 (17,21)]*.

3. Screening for diabetic retinopathy should be performed by experienced professionals, either in person or through interpretation of retinal photographs taken though dilated pupils *[Grade A, Level 1 (31)]*.

4. To prevent the onset and delay the progression of diabetic retinopathy, people with diabetes should be treated to achieve optimal control of blood glucose *[Grade A, Level 1A (42,45)]* and BP *[Grade A, Level 1A (52)]*. People with abnormal lipids should be considered at high risk for retinopathy *[Grade A, Level 1 (54)]*.

5. Patients with sight-threatening diabetic retinopathy should be assessed by a general ophthalmologist or retina specialist *[Grade D, Consensus]*. Laser therapy and/or vitrectomy *[Grade A, Level 1A (10,12,58,59)]* and/or pharmacologic intervention *[Grade B, Level 2 (65)]* should be considered.

6. Visually disabled people should be referred for low-vision evaluation and rehabilitation *[Grade D, Consensus]*.

OTHER RELEVANT GUIDELINES

REFERENCES

1. Klein R, Klein BEK. Vision disorders in diabetes. In: *Diabetes in America*. 2nd ed. Bethesda, MD: National Diabetes Data Group, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health; 1995:293-338.

2. Kempen JH, O'Colmain BJ, Leske MC, et al. The prevalence of diabetic retinopathy among adults in the United States. *Arch Ophthalmol.* 2004;122:552-563.

3. Klein R, Klein BEK, Moss SE. Epidemiology of proliferative diabetic retinopathy. *Diabetes Care.* 1992;15:1875-1891.

4. Klein R, Klein BEK, Moss SE, et al. The Wisconsin epidemiologic study of diabetic retinopathy. IV. Diabetic macular edema. *Ophthalmology*. 1984;91:1464-1474.

5. Maberley D, Walker H, Koushik A, et al. Screening for diabetic retinopathy in James Bay, Ontario: a cost-effectiveness analysis. *CMAJ* 2003;168:160-164.

6. Kaur H, Maberley D, Chang A, et al. The current status of diabetes care, diabetic retinopathy screening and eye-care in British Columbia's First Nations Communities. *Int J Circumpolar Health.* 2004;63:277-285.

7. *A Clear Vision. Solutions to Canada's Vision Loss Crisis*. Toronto, ON: Canterbury Communications; 2004. Available at: http://www.costofblindness.org. Accessed September 1, 2008.

8. Vu HT, Keeffe JE, McCarty CA, et al. Impact of unilateral and bilateral vision loss on quality of life. *Br J Ophthalmol.* 2005; 89:360-363.

9. Cusick M, Meleth AD, Agron E, et al. Associations of mortality and diabetes complications in patients with type 1 and type 2 diabetes: Early Treatment Diabetic Retinopathy Study report no. 27. *Diabetes Care.* 2005;28:617-625.

10. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. *Arch Ophthalmol.* 1985;103:1796-1806.

11. Ferris FL III. How effective are treatments for diabetic retinopathy? *JAMA.* 1993;269:1290-1291.

12. The Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy: the second report of Diabetic Retinopathy Study findings. *Ophthalmology*. 1978;85:82-106.

13. Ferris F. Early photocoagulation in patients with either type I or type II diabetes. *Trans Am Ophthalmol Soc.* 1996;94:505-537.

14. Younis N, Broadbent DM, Harding SP, et al. Incidence of sight-threatening retinopathy in type 1 diabetes in a systematic screening programme. *Diabet Med.* 2003;20:758-765.

15. Younis N, Broadbent DM, Vora JP, et al. Incidence of sight-threatening retinopathy in patients with type 2 diabetes in the Liverpool Diabetic Eye Study: a cohort study. *Lancet*. 2003; 361:195-200.

16. Klein R, Klein BEK, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. IX. Four-year incidence and progression of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch Ophthalmol.* 1989;107:237-243.

17. Klein R, Klein BEK, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. X. Four-year incidence and progression of diabetic retinopathy when age at diagnosis is 30 years or more. *Arch Ophthalmol.* 1989;107:244-249.

18. Klein R, Klein BEK, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch Ophthalmol.* 1984;102:520-526.

19. Klein R, Klein BEK, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. *Arch Ophthalmol.* 1984;102:527-532.

20. Klein R, Klein BEK, Moss SE, et al. Severe retinopathy in insulin-taking children and young adults. *Pediat Adolesc Endocr.* 1988;17:146-152.

21. Klein R, Klein BEK, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. VII. Diabetic nonproliferative retinal lesions. *Ophthalmology*. 1987;94:1389-1400.

22. Klein R, Moss SE, Klein BEK, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XI. The incidence of macular edema. *Ophthalmology*. 1989;96:1501-1510.

23. Kohner EM, Aldington SJ, Stratton IM, et al. United Kingdom Prospective Diabetes Study, 30: diabetic retinopathy at diagnosis of non-insulin-dependent diabetes mellitus and associated risk factors. *Arch Ophthalmol.* 1998;116:297-303.

24. Kohner EM, Stratton IM, Aldington SJ, et al. Relationship between the severity of retinopathy and progression to photocoagulation in patients with type 2 diabetes mellitus in the UKPDS (UKPDS 52). *Diabet Med.* 2001;18:178-184.

25. Maguire A, Chan A, Cusumano J, et al. The case for biennial retinopathy screening in children and adolescents. *Diabetes Care.* 2005;28:509-513.

26. Klein R. Screening interval for retinopathy in type 2 diabetes. *Lancet*. 2003;361:190-191.

27. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House classification. ETDRS report number 10. *Ophthalmology*. 1991;98: 786-806.

28. Hutchinson A, McIntosh A, Peters J, et al. Effectiveness of screening and monitoring tests for diabetic retinopathy—a systematic review. *Diabet Med.* 2000;17:495-506.

29. Nathan DM, Fogel HA, Godine JE, et al. Role of diabetologist in evaluating diabetic retinopathy. *Diabetes Care*. 1991;14:26-33.

30. Sussman EJ, Tsiaras WG, Soper KA. Diagnosis of diabetic eye disease. *JAMA.* 1982;247:3231-3234.

31. Buxton MJ, Sculpher MJ, Ferguson BA, et al. Screening for treatable diabetic retinopathy: a comparison of different methods. *Diabet Med.* 1991;8:371-377.

32. Scanlon PH, Malhotra R, Greenwood RH, et al. Comparison of two reference standards in validating two field mydriatic digital photography as a method of screening for diabetic retinopathy. *Br J Ophthalmol.* 2003;87:1258-1263.

33. Lang GE. Optical coherence tomography findings in diabetic

retinopathy. *Dev Ophthalmol*. 2007;39:31-47.

34. Massin P, Girach A, Erginay A, et al. Optical coherence tomography: a key to the future management of patients with diabetic macular oedema. *Acta Ophthalmol Scand*. 2006;84:466-474.

35. Whited JD. Accuracy and reliability of teleophthalmology for diagnosing diabetic retinopathy and macular edema: a review of the literature. *Diabetes Technol Ther*. 2006;8:102-122.

36. Davis MD, Fisher MR, Gangnon RE, et al. Risk factors for high-risk proliferative diabetic retinopathy and severe visual loss: Early Treatment Diabetic Retinopathy Study report #18. *Invest Ophthalmol Vis Sci*. 1998;39:233-252.

37. Klein BEK, Moss SE, Klein R. Effect of pregnancy on progression of diabetic retinopathy. *Diabetes Care*. 1990;13:34-40.

38. Chew EY, Klein ML, Ferris FL III, et al. Association of elevated serum lipid levels with retinal hard exudate in diabetic retinopathy. Early Treatment Diabetic Retinopathy Study (ETDRS) report 22. *Arch Ophthalmol*. 1996;114:1079-1084.

39. Qiao Q, Keinänen-Kiukaanniemi S, Läärä E. The relationship between hemoglobin levels and diabetic retinopathy. *J Clin Epidemiol*. 1997;50:153-158.

40. The Diabetes Control and Complications Trial Research Group. Effect of pregnancy on microvascular complications in the Diabetes Control and Complications Trial. *Diabetes Care*. 2000;23:1084-1091.

41. Chew EY, Mills JL, Metzger BE, et al. Metabolic control and progression of retinopathy. The Diabetes in Early Pregnancy Study. *Diabetes Care*. 1995;18:631-637.

42. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329:977-986.

43. The Diabetes Control and Complications Trial Research Group. The effect of intensive diabetes treatment on the progression of diabetic retinopathy in insulin-dependent diabetes mellitus. *Arch Ophthalmol*. 1995;113:36-51.

44. The Diabetes Control and Complications Trial Research Group. Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. *Arch Ophthalmol*. 1998;116:874-886.

45. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352:837-853.

46. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract*. 1995;28:103-117.

47. Klein R, Klein BEK, Moss SE, et al. Relationship of hyperglycemia to the long-term incidence and progression of diabetic retinopathy. *Arch Intern Med*. 1994;154:2169-2178.

48. Sivagnanam G. Rosiglitazone and macular edema. *CMAJ*. 2006;175:276.

49. Kendall C, Wooltoroton E. Rosiglitazone (Avandia) and macular edema. *CMAJ*. 2006;174:623.

50. Klein R, Klein BEK, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XV. The long-term incidence of macular edema. *Ophthalmology*. 1995;102:7-16.

51. Moss SE, Klein R, Klein BEK. Ten-year incidence of visual loss in a diabetic population. *Ophthalmology*. 1994;101:1061-1070.

52. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ*. 1998;317:703-713.

53. Schrier RW, Estacio RO, Esler A, et al. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. *Kidney Int*. 2002;61:1086-1097.

54. Miljanovic B, Glynn RJ, Nathan DM, et al. A prospective study of serum lipids and risk of diabetic macular edema in type 1 diabetes. *Diabetes*. 2004;53:2883-2892.

55. Fonda GE. Optical treatment of residual vision in diabetic retinopathy. *Ophthalmology*. 1994;101:84-88.

56. Bernbaum M, Albert SG. Referring patients with diabetes and vision loss for rehabilitation: who is responsible? *Diabetes Care*. 1996;19:175-177.

57. Chew EY, Ferris FL III, Csaky KG, et al. The long-term effects of laser photocoagulation treatment in patients with diabetic retinopathy: the Early Treatment Diabetic Retinopathy Follow-up Study. *Ophthalmology*. 2003;110:1683-1689.

58. The Diabetic Retinopathy Vitrectomy Study Research Group. Early vitrectomy for severe vitreous hemorrhage in diabetic retinopathy. Four-year results of a randomized trial: Diabetic Retinopathy Study report 5. *Arch Ophthalmol*. 1990;108:958-964.

59. The Diabetic Retinopathy Vitrectomy Study Research Group. Early vitrectomy for severe proliferative diabetic retinopathy in eyes with useful vision. Results of a randomized trial—Diabetic Retinopathy Vitrectomy Study report 3. *Ophthalmology*. 1988;95:1307-1320.

60. Smiddy WE, Flynn HW. Vitrectomy in the management of diabetic retinopathy. *Surv Ophthalmol*. 1999;43:491-507.

61. Stolba U, Binder S, Gruber D, et al. Vitrectomy for persistent diffuse macular edema. *Am J Ophthalmol*. 2005;140:295-301.

62. Chew EY, Klein ML, Murphy RP, et al. Effects of aspirin on vitreous/preretinal hemorrhage in patients with diabetes mellitus. Early Treatment Diabetic Retinopathy Study report no. 20. *Arch Ophthalmol*. 1995;113:52-55.

63. Early Treatment Diabetic Retinopathy Study Research Group. Effects of aspirin treatment on diabetic retinopathy. ETDRS report number 8. *Ophthalmology*. 1991;98(5 suppl):757-765.

64. Chew EY, Benson WE, Remaley NA, et al. Results after lens extraction in patients with diabetic retinopathy: Early Treatment Diabetic Retinopathy Study report number 25. *Arch Ophthalmol*. 1999;117:1600-1606.

65. Cunningham ET Jr, Adamis AP, Altaweel M, et al. A phase II randomized double-masked trial of pegaptanib, an anti-

vascular endothelial growth factor aptamer, for diabetic macular edema. *Ophthalmology*. 2005;112:1747-1757.

66. Chun DW, Heier JS, Topping TM, et al. A pilot study of multiple intravitreal injections of ranibizumab in patients with center-involving clinically significant diabetic macular edema. *Ophthalmology*. 2006;113:1706-1712.

67. Adamis AP, Altaweel M, Bressler NM, et al. Changes in retinal neovascularization after pegaptanib (Macugen) therapy in diabetic individuals. *Ophthalmology*. 2006;113:23-28.

68. Grover D, Li J, Chong CW. Intravitreal steroid for macular edema in diabetes. *Cochrane Database Syst Rev.* 2008;(1):CD005656.

69. Avitabile T, Longo A, Reibaldi A. Intravitreal triamcinolone compared with macular laser grid photocoagulation for the treatment of cystoid macular edema. *Am J Ophthalmol.* 2005; 140;695-702.

70. Jonas JB, Kampperter BA, Harder B, et al. Intravitreal triamcinolone acetonide for diabetic macular edema: a prospective, randomized study. *J Ocul Pharmacol Ther*. 2006;22:200-207.

71. Sutter FK, Simpson JM, Gilles MC. Intravitreal triamcinolone for diabetic macular edema that persists after laser treatment: three-month efficacy and safety results of a prospective, randomized, double-masked, placebo-controlled clinical trial. *Ophthalmology*. 2004;111:2044-2049.

72. Pearson PA, Baker CW, Eliott D, et al. Fluocinolone acetonide intravitreal implant for diabetic macular edema: 2 year results. Association for Research in Vision and Ophthalmology Annual Meeting; April 25-29, 2004; Fort Lauderdale, FL.

73. Pearson PA, Levy B, Comstock T. Fluocinolone acetonide Implant Study Group. Fluocinolone acetonide intravitreal implant to treat diabetic macular edema: 3-year results of a multi-center clinical trial. Association for Research in Vision and Ophthalmology Annual Meeting; April 30 to May 4, 2006; Fort Lauderdale, FL.

74. Kuppermann BD, Blumenkranz MS, Haller JA, et al. Randomized controlled study of an intravitreous dexamethasone drug delivery system in patients with persistent macular edema. *Arch Ophthalmol.* 2007;125:309-317.

75. Sjølie AK, Porta M, Parving HH, et al; The DIRECT Programme Study Group. The DIabetic REtinopathy Candesartan Trials (DIRECT) Programme: baseline characteristics. *J Renin Angiotensin Aldosterone Syst.* 2005;6:25-32.

76. ADVANCE Management Committee. Study rational and design of ADVANCE: Action in Diabetes and Vascular Disease – preterax and diamicron MR controlled evaluation. *Diabetologia.* 2001;44:1118-1120.

77. Klein R, Zinman B, Gardiner R, et al. The relationship of diabetic retinopathy to preclinical diabetic glomerulopathy lesions in type 1 diabetic patients: the Renin-Angiotensin System Study. *Diabetes*. 2005;54:527-533.

78. Chaturvedi N, Sjolie AK, Stephenson JM, et al. Effect of lisinopril on progression of retinopathy in normotensive people with type 1 diabetes. The EUCLID Study Group. EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus. *Lancet*. 1998;351:28-31.

79. UK Prospective Diabetes Study (UKPDS) Group. Effects of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*. 1998;352:854-865.

Neuropathy

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee
**The initial draft of this chapter was prepared by Vera Bril MD FRCPC and
Bruce Perkins MD MPH FRCPC**

KEY MESSAGES

- Exposure to higher levels of glycemia, elevated triglycerides, high body mass index, smoking and hypertension are risk factors for neuropathy.

- Intensive glycemic control is effective for primary prevention or secondary intervention of neuropathy in people with type 1 diabetes.

- In people with type 2 diabetes, lower blood glucose levels are associated with reduced frequency of neuropathy.

INTRODUCTION

Detectable sensorimotor polyneuropathy will develop within 10 years of the onset of diabetes in 40 to 50% of people with type 1 or type 2 diabetes (1). Although <50% of these patients have motor or sensory symptoms, the neuropathic pain associated with symptomatic disease is frequently bothersome (2,3). While neuropathy is uncommon in people with type 1 diabetes within the first 5 years after onset of diabetes, people with type 2 diabetes may have neuropathy at the time of diagnosis (4). Risk factors for neuropathy are exposure to higher levels of glycemia, elevated triglycerides, high body mass index, smoking and hypertension (5). Foot ulceration, which depends on the degree of foot insensitivity (6), and amputation are important and costly sequelae of diabetic neuropathy (7). Both somatic and autonomic neuropathy may occur, and may require referral to a specialist experienced in managing the affected body system. Mononeuropathy, particularly carpal tunnel syndrome, is common in people with diabetes and can be difficult to diagnose (8).

Underdiagnosis of neuropathy is a fundamental problem in the primary care of people with diabetes, and impedes the benefits of early identification, the management necessary to achieve improved glycemic control and the prevention of neuropathy-related sequelae (9).

SCREENING FOR PERIPHERAL NEUROPATHY

Screening for neuropathy can be performed rapidly and reliably using the 10-g Semmes-Weinstein monofilament or 128-Hz tuning fork (10-13). Methods for using the monofilament or tuning fork to detect diabetic neuropathy are explained in Appendix 4. Other screening maneuvers can include assessment of pinprick sensation (10) and reflexes. In individuals with significant early progressive symptoms of neuropathy or in whom a clinical suspicion of nondiabetic neuropathy exists, referral for additional neurologic evaluation is indicated.

MANAGEMENT OF NEUROPATHY

Intensive glycemic control is effective for primary prevention of or secondary intervention for neuropathy in people with type 1 diabetes (3,14,15). In those with type 2 diabetes, lower blood glucose levels are associated with reduced frequency of neuropathy (2,16). Multiple medications are available for effective management of neuropathic pain. There are insufficient comparative studies to justify a recommendation on which oral medication should be attempted first. Commonly available and commonly used tricyclic antidepressants (17,18), anticonvulsants (19,20) and opioid analgesics (21) are shown in Table 1. Combination therapy with gabapentin and opioid has been shown to achieve better analgesia at lower doses of each drug (22). Other antidepressants include desipramine (18) (a tricyclic antidepressant), venlafaxine (23), nortriptyline and fluphenazine (24), and duloxetine (25) (a dual reuptake inhibitor). Other opioid analgesics include tramadol (26) and sustained-release oxycodone (21); other anticonvulsants include carbamazepine (27), oxcarbazepine (28), lamotrigine (29) and topiramate (30). Alternate therapeutic options include topical isosorbide dinitrate (31) and the antiarrhythmic mexiletine (32). The efficacy of topical capsaicin is less clear (33,34).

Although subclinical autonomic neuropathic manifestations are common, symptomatic involvement is infrequent. The diagnosis of symptomatic autonomic neuropathy is based on exclusion of specific cardiovascular, gastrointestinal or genitourinary pathology, usually requiring assessment by a specialist in the affected system. Treatment of autonomic neuropathy is based primarily on expert opinion, but research in this field remains active.

OTHER RELEVANT GUIDELINES

Table 1. Oral medications for the management of neuropathic pain*

Medication	Suggested starting dose†	Suggested titration†	Common or serious side effects
Tricyclic antidepressants			
Amitriptyline (17,18)	10 mg QHS	Increase weekly by 10 mg/day to a maximum of 150 mg/day	Dry mouth Blurred vision Constipation Urinary retention Dizziness Drowsiness Cardiac arrhythmias (particularly in the elderly)
Anticonvulsants			
Gabapentin (19)‡	300 mg TID	Increase weekly by 300 mg/day to a maximum of 3600 mg/day	Dizziness Somnolence Ataxia Fatigue Peripheral edema
Pregabalin (20)	75 mg BID	May double weekly to a maximum of 300 mg BID	Weight gain Peripheral edema Dizziness Somnolence
Opioid analgesics‡			
Sustained-release oxycodone (21)	10 mg BID	Increase every 3 days by 10 mg to a maximum of 60 mg BID	Constipation Nausea Somnolence

*Clinically important outcomes in the clinical trial setting are generally defined by a 30 to 50% decrease in pain (as assessed by visual analogue scores). Few patients achieve complete pain relief in these clinical trials.

†Dose ranges are for adults and are generalized from clinical trials – smaller starting doses and slower titration schedules may be indicated. Optimal doses are the lowest doses required for maximum efficacy without significant side effects. Although required for some agents, dose adjustments for renal and liver dysfunction are not shown here. Physicians should refer to the most current edition of the *Compendium of Pharmaceuticals and Specialties* (Canadian Pharmacists Association, Ottawa, Ontario, Canada) for product monographs and complete prescribing information.

‡Combination therapy with gabapentin and an opioid has been shown to achieve better analgesia at lower doses of each drug (22).

RECOMMENDATIONS

1. In people with type 2 diabetes, screening for peripheral neuropathy should begin at diagnosis of diabetes and occur annually thereafter. In people with type 1 diabetes, annual screening should commence after 5 years' post-pubertal duration of diabetes *[Grade D, Consensus]*.

2. Screening for peripheral neuropathy should be conducted by assessing loss of sensitivity to the 10-g monofilament or loss of sensitivity to vibration at the dorsum of the great toe *[Grade A, Level 1 (10)]*.

3. People with diabetes should be treated with intensified glycemic control to prevent the onset and progression of neuropathy *[Grade A, Level 1A, for type 1 diabetes (3,14); Grade B, Level 2 (16), for type 2 diabetes]*.

4. Antidepressants *[Grade A, Level 1A (23,25)]*, anticonvulsants *[Grade A, Level 1A (19,20,22,28)]*, opioid analgesics *[Grade A, Level 1A (22)]* and topical isosorbide dinitrate *[Grade B, Level 2 (31)]* should be considered alone or in combination for relief of painful peripheral neuropathy.

RELEVANT APPENDIX

Appendix 4: Rapid Screening for Diabetic Neuropathy

REFERENCES

1. Dyck PJ, Kratz KM, Karnes JL, et al. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. *Neurology*. 1993;43:817-824.

2. Partanen J, Niskanen L, Lehtinen J, et al. Natural history of peripheral neuropathy in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med*. 1995;333:89-94.

3. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329: 977-986.

4. Singleton JR, Smith AG, Bromberg MB. Increased prevalence of impaired glucose tolerance in patients with painful sensory neuropathy. *Diabetes Care*. 2001;24:1448-1453.

5. Tesfaye S, Chaturvedi N, Eaton SE, et al; EURODIAB Prospective Complications Study Group. Vascular risk factors and diabetic neuropathy. *N Engl J Med.* 2005;352:341-350.

6. Young MJ, Breddy JL, Veves A, et al. The prediction of diabetic neuropathic foot ulceration using vibration perception thresholds. A prospective study. *Diabetes Care.* 1994;17:557-560.

7. Reiber GE, Boyko EJ, Smith DG. Lower extremity foot ulcers and amputations in diabetes. In: *Diabetes in America.* 2nd ed. Bethesda, MD: National Diabetes Data Group, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 1995:409-428.

8. Perkins BA, Olaleye D, Bril V. Carpal tunnel syndrome in patients with diabetic polyneuropathy. *Diabetes Care.* 2002; 25:565-569.

9. Herman WH, Kennedy L. Underdiagnosis of peripheral neuropathy in type 2 diabetes. *Diabetes Care.* 2005;28:1480-1481.

10. Perkins BA, Olaleye D, Zinman B, et al. Simple screening tests for peripheral neuropathy in the diabetes clinic. *Diabetes Care.* 2001;24:250-256.

11. Rith-Najarian SJ, Stolusky T, Gohdes DM. Identifying diabetic patients at high risk for lower-extremity amputation in a primary health care setting. A prospective evaluation of simple screening criteria. *Diabetes Care.* 1992;15:1386-1389.

12. Kästenbauer T, Sauseng S, Brath H, et al. The value of the Rydel-Seiffer tuning fork as a predictor of diabetic polyneuropathy compared with a neurothesiometer. *Diabet Med.* 2004; 21:563-567.

13. Rahman M, Griffin SJ, Rathmann W, et al. How should peripheral neuropathy be assessed in people with diabetes in primary care? A population-based comparison of four measures. *Diabet Med.* 2003;20:368-374.

14. Reichard P, Berglund B, Britz A, et al. Intensified conventional insulin treatment retards the microvascular complications of insulin-dependent diabetes mellitus (IDDM): the Stockholm Diabetes Intervention Study (SDIS) after 5 years. *J Intern Med.* 1991;230:101-108.

15. The Diabetes Control and Complications Trial Research Group. The effect of intensive diabetes therapy on the development and progression of neuropathy. *Ann Intern Med.* 1995; 122:561-568.

16. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet.* 1998;352: 837-853.

17. Max MB, Culnane M, Schafer SC, et al. Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed mood. *Neurology.* 1987;37:589-596.

18. Max MB, Lynch SA, Muir J, et al. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. *N Engl J Med.* 1992;326:1250-1256.

19. Backonja M, Beydoun A, Edwards KR, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. *JAMA.* 1998;280:1831-1836.

20. Richter RW, Portenoy R, Sharma U, et al. Relief of painful diabetic peripheral neuropathy with pregabalin: a randomized, placebo-controlled trial. *J Pain.* 2005;6:253-260.

21. Gimbel JS, Richards P, Portenoy RK. Controlled-release oxycodone for pain in diabetic neuropathy: a randomized controlled trial. *Neurology.* 2003;60:927-934.

22. Gilron I, Bailey JM, Tu D, et al. Morphine, gabapentin, or their combination for neuropathic pain. *N Engl J Med.* 2005;352: 1324-1334.

23. Rowbotham MC, Goli V, Kunz NR, et al. Venlafaxine extended release in the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled study. *Pain.* 2004;110:697-706.

24. Gomez-Perez FJ, Rull JA, Dies H, et al. Nortriptyline and fluphenazine in the symptomatic treatment of diabetic neuropathy. A double-blind cross-over study. *Pain.* 1985;23:395-400.

25. Raskin J, Smith TR, Wong K, et al. Duloxetine versus routine care in the long-term management of diabetic peripheral neuropathic pain. *J Palliat Med.* 2006;9:29-40.

26. Harati Y, Gooch C, Swenson M, et al. Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy. *Neurology.* 1998;50:1842-1846.

27. McQuay H, Carroll D, Jadad AR, et al. Anticonvulsant drugs for management of pain: a systematic review. *BMJ.* 1995; 311:1047-1052.

28. Dogra S, Beydoun S, Mazzola J, et al. Oxcarbazepine in painful diabetic neuropathy: a randomized, placebo-controlled study. *Eur J Pain.* 2005;9:543-554.

29. Vinik AI, Tuchman M, Safirstein B, et al. Lamotrigine for treatment of pain associated with diabetic neuropathy: results of two randomized, double-blind, placebo-controlled studies. *Pain.* 2007;128:169-179.

30. Raskin P, Donofrio PD, Rosenthal NR, et al; CAPSS-141 Study Group. Topiramate vs placebo in painful diabetic neuropathy: analgesic and metabolic effects. *Neurology.* 2004;63:865-873.

31. Yuen KC, Baker NR, Rayman G. Treatment of chronic painful diabetic neuropathy with isosorbide dinitrate spray: a double-blind placebo-controlled cross-over study. *Diabetes Care.* 2002; 25:1699-1703.

32. Stracke H, Meyer UE, Schumacher HE, et al. Mexiletine in the treatment of diabetic neuropathy. *Diabetes Care.* 1992;15:1550-1555.

33. Low PA, Opfer-Gehrking TL, Dyck PJ, et al. Double-blind, placebo-controlled study of the application of capsaicin cream in chronic distal painful polyneuropathy. *Pain.* 1995;62:163-168.

34. The Capsaicin Study Group. Treatment of painful diabetic neuropathy with topical capsaicin. A multicenter, double-blind, vehicle-controlled study. *Arch Intern Med.* 1991;151:2225-2229.

Foot Care

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee
The initial draft of this chapter was prepared by Keith Bowering MD FRCPC FACP, Jean-Marie Ekoé MD CSPQ and Timothy P. Kalla BSc DPM FACFAS

KEY MESSAGES

- Foot problems are a major cause of morbidity and mortality in people with diabetes and contribute to increased healthcare costs.

- Management of foot ulceration requires an interdisciplinary approach that addresses glycemic control, infection, lower extremity vascular status and local wound care.

- Uncontrolled diabetes can result in immunopathy with a blunted cellular response to foot infection.

INTRODUCTION

Foot problems are a major cause of morbidity and mortality in people with diabetes and contribute to increased health-care costs (1,2). The sequence of events leading to lower-extremity amputation is well known. In people with neuropathy (3) or peripheral vascular disease (4), minor trauma to the foot leads to skin ulceration, infection and ultimately gangrene, resulting in amputation (5-9). Foot complications are a major reason for admission to the hospital for people with diabetes, accounting for approximately 20% of all diabetes-related admissions in the North American population (7,8,10-12). After amputation of 1 limb, the prognosis for the contralateral limb is poor (13,14).

RISK ASSESSMENT AND PREVENTIVE CARE

A number of wound classification systems exist for documentation of diabetic foot ulcers. Of these, the University of Texas Diabetic Wound Classification System has been validated as a predictor of serious outcomes in patients with diabetes with foot ulcers (15) (Table 1).

Characteristics that have been shown to confer high risk of ulceration include previous ulceration, neuropathy, structural deformity and limited joint mobility, peripheral vascular disease and microvascular complications (16,17). Noninvasive assessments for peripheral arterial disease in diabetes include the use of the ankle-brachial index, determination of systolic toe pressure by photoplethysmography (measurement of the intensity of light reflected from the skin surface and the red cells below, which is indicative of arterial pulse flow in the arterioles of the respective area), transcutaneous oximetry (tcPO$_2$), and Doppler arterial-flow studies (18,19). The ankle-brachial index may be arti-ficially high in some individuals with diabetes due to medi-al arterial-wall calcification in lower-extremity arteries (20). Iodinated contrast arteriography has provided the most definitive evaluation of peripheral atherosclerosis, but can precipitate renal failure in individuals with renal insufficiency. Advanced magnetic resonance angiography has been used as an alternative to iodinated contrast studies in people at risk for renal complications (21,22), although caution may be necessary in view of a possible association with the gadolinium-based contrast agents used in magnetic resonance angiography and the development of nephrogenic systemic fibrosis in individuals with poor renal function (23,24).

Prevention of amputations necessitates the use of various measures, including regular foot examination and evaluation of amputation risk, regular callus debridement, education, professionally fitted therapeutic footwear to reduce plantar pressure and accommodate foot deformities, and early detection and treatment of diabetic foot ulcers (10,25-28). Callus should be considered a sign of increased pressure and risk for ulceration (29). Foot examination should also include skin temperature assessment. Increased warmth is the first indicator of inflammation in an insensate foot and may be the first sign of acute Charcot neuroarthropathy as a complication of loss of protective sensation in the foot (30-

Table 1. University of Texas Diabetic Wound Classification System (15)				
Stage	**Grade**			
	0	**I**	**II**	**III**
A (no infection or ischemia)	Pre- or postulcerative lesion completely epithelialized	Superficial wound not involving tendon, capsule or bone	Wound penetrating to tendon or capsule	Wound penetrating to bone or joint
B	Infection	Infection	Infection	Infection
C	Ischemia	Ischemia	Ischemia	Ischemia
D	Infection and ischemia	Infection and ischemia	Infection and ischemia	Infection and ischemia

32). In addition, an acute Charcot foot may be associated with erythema and swelling, with overall clinical characteristics very similar to cellulitis (33,34).

MANAGEMENT

Appropriate management can prevent or heal diabetic foot ulcers, thereby greatly reducing the amputation rate (6,9,10,25,26,35,36). All people with diabetes should be instructed on proper foot care (including smoking cessation strategies) (Appendix 5), should strive to reach recommended glycemic targets, and should receive early referrals to a healthcare professional trained in foot care management if problems occur (37).

Management of foot ulceration requires an interdisciplinary approach (38) that addresses glycemic control, infection, lower-extremity vascular status and local wound care (39).

Essentials of good wound care involve provision of an optimal wound environment, off-loading of the ulcer site, and, in nonischemic wounds, regular debridement of nonviable tissue. In general, wound dressings that maintain a moist wound environment should be selected (40) (Appendix 6). Expeditious debridement may be performed with sharp instruments or biologically with medical-grade maggots (41,42).

Pressure offloading may be achieved with temporary footwear until the ulcer heals and the character of the foot stabilizes. Removable and irremovable cast-walkers and total-contact casting have demonstrated proven efficacy as pressure-reducing devices in plantar-surface ulcers (43-45). Although very effective in healing noninfected, non-ischemic plantar-surface neuropathic ulcers, total-contact casting requires careful individual selection and personnel trained specifically in its application due to its potential for complications (46).

Infections that complicate diabetic foot ulcers occur frequently and may be imminently limb threatening (47). Surface cultures (as opposed to cultures of deeper tissues) of ulcers in people with diabetes have produced inconsistent results in determining the bacterial pathogens involved (48-50). Initial antibiotic therapy is typically empiric and broad spectrum, with subsequent antibiotics tailored to results from appropriate cultures. Studies to date do not clearly identify a particular antibiotic agent that is more efficacious in reducing amputation, accelerating ulcer healing or resolving infection (51). Uncontrolled diabetes can result in immunopathy with a blunted cellular response to infection. Up to 50% of patients with diabetes who have a significant limb infection may not have systemic signs of fever or leukocytosis at presentation (52). Deep infections require prompt surgical debridement in addition to appropriate antibiotic therapy (53).

In medically suitable individuals with peripheral arterial disease, distal limb revascularization has proven benefit in long-term limb salvage (54). Where bony foot deformities prevent fitting of appropriate footwear and/or offloading of pressure-related ulcers, consultation from a surgeon skilled in foot sur-

gery may be considered to address the deformity (55-57).

Hyperbaric oxygen therapy may be useful as an adjunct to systemic antibiotics in individuals with deep, long-standing, nonhealing foot infections, provided there is an adequate perfused capillary bed in the wound area (i.e. by measuring tcPO$_2$ response to 100% oxygen challenge). Few studies support its use in treating uncomplicated neuropathic or ischemic diabetic foot ulcers. There are no evidence-based criteria to select people for hyperbaric oxygen therapy and to predict their response (58).

RECOMMENDATIONS

1. In people with diabetes, foot examinations by both the individual and healthcare providers should be an integral component of diabetes management to decrease the risk of foot lesions and amputations *[Grade B, Level 2 (26,37)]*, and should be performed at least annually and at more frequent intervals in those at high risk *[Grade D, Consensus]*. Assessment by healthcare providers should include structural abnormalities (e.g. range of motion of ankles and toe joints, callus pattern, bony deformities, skin temperatures), evaluation for neuropathy and peripheral arterial disease, ulcerations and evidence of infection *[Grade D, Level 4 (9,50)]*.

2. People at high risk of foot ulceration and amputation should receive foot care education (including counselling to avoid foot trauma), professionally fitted footwear, smoking cessation strategies and early referrals to a healthcare professional trained in foot care management if problems occur *[Grade B, Level 2 (37)]*.

3. Individuals who develop a foot ulcer should be managed by a multidisciplinary healthcare team with expertise in the management of foot ulcers to prevent recurrent foot ulcers and amputation *[Grade C, Level 3 (38)]*.

4. Any infection in a diabetic foot must be treated aggressively *[Grade D, Level 4 (53)]*.

OTHER RELEVANT GUIDELINES
Targets for Glycemic Control, p. S29
Neuropathy, p. S140

RELEVANT APPENDICES
Appendix 5: Diabetes and Foot Care: A Patient's Checklist
Appendix 6: Diabetic Foot Ulcers: Essentials of Management

REFERENCES

1. American Diabetes Association: clinical practice recommendations 2004. *Diabetes Care.* 2004;27(suppl 1):S63-64.

2. Reiber GE, Boyko EJ, Smith DG. Lower extremity foot ulcers and amputations in diabetes. In: *Diabetes in America.* 2nd ed. Bethesda, MD: National Diabetes Data Group, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 1995:409-428.

3. Eastman RC. Neuropathy in diabetes. In: *Diabetes in America.*

2nd ed. Bethesda, MD: National Diabetes Data Group, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 1995:339-348.

4. Palumbo PJ, Melton LJ III. Peripheral vascular disease and diabetes. In: *Diabetes in America*. 2nd ed. Bethesda, MD: National Diabetes Data Group, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 1995:401-408.

5. Boyko EJ, Lipsky BA. Infection and diabetes. In: *Diabetes in America*. 2nd ed. Bethesda, MD: National Diabetes Data Group, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 1995:485-499.

6. Frykberg RG. Diabetic foot ulcerations. In: Frykberg RG, ed. *The High Risk Foot in Diabetes Mellitus*. New York, NY: Churchill Livingstone; 1991:151-195.

7. Frykberg RG, Veves A. Diabetic foot infections. *Diabetes Metab Rev*. 1996;12:255-270.

8. Gibbons GW, Eliopoulos GM, Kozak GP, et al. Infection of the diabetic foot. In: Kozak GP, Campbell DR, Frykberg RG, et al, eds. *Management of Diabetic Foot Problems*. Philadelphia, PA: WB Saunders; 1995:121.

9. Reiber GE, Pecoraro RE, Koepsell TD. Risk factors for amputation in patients with diabetes mellitus. A case-control study. *Ann Intern Med*. 1992;117:97-105.

10. Bild DE, Selby JV, Sinnock P, et al. Lower-extremity amputation in people with diabetes. Epidemiology and prevention. *Diabetes Care*. 1989;12:24-31.

11. Reiber GE. Epidemiology of the diabetic foot. In: Levin ME, O'Neal LW, Bowker JH, eds. *The Diabetic Foot*. 5th ed. St. Louis, MO: Mosby; 1993:1-15.

12. Crude and age-adjusted hospital discharge rates for a lower extremity condition as the first-listed or any-listed diagnosis per 1,000 diabetic population, United States, 1980-2003. Atlanta, GA: Department of Health & Human Services, Centers for Disease Control and Prevention; 2007. Available at: http://www.cdc.gov/diabetes/statistics/hosplea/diabetes_complications/fig6.htm. Accessed September 1, 2008.

13. Ebskov B, Josephsen P. Incidence of reamputation and death after gangrene of the lower extremity. *Prosthet Orthot Int*. 1980; 4:77-80.

14. Most RS, Sinnock P. The epidemiology of lower extremity amputations in diabetic individuals. *Diabetes Care*. 1983;6:87-91.

15. Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation. *Diabetes Care*. 1998;21:855-859.

16. Boyko EJ, Ahroni JH, Stensel V, et al. A prospective study of risk factors for diabetic foot ulcer. The Seattle Diabetic Foot Study. *Diabetes Care*. 1999;22:1036-1042.

17. Fernando DJ, Masson EA, Veves A, et al. Relationship of limited joint mobility to abnormal foot pressures and diabetic foot ulceration. *Diabetes Care*. 1991;14:8-11.

18. Kalani M, Brismar K, Fagrell B, et al. Transcutaneous oxygen tension and toe blood pressure as predictors for outcome of diabetic foot ulcers. *Diabetes Care*. 1999;22:147-151.

19. Faglia E, Caravaggi C, Marchetti R, et al; SCAR (SCreening for ARteriopathy) Study Group. Screening for peripheral arterial disease by means of the ankle-brachial index in newly diagnosed type 2 diabetic patients. *Diabet Med*. 2005;22:1310-1314.

20. Young MJ, Adams JE, Anderson GF, et al. Medial arterial calcification in the feet of diabetic patients and matched non-diabetic control subjects. *Diabetologia*. 1993;36:615-621.

21. Brillet PY, Vayssairat M, Tassart M, et al. Gadolinium-enhanced MR angiography as first-line preoperative imaging in high-risk patients with lower limb ischemia. *J Vasc Interv Radiol*. 2003; 14:1139-1145.

22. Lapeyre M, Kobeiter H, Desgranges P, et al. Assessment of critical limb ischemia in patients with diabetes: comparison of MR angiography and digital subtraction angiography. *AJR Am J Roentgenol*. 2005;185:1641-1650.

23. Pedersen M. Safety update on the possible causal relationship between gadolinium-containing MRI agents and nephrogenic systemic fibrosis. *J Magn Reson Imaging*. 2007;25:881-883.

24. Centers for Disease Control and Prevention (CDC). Nephrogenic fibrosing dermopathy associated with exposure to gadolinium-containing contrast agents – St. Louis, Missouri, 2002-2006. *MMWR Morb Mortal Wkly Rep*. 2007;56:137-141.

25. Assal JP, Mühlhauser I, Pernet A, et al. Patient education as the basis for diabetes care in clinical practice and research. *Diabetologia*. 1985;28:602-613.

26. Litzelman DK, Slemenda CW, Langefeld CD, et al. Reduction of lower extremity clinical abnormalities in patients with non-insulin-dependent diabetes mellitus. A randomized, controlled trial. *Ann Intern Med*. 1993;119:36-41.

27. Malone JM, Snyder M, Anderson G, et al. Prevention of amputation by diabetic education. *Am J Surg*. 1989;158:520-524.

28. Viswanathan V, Madhavan S, Gnanasundaram S, et al. Effectiveness of different types of footwear insoles for the diabetic neuropathic foot: a follow-up study. *Diabetes Care*. 2004; 27:474-477.

29. Sage RA, Webster JK, Fisher SG. Outpatient care and morbidity reduction in diabetic foot ulcers associated with chronic pressure callus. *J Am Podiatr Med Assoc*. 2001;91:275-279.

30. Lavery LA, Higgins KR, Lanctot DR, et al. Preventing diabetic foot ulcer recurrence in high-risk patients: use of temperature monitoring as a self-assessment tool. *Diabetes Care*. 2007; 30:14-20.

31. Armstrong DG, Lavery LA. Monitoring healing of acute Charcot's arthropathy with infrared dermal thermometry. *J Rehabil Res Dev*. 1997;34:317-321.

32. Yu GV, Hudson JR. Evaluation and treatment of stage 0 Charcot's neuroarthropathy of the foot and ankle. *J Am Podiatr Med Assoc*. 2002;92:210-220.

33. Frykberg RG, Zgonis T, Armstrong DG, et al; American College of Foot and Ankle Surgeons. Diabetic foot disorders. A clinical practical guideline (2006 revision). *J Foot Ankle Surg*. 2006;45(5 suppl):S1-S66.

34. Ledermann HP, Morrison WB. Differential diagnosis of pedal

osteomyelitis and diabetic neuroarthropathy: MR imaging. *Semin Musculoskelet Radiol.* 2005;9:272-283.

35. Apelqvist J, Larsson J. What is the most effective way to reduce incidence of amputation in the diabetic foot? *Diabetes Metab Res Rev.* 2000;16(suppl 1):S75-S83.

36. Valk GD, Kriegsman DM, Assendelft WJ. Patient education for preventing diabetic foot ulceration. *Cochrane Database Syst Rev.* 2001;(4):CD001488.

37. McCabe CJ, Stevenson RC, Dolan AM. Evaluation of a diabetic foot screening and protection programme. *Diabet Med.* 1998; 15:80-84.

38. Dargis V, Pantelejeva O, Jonushaite A, et al. Benefits of a multidisciplinary approach in the management of recurrent diabetic foot ulceration in Lithuania: a prospective study. *Diabetes Care.* 1999;22:1428-1431.

39. Margolis DJ, Kantor J, Berlin JA. Healing of diabetic neuropathic foot ulcers receiving standard treatment. A meta-analysis. *Diabetes Care.* 1999;22:692-695.

40. Atiyeh BS, Ioannovich J, Al-Amm CA, et al. Management of acute and chronic open wounds: the importance of moist environment in optimal wound healing. *Curr Pharm Biotechnol.* 2002;3:179-195.

41. Steed DL, Donohoe D, Webster MW, et al. Effect of extensive debridement and treatment on the healing of diabetic foot ulcers. Diabetic Ulcer Study Group. *J Am Coll Surg.* 1996;183: 61-64.

42. Sherman RA. Maggot therapy for treating diabetic foot ulcers unresponsive to conventional therapy. *Diabetes Care.* 2003;26: 446-451.

43. Armstrong DG, Lavery LA, Wu S, et al. Evaluation of removable and irremovable cast walkers in the healing of diabetic foot wounds: a randomized controlled trial. *Diabetes Care.* 2005;28:551-554.

44. Katz IA, Harlan A, Miranda-Palma B, et al. A randomized trial of two irremovable off-loading devices in the management of plantar neuropathic diabetic foot ulcers. *Diabetes Care.* 2005;28:555-559.

45. Armstrong DG, Nguyen HC, Lavery LA, et al. Off-loading the diabetic foot wound: a randomized clinical trial. *Diabetes Care.* 2001;24:1019-1022.

46. Nabuurs-Franssen MH, Sleegers R, Huijberts MS, et al. Total contact casting of the diabetic foot in daily practice: a prospective follow-up study. *Diabetes Care.* 2005;28:243-247.

47. Lavery LA, Armstrong DG, Wunderlich RP, et al. Risk factors for foot infections in individuals with diabetes. *Diabetes Care.* 2006;29:1288-1293.

48. Perry CR, Pearson RL, Miller GA. Accuracy of cultures of material from swabbing of the superficial aspect of the wound and needle biopsy in the preoperative assessment of osteomyelitis. *J Bone Joint Surg Am.* 1991;73:745-749.

49. Senneville E, Melliez H, Beltrand E, et al. Culture of percutaneous bone biopsy specimens for diagnosis of diabetic foot osteomyelitis: concordance with ulcer swab cultures. *Clin Infect Dis.* 2006;42:57-62.

50. Slater RA, Lazarovitch T, Boldur I, et al. Swab cultures accurately identify bacterial pathogens in diabetic foot wounds not involving bone. *Diabet Med.* 2004;21:705-709.

51. Nelson EA, O'Meara S, Golder S, et al; DASIDU Steering Group. Systematic review of antimicrobial treatments for diabetic foot ulcers. *Diabet Med.* 2006;23:348-359.

52. Eneroth M, Apelqvist J, Stenström A. Clinical characteristics and outcome in 223 diabetic patients with deep foot infections. *Foot Ankle Int.* 1997;18:716-722.

53. Tan JS, Friedman NM, Hazelton-Miller C, et al. Can aggressive treatment of diabetic foot infections reduce the need for above-ankle amputation? *Clin Infect Dis.* 1996;23:286-291.

54. Pomposelli FB, Kansal N, Hamdan AD, et al. A decade of experience with dorsalis pedis artery bypass: analysis of outcome in more than 1000 cases. *J Vasc Surg.* 2003;37:307-315.

55. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. *JAMA.* 2005;293:217-228.

56. Blume PA, Paragas LK, Sumpio BE, et al. Single-stage surgical treatment of noninfected diabetic foot ulcers. *Plast Reconstr Surg.* 2002;109:601-609.

57. Sayner LR, Rosenblum BI, Giurini JM. Elective surgery of the diabetic foot. *Clin Podiatr Med Surg.* 2003;20:783-792.

58. Räkel A, Huot C, Ekoé JM. Canadian Diabetes Association Technical Review: The diabetic foot and hyperbaric oxygen therapy. *Can J Diabetes.* 2006;30:411-421.

Erectile Dysfunction

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Gerald Brock MD FRCPC, Richard Bebb MD ABIM FRCPC and William Harper MD FRCPC

KEY MESSAGES

- Erectile dysfunction (ED) affects approximately 34 to 45% of men with diabetes, has been demonstrated to negatively impact quality of life among those affected across all age strata, and may be the earliest sign of cardiovascular disease.

- All adult men with diabetes should be regularly screened for ED with a sexual function history.

- The current mainstays of therapy are phosphodiesterase type 5 inhibitors. They have been reported to have a major impact on erectile function and quality of life, and should be offered as first-line therapy to men with diabetes wishing treatment for ED.

INTRODUCTION

Erectile dysfunction (ED) affects approximately 34 to 45% of men with diabetes, and has been demonstrated to negatively impact quality of life among those affected across all age strata. Furthermore, studies indicate that 40% of diabetic men >60 years of age have complete ED (1-9). Among the diabetic population, risk factors include increasing age, duration of diabetes, poor glycemic control, cigarette smoking, hypertension, dyslipidemia, androgen deficiency states (10) and cardiovascular disease (CVD) (5,7,11,12). ED as a marker of potential CV events has been reported by numerous investigators (13-20). Diabetic retinopathy has been shown to correlate with the presence of ED (5,7,21). Organic causes of ED include microvascular and macrovascular disease, and neuropathy. In addition, psychological or situational factors may cause or contribute to ED.

Compared with the general population, multiple studies have reported men with diabetes having higher rates of hypogonadism (10,22-24). Importantly, phosphodiesterase type 5 (PDE5) inhibitors appear to be less effective in hypogonadal states (23,25,26), where treatment of nonresponders to PDE5 with testosterone replacement is successful in roughly 50% of individuals. In addition, ED is a side effect of many drugs commonly prescribed to men with diabetes, such as some antihypertensives and antidepressants.

SCREENING

All adult men with diabetes should be regularly screened for ED with a sexual function history. Screening for ED in men with type 2 diabetes should begin at diagnosis of diabetes. Validated questionnaires (e.g. International Index of Erectile Function [27,28] or Sexual Health Inventory for Men [29]) have been shown to be both sensitive and specific in determining the presence of ED and providing a means of assessing response to therapy.

TREATMENT

While no randomized clinical trials have demonstrated that interventions that improve glycemic control also reduce the incidence and progression of ED, the Diabetes Control and Complications Trial and United Kingdom Prospective Diabetes Study showed that intensive glycemic control was effective for primary prevention of and secondary intervention for neuropathy, a condition that can impair sensory feedback from the penis, leading to reduced erectile function (30-32). The current data still show that tight glycemic control does not reverse ED (33-35).

The current mainstays of therapy are PDE5 inhibitors. They have been reported to have a major impact on erectile function, quality of life, and should be offered as first-line therapy to men with diabetes wishing treatment for ED (36-41).

Evolving evidence supports the potential beneficial effects of PDE5 inhibitors on endothelial function and lower urinary tract symptoms. Contraindications for the use of PDE5 inhibitors include unstable angina or untreated cardiac ischemia and concomitant use of nitrates (42,43).

Referral to a specialist in ED should be offered to men who do not respond to PDE5 inhibitors or for whom the use of PDE5 inhibitors is contraindicated. Second-line therapies (e.g. vacuum constriction devices, intracorporal injection therapy with prostaglandin E1 [PGE1] alone or in combination with papaverine and phentolamine [triple therapy], intraurethral therapy using PGE1) or third-line therapy (penile prosthesis) may be considered for these men (44).

EJACULATORY DISORDERS

Ejaculatory disorders are another common disorder of sexual function in men with diabetes, occurring in up to 32% (45). They range in scope from retrograde ejaculation, usually secondary to autonomic neuropathy with incomplete closure of the bladder neck during ejaculation, to premature or retarded ejaculation.

RECOMMENDATIONS

1. All adult men with diabetes should be regularly screened for ED with a sexual function history *[Grade D, Consensus]*.

2. A PDE5 inhibitor should be offered as first-line therapy to men with diabetes with ED if there are no contraindications to its use *[Grade A, Level 1A (36-43)]*

3. Referral to a specialist in ED should be considered for eugonadal men who do not respond to PDE5 inhibitors, or for whom the use of PDE5 inhibitors is contraindicated *[Grade D, Consensus]*.

4. Men with diabetes and ED who do not respond to PDE5 therapy should be investigated for hypogonadism *[Grade D, Level 4 (22,23,25,26)]*.

5. Men with diabetes and ejaculatory dysfunction who wish fertility should be referred to a healthcare professional experienced in the treatment of ejaculatory dysfunction *[Grade D, Consensus]*.

OTHER RELEVANT GUIDELINES

Screening for the Presence of Coronary Artery Disease, p. S99

Diabetes in the Elderly, p. S181

REFERENCES

1. Chew KK, Earle CM, Stuckey BG, et al. Erectile dysfunction in general medicine practice: prevalence and clinical correlates. *Int J Impot Res.* 2000;12:41-45.

2. Maatman TJ, Montague DK, Martin LM. Erectile dysfunction in men with diabetes mellitus. *Urology.* 1987;29:589-592.

3. Rubin A, Babbott D. Impotence and diabetes mellitus. *JAMA.* 1958;168:498-500.

4. Kolodny RC, Kahn CB, Goldstein HH, et al. Sexual dysfunction in diabetic men. *Diabetes.* 1974;23:306-309.

5. McCulloch DK, Campbell IW, Wu FC, et al. The prevalence of diabetic impotence. *Diabetologia.* 1980;18:279-283.

6. Zemel P. Sexual dysfunction in the diabetic patient with hypertension. *Am J Cardiol.* 1988;61:27H-33H.

7. McCulloch DK, Young RJ, Prescott RJ, et al. The natural history of impotence in diabetic men. *Diabetologia.* 1984;26:437-440.

8. Bacon CG, Hu FB, Giovannucci E, et al. Association of type and duration of diabetes with erectile dysfunction in a large cohort of men. *Diabetes Care.* 2002;25:1458-1463.

9. De Berardis G, Pellegrini F, Franciosi M, et al. Identifying patients with type 2 diabetes with a higher likelihood of erectile dysfunction: the role of the interaction between clinical and psychological factors. *J Urol.* 2003;169:1422-1428.

10. Alexopoulou O, Jamart J, Maiter D, et al. Erectile dysfunction and lower androgenicity in type 1 diabetic patients. *Diabetes Metab.* 2001;27:329-336.

11. Naliboff BD, Rosenthal M. Effects of age on complications in adult onset diabetes. *J Am Geriatr Soc.* 1989;37:838-842.

12. Feldman HA, Goldstein I, Hatzichristou DG, et al. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol.* 1994;151:54-61.

13. Grover SA, Lowensteyn I, Kaouache M, et al. The prevalence of erectile dysfunction in the primary care setting: importance of risk factors for diabetes and vascular disease. *Arch Intern Med.* 2006;166:213-219.

14. Barrett-Connor E. Cardiovascular risk stratification and cardiovascular risk factors associated with erectile dysfunction: assessing cardiovascular risk in men with erectile dysfunction. *Clin Cardiol.* 2004;27(suppl 1):I8-I13.

15. Billups KL. Erectile dysfunction as an early sign of cardiovascular disease. *Int J Impot Res.* 2005;17(suppl 1):S19-S24.

16. Thompson IM, Tangen CM, Goodman PJ, et al. Erectile dysfunction and subsequent cardiovascular disease. *JAMA.* 2005;294:2996-3002.

17. Gazzaruso C. Erectile dysfunction and coronary atherothrombosis in diabetic patients: pathophysiology, clinical features and treatment. *Expert Rev Cardiovasc Ther.* 2006;4:173-180.

18. Barrett-Connor E. Heart disease risk factors predict erectile dysfunction 25 years later (the Rancho Bernardo Study). *Am J Cardiol.* 2005;96:3M-7M.

19. Min JK, Williams KA, Okwuosa TM, et al. Prediction of coronary heart disease by erectile dysfunction in men referred for nuclear stress testing. *Arch Intern Med.* 2006;166:201-206.

20. Chiurlia E, D'Amico R, Ratti C, et al. Subclinical coronary artery atherosclerosis in patients with erectile dysfunction. *J Am Coll Cardiol.* 2005;46:1503-1506.

21. Klein R, Klein BEK, Lee KE, et al. Prevalence of self-reported erectile dysfunction in people with long-term IDDM. *Diabetes Care.* 1996;19:135-141.

22. Dhindsa S, Prabhakar S, Sethi M, et al. Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. *J Clin Endocrinol Metab.* 2004;89:5462-5468.

23. Boyanov MA, Boneva Z, Christov VG. Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. *Aging Male.* 2003;6:1-7.

24. Shabsigh R, Rajfer J, Aversa A, et al. The evolving role of testosterone in the treatment of erectile dysfunction. *Int J Clin Pract.* 2006;60:1087-1092.

25. Shabsigh R, Kaufman JM, Steidle C, et al. Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. *J Urol.* 2004;172:658-663.

26. Kalinchenko SY, Kozlov GI, Gontcharov NP, et al. Oral testosterone undecanoate reverses erectile dysfunction associated with diabetes mellitus in patients failing on sildenafil citrate therapy alone. *Aging Male.* 2003;6:94-99.

27. Rosen RC, Riley A, Wagner G, et al. The International Index of Erectile Function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology.* 1997;49:822-830.

28. Cappelleri JC, Rosen RC, Smith MD, et al. Diagnostic evaluation of the erectile function domain of the International Index

of Erectile Function. *Urology*. 1999;54:346-351.

29. Ramanathan R, Mulhall J, Rao S, et al. Prospective correlation between the International Index of Erectile Function (IIEF) and Sexual Health Inventory for Men (SHIM): implications for calculating a derived SHIM for clinical use. *J Sex Med*. 2007; 4:1334-1344.

30. Valiquette L, Montorsi F, Auerbach S; Vardenafil Study Group. First-dose success with vardenafil in men with erectile dysfunction and associated comorbidities: RELY-I. *Int J Clin Pract*. 2006;60:1378-1385.

31. The Diabetes Control and Complications Trial Research Group. The effect of intensive diabetes therapy on the development and progression of neuropathy. *Ann Intern Med*. 1995; 122:561-568.

32. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med.* 1993;329: 977-986.

33. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352: 837-853.

34. Azad N, Emanuele NV, Abraira C, et al. The effects of intensive glycemic control on neuropathy in the VA Cooperative Study on Type II Diabetes Mellitus (VA CSDM). *J Diabetes Complications.* 1990;13:307-313.

35. El-Sakka AI, Hassoba HM, Sayed HM, et al. Pattern of endocrinal changes in patients with sexual dysfunction. *J Sex Med.* 2005;2:551-558.

36. Fonseca V, Seftel A, Denne J, et al. Impact of diabetes mellitus on the severity of erectile dysfunction and response to treatment: analysis of data from tadalafil clinical trials. *Diabetologia*. 2004;47:1914-1923.

37. Rendell MS, Rajfer J, Wicker PA, et al. Sildenafil for treatment of erectile dysfunction in men with diabetes: a randomized controlled trial. *JAMA*. 1999;281:421-426.

38. Boulton AJM, Selam J-L, Sweeney M, et al. Sildenafil citrate for the treatment of erectile dysfunction in men with type II diabetes mellitus. *Diabetologia*. 2001;44:1296-1301.

39. Goldstein I, Young JM, Fischer J, et al. Vardenafil, a new phosphodiesterase type 5 inhibitor, in the treatment of erectile dysfunction in men with diabetes: a multicenter double-blind placebo-controlled fixed-dose study. *Diabetes Care*. 2003;26: 777-783.

40. Sáenz de Tejada I, Anglin G, Knight JR, et al. Effects of tadalafil on erectile dysfunction in men with diabetes. *Diabetes Care*. 2002;25:2159-2164.

41. Carson CC, Lue TF. Phosphodiesterase type 5 inhibitors for erectile dysfunction. *BJU Int.* 2005;96:257-280.

42. Briganti A, Salonia A, Gallina A, et al. Drug insight: oral phosphodiesterase type 5 inhibitors for erectile dysfunction. *Nat Clin Pract Urol.* 2005;2:239-247.

43. DeBusk R, Drory Y, Goldstein I, et al. Management of sexual dysfunction in patients with cardiovascular disease: recommendations of the Princeton Consensus Panel. *Am J Cardiol.* 2000;86:175-181.

44. Herschorn S. Cardiovascular safety of PDE5 inhibitors. *Can J Urol.* 2003;10(suppl 1):23-28.

45. Carson CC, Mulcahy JJ, Govier FE. Efficacy, safety and patient satisfaction outcomes of the AMS 700CX inflatable penile prosthesis: results of a long-term multicenter study. *J Urol.* 2000;164:376-380.

COMPLICATIONS AND COMORBIDITIES

Type 1 Diabetes in Children and Adolescents

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee
The initial draft of this chapter was prepared by Margaret L. Lawson MD MSc FRCPC, Danièle Pacaud MD FRCPC and Diane Wherrett MD FRCPC

KEY MESSAGES

- Suspicion of diabetes in a child should lead to immediate confirmation of the diagnosis and initiation of treatment to reduce the likelihood of diabetic ketoacidosis (DKA).

- Management of pediatric DKA differs from DKA in adults because of the increased risk for cerebral edema. Pediatric protocols should be used.

- Children should be referred for diabetes education and ongoing care to a diabetes team with pediatric expertise.

Unless otherwise specified, the term "child" or "children" is used for individuals 0 to 18 years of age, and the term "adolescent" for those 13 to 18 years of age.

INTRODUCTION

Diabetes mellitus is the most common endocrine disease and one of the most common chronic conditions in children. Type 2 diabetes and other types of diabetes, including genetic defects of beta cell function such as maturity-onset diabetes of the young (MODY), are increasing in frequency and should be considered when clinical presentation is atypical for type 1 diabetes. This section addresses those areas of type 1 diabetes management that are specific to children.

EDUCATION

Children with new-onset type 1 diabetes and their families require intensive diabetes education by an interdisciplinary pediatric diabetes healthcare (DHC) team to provide them with the necessary skills and knowledge to manage this disease. The complex physical, developmental and emotional needs of children and their families necessitate specialized care to ensure the best long-term outcomes (1). Education topics must include insulin action and administration, dosage adjustment, blood glucose (BG) and ketone testing, sick-day management and prevention of diabetic ketoacidosis (DKA), nutrition therapy, exercise, and prevention, detection, and treatment of hypoglycemia. Anticipatory guidance and lifestyle counselling should be part of routine care, especially during critical developmental transitions (e.g. upon school entry, beginning high school). Healthcare providers should regularly initiate discussions with children and their families about school, diabetes camp, psychological issues, substance abuse, driver's licence and career choices.

Children with new-onset diabetes who present with DKA require a short period of hospitalization to stabilize the associated metabolic derangements and to initiate insulin therapy. Outpatient education for well children with new-onset diabetes has been shown to be less expensive than inpatient education and associated with similar or slightly better outcomes when appropriate resources are available (2).

GLYCEMIC TARGETS

As improved metabolic control reduces both the onset and progression of diabetes-related complications in adults and adolescents with type 1 diabetes (3,4) aggressive attempts should be made to reach the recommended glycemic targets outlined in Table 1. However, clinical judgement is required to determine which children can reasonably and safely achieve these targets. Treatment goals and strategies must be tailored to each child, with consideration given to individual risk factors. Young age at diabetes onset (<7 years of age) has been associated with poorer cognitive function in many studies (5). Episodes of severe hypoglycemia have been associated with poorer cognitive function in some follow-up studies, while other studies have found chronic hyperglycemia in young children to be associated with poorer cognitive performance (6-8).

INSULIN THERAPY

Insulin therapy is the mainstay of medical management of type 1 diabetes. A variety of insulin regimens can be employed, but few have been studied specifically in children with new-onset diabetes. The choice of insulin regimen depends on many factors, including the child's age, duration of diabetes, family lifestyle, socioeconomic factors, and family, patient and physician preferences. Regardless of the insulin regimen used, all children should be treated to meet glycemic targets.

The honeymoon period, which can last up to 2 years post-diagnosis, is characterized by good glycemic control and low insulin requirements (<0.5 units/kg/day). At the end of this period, more intensive management may be required to continue meeting glycemic targets. Two methods of intensive diabetes management have been used: multiple daily injection (MDI) regimens and continuous subcutaneous insulin infusion (CSII, insulin pump therapy). CSII is safe and effective and can be initiated at any age (9). Most (10-13), but not all (14), randomized controlled trials (RCTs) of CSII in children

through earlier recognition and initiation of insulin therapy. Public awareness campaigns about the early signs of diabetes have significantly reduced the frequency of DKA in new-onset diabetes (33). In children with established diabetes, DKA results from failing to take insulin or poor sick-day management. Risk is increased in children with poor metabolic control or previous episodes of DKA, peripubertal and adolescent girls, children with psychiatric disorders and those with difficult family circumstances (34). The frequency of DKA in established diabetes can be decreased with education and family support (35) as well as access to 24-hour telephone services for parents of children with diabetes (36,37).

Management of DKA

While most cases of DKA are corrected without event, 0.7 to 3.0% of pediatric cases are complicated by cerebral edema (CE) (38), which is associated with significant morbidity (21 to 35%) and mortality (21 to 24%) (39). In contrast, CE has rarely been reported in adults (34,39). Although the cause of CE is still unknown, several factors are associated with increased risk (Table 2) (40-43). A bolus of insulin prior to infusion is not recommended (44) since it does not offer any faster resolution of acidosis (45,46) and may contribute to CE (47). Recent evidence suggests early insulin administration (within the first hour of fluid replacement) may increase the risk for CE (48). Special caution should be exercised in young children with DKA and new-onset diabetes or a greater degree of acidosis and extracellular fluid volume (ECFV) depletion because of the increased risk of CE. Use of bedside criteria may allow earlier identification of patients who require treatment for CE (49). DKA should be managed according to published protocols for management of pediatric DKA (50) (Figure 1).

IMMUNIZATION

Historically, national guidelines have recommended influenza and pneumococcal immunization for children with type 1 diabetes (51-53). Currently, there is no evidence supporting increased morbidity or mortality from influenza or pneumococcus in children with type 1 diabetes (54,55). However,

Table 2. Risks factors for CE
• Younger age (<5 years)
• New-onset diabetes
• High initial serum urea
• Low initial partial pressure of arterial carbon dioxide (pCO$_2$)
• Rapid administration of hypotonic fluids
• IV bolus of insulin
• Early IV insulin infusion (within first hour of administration of fluids)
• Failure of serum sodium to rise during treatment
• Use of bicarbonate

CE = cerebral edema
IV = intravenous

the management of type 1 diabetes can be complicated by illness, thus requiring parental knowledge of sick-day management and increased attention during periods of illness. For this reason, parents may choose to immunize their children.

SMOKING PREVENTION AND CESSATION

Smoking is a significant risk factor for both macrovascular and microvascular complications of diabetes (56). Smoking prevention should be emphasized throughout childhood and adolescence.

CONTRACEPTION AND SEXUAL HEALTH COUNSELLING

Adolescents with diabetes should receive regular counselling about sexual health and contraception. Unplanned pregnancies should be avoided, as pregnancy in females with type 1 diabetes with suboptimal metabolic control results in higher risks of maternal and fetal complications (57).

PSYCHOLOGICAL ISSUES

Some children and their parents have adjustment problems soon after the diagnosis of diabetes (58,59). Although most resolve these problems within the first year after diagnosis, those who do not are at risk for poor adaptation to diabetes, including regimen adherence problems, poor glycemic control and continued psychosocial difficulties (60,61). Stress (general and diabetes-specific) (62), inadequate social and family support (63,64), inappropriate beliefs about the nature of diabetes (63) and poor coping skills (65) may have a negative impact on self-care behaviours and glycemic control.

The diagnosis of diabetes may precipitate or exacerbate existing psychological disorders (66). As quality of life and diabetes control may be adversely affected by the presence of comorbid psychological disorders and health complications (66), the identification of potential psychiatric conditions, such as depression, anxiety and eating disorders, is critical. All children with diabetes and their families should be regularly screened for symptoms of psychological distress (67,68) (See "Psychological Aspects of Diabetes," p. S82).

Eating disorders

Ten percent of adolescent females with type 1 diabetes meet the *Diagnostic and Statistical Manual of Mental Disorders (4th Edition)* criteria for eating disorders compared to 4% of their age-matched peers without diabetes (69). Furthermore, eating disorders are associated with poor metabolic control and earlier onset and more rapid progression of microvascular complications (70). Eating disorders should be suspected in those adolescent and young adult females who are unable to achieve and maintain metabolic targets especially when insulin omission is suspected. It is important to identify individuals with eating disorders because different management strategies are required to optimize metabolic control and prevent microvascular complications (71).

Figure 1. Immediate assessment and management of DKA in children

Immediate assessment

Clinical history
- Polyuria
- Polydipsia
- Weight loss (weigh)
- Abdominal pain
- Tiredness
- Vomiting
- Confusion

Clinical signs
- Dehydration (assess)
- Deep sighing respiration (Kussmaul)
- Smell of ketones
- Lethargy/drowsiness ± vomiting

Biochemical features and investigations
- Ketones in urine
- Elevated BG
- Acidemia
- Blood gases, urea, electrolytes
- Other investigations as indicated

Diagnosis of DKA confirmed
Contact senior staff

- Shock (reduced peripheral pulses)
- Reduced consciousness or coma

- Dehydration >5%
- Not in shock
- Acidotic (hyperventilation)
- Vomiting

- Minimal dehydration
- Tolerating oral fluid

Resuscitation
- Airway ± nasogastric tube
- Breathing (100% O_2)
- Circulation (0.9% NaCl 10–20 mL/kg over 1–2 h), and repeat until circulation is restored), but do not exceed 30 mL/kg

IV therapy
- Calculate fluid requirements
- Correct over 48 hours
- 0.9% NaCl
- ECG for abnormal T-waves
- Add 40 mmol/L KCl

Therapy
- Start with SC insulin
- Continue oral hydration

No improvement

Continuous IV insulin infusion 0.1 U/kg/h
to be started 1–2 hours after IV rehydration initiated

Critical observations
- Hourly BG
- Hourly fluid input and output
- **Neurologic status** at least hourly
- Electrolytes every 2 h after start of IV therapy
- Monitor ECG for T-wave changes

Acidosis not improving

PG 14.0–17.0 mmol/L; or PG falling >5.0 mmol/L/h

Neurological deterioration (**Warning signs:** headache, slowing heart rate, irritability, decreased level of consciousness, incontinence, specific neurological signs)

Re-evaluation
- IV fluid calculations
- Insulin delivery system and dose
- Need for additional resuscitation
- Consider sepsis

IV therapy
- Change to 0.45% NaCl + 5% glucose
- Adjust [Na^+] infusion to promote an increase in measured serum [Na^+]

Exclude hypoglycemia
Is it cerebral edema?

Improvement
- Clinically well
- Tolerating oral fluids

Management
- Give mannitol 0.5–1 g/kg
- Restrict IV fluids by one-third
- Call senior staff
- Move to ICU
- Consider cranial imaging only after patient stabilized

Transition to SC insulin
Start SC insulin **then** stop IV insulin after an appropriate interval

BG = blood glucose
DKA = diabetic ketoacidosis
ECG = electrocardiogram
ICU = intensive care unit
IV = intravenous
PG = plasma glucose
SC = subcutaneous

Adapted with permission from Reference 50.

DIABETES IN CHILDREN AND ADOLESCENTS

COMORBID CONDITIONS

Autoimmune thyroid disease

Clinical autoimmune thyroid disease (AITD) occurs in 15 to 30% of individuals with type 1 diabetes (72). The risk for AITD during the first decade of diabetes is directly related to the presence or absence of thyroid antibodies at diabetes diagnosis (73). Early detection and treatment of hypothyroidism will prevent growth failure and symptoms of hypothyroidism (Table 3).

Addison disease

Addison disease is rare, even in those with type 1 diabetes (74). Targeted screening is required in those with unexplained recurrent hypoglycemia and decreasing insulin requirements (Table 3).

Celiac disease

Celiac disease can be identified in 4 to 9% of children with type 1 diabetes (72), but in 60 to 70% of these children the disease is asymptomatic (silent celiac disease). Children with type 1 diabetes are at increased risk for classic or atypical celiac disease during the first 10 years of diabetes (75). There is good evidence that treatment of classic or atypical celiac disease with a gluten-free diet improves intestinal and extra-intestinal symptoms (76) and prevents the long-term sequelae of untreated classic celiac disease (77). However, there is no evidence that untreated asymptomatic celiac disease is associated with short- or long-term health risks (78) or that a gluten-free diet improves health in these individuals (79). Thus, universal screening for and treatment of asymptomatic celiac disease remain controversial (Table 3).

DIABETES COMPLICATIONS

There are important age-related considerations regarding surveillance for diabetes complications and interpretation of investigations (Table 4).

Nephropathy

A first morning urine albumin to creatinine ratio (ACR) has high sensitivity and specificity for the detection of microalbuminuria (80,81). Although screening with a random ACR is associated with greater compliance than with a first morning sample, its specificity may be compromised in adolescents due to their higher frequency of exercise-induced proteinuria and benign postural proteinuria. Abnormal random ACRs require confirmation with a first morning ACR or timed urine collection.

Microalbuminuria is rare in prepubertal children, regardless of the duration of diabetes or metabolic control (82). Furthermore, the likelihood of transient or intermittent microalbuminuria is higher during the early peripubertal years (83). Individuals with transient or intermittent microalbuminuria may be at increased risk of progression to overt nephropathy (84). Abnormal screening results require confirmation and follow-up to demonstrate persistent abnormalities.

Treatment is indicated only for those adolescents with persistent microalbuminuria. One short-term RCT in adolescents demonstrated that angiotensin-converting enzyme (ACE) inhibitors were effective in reducing microalbuminuria compared to placebo (85). However, there are no long-term intervention studies assessing the effectiveness of ACE inhibitors or angiotensin II receptor antagonists in delaying progression to overt nephropathy in adolescents with microalbuminuria. Therefore, treatment of adolescents with persistent microalbuminuria is based on the effectiveness of treatments in adults with type 1 diabetes (86).

Retinopathy

Retinopathy is rare in prepubertal children with type 1 diabetes and in postpubertal adolescents with good metabolic control (87,88).

Neuropathy

When present, neuropathy is mostly subclinical in children (89). While prospective nerve conduction studies and autonomic neuropathy assessment studies have demonstrated increased prevalence of abnormalities over time (90), persistence of abnormalities is an inconsistent finding (91).

Table 3. Recommendations for screening for comorbid conditions in children with type 1 diabetes			
Condition	*Indications for screening*	*Screening test*	*Frequency*
Autoimmune thyroid disease	All children with type 1 diabetes	Serum TSH level + thyroperoxidase antibodies	At diagnosis and every 2 years thereafter
	Positive thyroid antibodies, thyroid symptoms or goiter	Serum TSH level + thyroperoxidase antibodies	Every 6–12 months
Addison disease	Unexplained recurrent hypoglycemia and decreasing insulin requirements	8 AM serum cortisol + serum sodium and potassium	As clinically indicated
Celiac disease	Recurrent gastrointestinal symptoms, poor linear growth, poor weight gain, fatigue, anemia, unexplained frequent hypoglycemia or poor metabolic control	Tissue transglutaminase + immunoglobulin A levels	As clinically indicated

TSH = thyroid-stimulating hormone

Vibration and monofilament testing have suboptimal sensitivity and specificity in adolescents (92). With the exception of intensifying diabetes management to achieve and maintain glycemic targets, no other treatment modality has been studied in children and adolescents.

Dyslipidemia
Most children with type 1 diabetes should be considered at low risk for vascular disease associated with dyslipidemia. The exceptions are those with longer duration of disease, microvascular complications or other cardiovascular disease (CVD) risk factors including smoking, hypertension, obesity and/or family history of premature CVD (93). Dyslipidemia screening should be targeted at those >12 years of age and younger children with specific risk factors for dyslipidemia. Statin therapy has not been studied specifically in children with diabetes, and there is no evidence linking specific low-density lipoprotein cholesterol (LDL-C) cutoffs in children with diabetes with long-term outcomes. In pubertal children without diabetes but with familial hypercholesterolemia, statin therapy is safe and effective at lowering LDL-C levels, and attenuating progression of carotid intima-media thickness, a surrogate marker for future vascular disease (94).

Hypertension
Up to 16% of adolescents with type 1 diabetes have hypertension (95). Twenty-four-hour ambulatory blood pressure (BP) monitoring has been used to exclude white coat hypertension and to identify loss of diurnal systolic rhythm (nondippers) with nocturnal hypertension in some normotensive adolescents with type 1 diabetes (96). These abnormalities may be predictive of future microalbuminuria (96). However, the role of ambulatory BP monitoring in routine care remains uncertain. Children with type 1 diabetes and confirmed hypertension should be treated according to the guidelines for children without diabetes (97).

TRANSITION TO ADULT CARE
The change of physician or DHC team can have a major impact on disease management and metabolic control in the person with diabetes. Between 25 and 65% of young adults have no medical follow-up during the transition from pediatric to adult diabetes care services (98,99). Those with no follow-up are more likely to experience hospitalization for DKA during this period. Organized transition services may decrease the rate of loss of follow-up (100).

Table 4. Screening for diabetes complications, dyslipidemia and hyperglycemia in children with type 1 diabetes

Complication	Indications and intervals for screening	Screening method
Nephropathy	• Yearly screening commencing at 12 years of age in those with duration of type 1 diabetes >5 years	• First morning (preferred) or random ACR • Abnormal ACR requires confirmation at least 1 month later with a first morning ACR, and if abnormal, followed by timed, overnight or 24-hour split urine collections for albumin excretion rate • Repeated sampling should be done every 3–4 months over a 12-month period to demonstrate persistence
Retinopathy	• Yearly screening commencing at 15 years of age with duration of type 1 diabetes >5 years • Screening interval can increase to 2 years if good glycemic control, duration of diabetes <10 years, and no retinopathy at initial assessment	• 7-standard field, stereoscopic-colour fundus photography with interpretation by a trained reader (gold standard); or • Direct ophthalmoscopy or indirect slit-lamp fundoscopy through dilated pupil; or • Digital fundus photography
Neuropathy	• Postpubertal adolescents with poor metabolic control should be screened yearly after 5 years' duration of type 1 diabetes	• Question and examine for symptoms of numbness, pain, cramps and paresthesia, as well as skin sensation, vibration sense, light touch and ankle reflexes
Dyslipidemia	• Delay screening post-diabetes diagnosis until metabolic control has stabilized • Screen at 12 and 17 years of age • <12 years of age: screen only those with BMI >95th percentile, family history of hyperlipidemia or premature CVD	• Fasting total cholesterol, high-density lipoprotein cholesterol, triglycerides, calculated low-density lipoprotein cholesterol
Hypertension	• Screen all children with type 1 diabetes at least twice a year	• Use appropriate cuff size

ACR = albumin to creatinine ratio   BMI = body mass index   CVD = cardiovascular disease

RECOMMENDATIONS

Delivery of care

1. All children with diabetes should have access to an experienced pediatric DHC team and specialized care starting at diagnosis *[Grade D, Level 4 (1)]*.

2. Children with new-onset type 1 diabetes who are medically stable should receive their initial education and management in an outpatient setting, providing appropriate personnel and daily telephone consultation service are available in the community *[Grade B, Level 1A (2)]*.

3. To ensure ongoing and adequate metabolic control, pediatric and adult diabetes care services should collaborate to prepare adolescents and young adults for the transition to adult diabetes care *[Grade C, Level 3 (100)]*.

Glycemic targets

4. Glycemic targets should be graduated with age (Table 1):
   - Children <6 years of age should aim for an A1C of <8.5% *[Grade D, Consensus]*. Extra caution should be used to minimize hypoglycemia because of the potential association in this age group between severe hypoglycemia and later cognitive impairment *[Grade D, Level 4 (101)]*.
   - Children 6 to 12 years of age should aim for an A1C target of <8.0% *[Grade D, Consensus]*.
   - Adolescents should aim for the same glycemic targets as adults *[Grade A, Level 1A (4)]*.

5. Children with persistently poor diabetes control (e.g. A1C >10%) should be referred to a tertiary pediatric diabetes team and/or mental health professional for a comprehensive interdisciplinary assessment *[Grade D, Consensus]*. Intensive family and individualized psychological interventions aimed at improving glycemic control should be considered to improve chronically poor metabolic control *[Grade A, Level 1A (102,103)]*.

Insulin therapy

6. Children with new-onset diabetes should be started on at least 2 daily injections of short-acting insulin or rapid-acting insulin analogues combined with an intermediate- or long-acting insulin *[Grade D, Consensus]*.

7. Insulin therapy should be assessed at each clinical encounter to ensure it still enables the child to meet A1C targets, minimizes the risk of hypoglycemia and allows flexibility in carbohydrate intake, daily schedule and activities *[Grade D, Consensus]*. This assessment should include consideration of:
   - Increased frequency of injections *[Grade D, Consensus]*
   - Change in the type of basal (long-acting analogue) and/or prandial (rapid-acting analogue) insulin *[Grade B, Level 2 (17), for adolescents; Grade D, Consensus, for younger children]*.
   - Change to CSII therapy *[Grade C, Level 3 (104)]*.

Hypoglycemia

8. In children, the use of mini-doses of glucagon (20 µg per year of age to a maximum of 150 µg) should be considered in the home management of mild or impending hypoglycemia associated with inability or refusal to take oral carbohydrate *[Grade D, Level 4 (27)]*.

9. In the home situation, severe hypoglycemia in an unconscious child >5 years of age should be treated with 1 mg of glucagon subcutaneously or intramuscularly. In children ≤5 years of age, a dose of 0.5 mg of glucagon should be given. The episode should be discussed with the diabetes healthcare team as soon as possible and consideration given to reducing insulin doses for the next 24 hours to avoid further severe hypoglycemia *[Grade D, Consensus]*.

10. Dextrose 0.5 to 1 g/kg should be given over 1 to 3 minutes to treat severe hypoglycemia with unconsciousness when IV access is available *[Grade D, Consensus]*.

Diabetic ketoacidosis

11. To prevent DKA in children with diabetes:
    - Targeted public awareness campaigns should be considered to educate parents and other caregivers (e.g. teachers) about the early symptoms of diabetes *[Grade C, Level 3 (33)]*.
    - Comprehensive education and support services *[Grade C, Level 3 (35)]*, as well as 24-hour telephone services *[Grade C, Level 3 (36)]*, should be available for families of children with diabetes.

12. DKA in children should be treated according to pediatric-specific protocols *[Grade D, Consensus]*. If appropriate expertise/facilities are not available locally, there should be immediate consultation with a centre with expertise in pediatric diabetes *[Grade D, Consensus]*.

13. In children in DKA, rapid administration of hypotonic fluids should be avoided *[Grade D, Level 4 (41)]*. Circulatory compromise should be treated with only enough isotonic fluids to correct circulatory inadequacy *[Grade D, Consensus]*. Restoration of ECFV should be extended over a 48-hour period with regular reassessments of fluid deficits *[Grade D, Level 4 (41)]*.

14. In children in DKA, IV insulin bolus should not be given; an IV infusion of short-acting insulin should be used at an initial dose of 0.1 units/kg/hour *[Grade D, Level 4 (45)]*. The insulin infusion should not be started until 1 hour after starting fluid replacement therapy *[Grade D, Level 4 (48)]*.

15. In children in DKA, the insulin infusion rate should be maintained until the plasma anion gap normalizes. Once PG reaches 14.0 to 17.0 mmol/L, IV glucose should be started to avoid hypoglycemia *[Grade D, Consensus]*.

16. In children in DKA, administration of sodium bicarbonate should be avoided except in extreme circulatory compromise, as this may contribute to CE *[Grade D, Level 4 (40)]*.

Microvascular complications

17. Prepubertal children and those in the first 5 years of diabetes should be considered at very low risk for microalbuminuria *[Grade A, Level 1 (82,83)]*. Screening for microalbuminuria should be performed annually commencing at 12 years of age in children with type 1 diabetes >5 years' duration *[Grade D, Consensus]*.

RECOMMENDATIONS

18. Adolescents with type 1 diabetes should be screened for microalbuminuria with a first morning urine ACR (preferred) [Grade B, Level 2 (81)] or a random ACR [Grade D, Consensus]. Abnormal results should be confirmed [Grade B, Level 2 (105)] at least 1 month later with a first morning ACR, and if abnormal, followed by timed, overnight, or 24-hour split urine collections for albumin excretion rate [Grade D, Consensus]. Microalbuminuria should not be diagnosed in adolescents unless it is persistent as demonstrated by 3 consecutive timed collections obtained at 3- to 4-month intervals over a 12-month period [Grade D, Consensus].

19. Adolescents with persistent microalbuminuria should be treated as per adult guidelines [Grade D, Consensus].

20. Proliferative retinopathy should be considered rare in pre-pubertal children, and within the first 5 years of diagnosis of diabetes [Grade B, Level 2 (87,106)]. In children ≥15 years of age with type 1 diabetes, screening and evaluation for retinopathy by an expert professional should be performed annually starting 5 years after the onset of diabetes [Grade D, Consensus]. The screening interval can be increased to every 2 years in children with type 1 diabetes who have good glycemic control, duration of diabetes <10 years, and no significant retinopathy (as determined by an expert professional) [Grade D, Consensus].

21. Postpubertal children with type 1 diabetes of >5 years' duration and poor metabolic control should be questioned about symptoms of numbness, pain, cramps and paresthesia, and examined for skin sensation, vibration sense, light touch and ankle reflexes [Grade D, Consensus].

Comorbid conditions and other complications

22. Children with type 1 diabetes who are <12 years of age should be screened for dyslipidemia if they have other risk factors such as obesity (BMI >95th percentile for age and gender), and/or a family history of dyslipidemia or premature CVD. Routine screening for dyslipidemia should begin at 12 years of age, with repeat screening after 5 years [Grade D, Consensus].

23. Children with type 1 diabetes and dyslipidemia should be treated as per lipid guidelines for adults with diabetes [Grade D, Consensus].

24. All children with type 1 diabetes should be screened for hypertension at least twice annually [Grade D, Consensus].

25. Children with type 1 diabetes and BP readings persistently above the 95th percentile for age should receive lifestyle counselling, including weight loss if overweight [Grade D, Level 4 (107)]. If BP remains elevated, treatment should be initiated based on recommendations for children without diabetes [Grade D, Consensus].

26. Influenza immunization should be offered to children with diabetes as a way to avoid an intercurrent illness that could complicate diabetes management [Grade D, Consensus].

27. Formal smoking prevention and cessation counselling should be part of diabetes management for children with diabetes [Grade D, Consensus].

28. Adolescent females with type 1 diabetes should receive counselling on contraception and sexual health in order to avoid unplanned pregnancy [Grade D, Consensus].

29. Adolescent females with type 1 diabetes have a 2-fold increased risk for eating disorders [Grade B, Level 2 (69)] and should be regularly screened using nonjudgemental questions about weight and shape concerns, dieting, binge eating and insulin omission for weight loss [Grade D, Consensus].

30. Children with type 1 diabetes who have thyroid antibodies should be considered high risk for autoimmune thyroid disease [Grade C, Level 3 (73)]. Children with type 1 diabetes should be screened at diabetes diagnosis with repeat screening every 2 years using a serum TSH and thyroperoxidase antibodies [Grade D, Consensus]. More frequent screening is indicated in the presence of positive thyroid antibodies, thyroid symptoms, or goiter [Grade D, Consensus].

31. Children with type 1 diabetes and symptoms of classic or atypical celiac disease (Table 3) should undergo celiac screening [Grade D, Consensus], and if confirmed, be treated with a gluten-free diet to improve symptoms [Grade D, Level 4 (76)] and prevent the long-term sequelae of untreated classic celiac disease [Grade D, Level 4 (77)]. Parents should be informed that the need for screening and treatment of asymptomatic (silent) celiac disease is controversial [Grade D, Consensus].

OTHER RELEVANT GUIDELINES

REFERENCES

1. Glasgow AM, Weissberg-Benchell J, Tynan WD, et al. Readmissions of children with diabetes mellitus to a children's hospital. Pediatrics. 1991;88:98-104.

2. Clar C, Waugh N, Thomas S. Routine hospital admission versus out-patient or home care in children at diagnosis of type 1 diabetes mellitus. Cochrane Database Syst Rev. 2006;(2):CD004099.

3. Diabetes Control and Complications Trial Research Group.

Effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med.* 1993;329:977-986.

4. Diabetes Control and Complications Trial Research Group. Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. *J Pediatr.* 1994;125:177-188.

5. Ryan C, Gurtunca N, Becker D. Hypoglycemia: a complication of diabetes therapy in children. *Pediatr Clin North Am.* 2005;52: 1705-1733.

6. Schoenle EJ, Schoenle D, Molinari L, et al. Impaired intellectual development in children with Type I diabetes: association with HbA(1c), age at diagnosis and sex. *Diabetologia.* 2002;45: 108-114.

7. Ferguson SC, Blane A, Wardlaw J, et al. Influence of an early-onset age of type 1 diabetes on cerebral structure and cognitive function. *Diabetes Care.* 2005;28:1431-1437.

8. Strudwick SK, Carne C, Gardiner J, et al. Cognitive functioning in children with early onset type 1 diabetes and severe hypoglycemia. *J Pediatr.* 2005;147:680-685.

9. Phillip M, Battelino T, Rodriguez H, et al. Use of insulin pump therapy in the pediatric age-group. Consensus statement from the European Society for Paediatric Endocrinology, the Lawson Wilkins Pediatric Endocrine Society, and the International Society for Pediatric and Adolescent Diabetes, endorsed by the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care.* 2007;30:1653-1662.

10. Fox LA, Buckloh LM, Smith SD, et al. A randomized controlled trial of insulin pump therapy in young children with type 1 diabetes. *Diabetes Care.* 2005;28:1277-1281.

11. DiMeglio LA, Pottorff TM, Boyd SR, et al. A randomized, controlled study of insulin pump therapy in diabetic preschoolers. *J Pediatr.* 2004;145:380-384.

12. Wilson DM, Buckingham BA, Kunselman EL, et al. A two-center randomized controlled feasibility trial of insulin pump therapy in young children with diabetes. *Diabetes Care.* 2005; 28:15-19.

13. Weintrob N, Benzaquen H, Galatzer A, et al. Comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens in children with type 1 diabetes: a randomized open crossover trial. *Pediatrics.* 2003;112:559-564.

14. Doyle EA, Weinzimer SA, Steffen AT, et al. A randomized, prospective trial comparing the efficacy of continuous subcutaneous insulin infusion with multiple daily injections using insulin glargine. *Diabetes Care.* 2004;27:1554-1558.

15. Weinzimer SA, Sikes KA, Steffen AT, et al. Insulin pump treatment of childhood type 1 diabetes. *Pediatr Clin North Am.* 2005; 52:1677-1688.

16. Alemzadeh R, Berhe T, Wyatt DT. Flexible insulin therapy with glargine insulin improved glycemic control and reduced severe hypoglycemia among preschool-aged children with type 1 diabetes mellitus. *Pediatrics.* 2005;115:1320-1324.

17. Murphy NP, Keane SM, Ong KK, et al. Randomized cross-over trial of insulin glargine plus lispro or NPH insulin plus regular human insulin in adolescents with type 1 diabetes on intensive insulin regimens. *Diabetes Care.* 2003;26:799-804.

18. Robertson KJ, Schoenle E, Gucev Z, et al. Insulin detemir compared with NPH insulin in children and adolescents with Type 1 diabetes. *Diabet Med.* 2007;24:27-34.

19. Nordly S, Mortensen HB, Andreasen AH, et al. Factors associated with glycaemic outcome of childhood diabetes care in Denmark. *Diabet Med.* 2005;22:1566-1573.

20. Diabetes Research in Children Network (DIRECNET) Study Group. The accuracy of the CGMS in children with type 1 diabetes: results of the diabetes research in children network (DirecNet) accuracy study. *Diabetes Technol Ther.* 2003;5:781-789.

21. Fiallo-Scharer R, Diabetes Research in Children Network Study Group. Eight-point glucose testing versus the continuous glucose monitoring system in evaluation of glycemic control in type 1 diabetes. *J Clin Endocrinol Metab.* 2005;90: 3387-3391.

22. Tansey MJ, Beck RW, Buckingham BA, et al. Accuracy of the modified Continuous Glucose Monitoring System (CGMS) sensor in an outpatient setting: results from a Diabetes Research in Children Network (DirecNet) Study. *Diabetes Technol Ther.* 2005;7:109-114.

23. Deiss D, Bolinder J, Riveline JP, et al. Improved glycemic control in poorly controlled patients with type 1 diabetes using real-time continuous glucose monitoring. *Diabetes Care.* 2006; 29:2730-2732.

24. Health Canada. *Eating Well with Canada's Food Guide.* Ottawa, ON: Health Canada, Health Products and Food Branch, Office of Nutrition Policy and Promotion; 2007. Publication H39-166/1990E.

25. Kaufman FR, Halvorson M, Carpenter S. Use of a plastic insulin dosage guide to correct blood glucose levels out of the target range and for carbohydrate counting in subjects with type 1 diabetes. *Diabetes Care.* 1999;22:1252-1257.

26. Patton SR, Dolan LM, Powers SW. Dietary adherence and associated glycemic control in families of young children with type 1 diabetes. *J Am Diet Assoc.* 2007;107:46-52.

27. Hartley M, Thomsett MJ, Cotterill AM. Mini-dose glucagon rescue for mild hypoglycaemia in children with type 1 diabetes: the Brisbane experience. *J Paediatr Child Health.* 2006; 42:108-111.

28. Haymond MW, Schreiner B. Mini-dose glucagon rescue for hypoglycemia in children with type 1 diabetes. *Diabetes Care.* 2001;24:643-645.

29. Northam EA, Todd S, Cameron FJ. Interventions to promote optimal health outcomes in children with Type 1 diabetes—are they effective? *Diabet Med.* 2006;23:113-121.

30. Wysocki T, Buckloh LM, Lochrie AS, et al. The psychologic context of pediatric diabetes. *Pediatr Clin North Am.* 2005; 52:1755-1778.

31. Levy-Marchal C, Patterson CC, Green A. Geographic variation

of presentation at diagnosis of type 1 diabetes in children: the EURODIAB study. *Diabetologia*. 2001;44(suppl 3):B75-80.

32. Dahlquist G, Kallen B. Mortality in childhood-onset type 1 diabetes: a population-based study. *Diabetes Care*. 2005;28: 2384-2387.

33. Vanelli M, Chiari G, Ghizzoni L, et al. Effectiveness of a prevention program for diabetic ketoacidosis in children: an 8-year study in schools and private practices. *Diabetes Care*. 1999; 22:7-9.

34. Keenan HT, Foster CM, Bratton SL. Social factors associated with prolonged hospitalization among diabetic children. *Pediatrics*. 2002;109:40-44.

35. Drozda DJ, Dawson VA, Long DJ, et al. Assessment of the effect of a comprehensive diabetes management program on hospital admission rates of children with diabetes mellitus. *Diabetes Educ*. 1990;16:389-393.

36. Hoffman WH, O'Neill P, Khoury C, et al. Service and education for the insulin-dependent child. *Diabetes Care*. 1978;1: 285-288.

37. Chiari G, Ghidini B, Vanelli M. Effectiveness of a toll-free telephone hotline for children and adolescents with type 1 diabetes. A 5-year study. *Acta Biomed*. 2003;74(suppl 1):45-48.

38. Edge JA, Hawkins MM, Winter DL, et al. The risk and outcome of cerebral oedema developing during diabetic ketoacidosis. *Arch Dis Child*. 2001;85:16-22.

39. Rosenbloom AL. Intracerebral crises during treatment of diabetic ketoacidosis. *Diabetes Care*. 1990;13:22-33.

40. Glaser N, Barnett P, McCaslin I, et al. Risk factors for cerebral edema in children with diabetic ketoacidosis. *N Engl J Med*. 2001;344:264-269.

41. Harris GD, Fiordalisi I, Harris WL, et al. Minimizing the risk of brain herniation during treatment of diabetic ketoacidemia: a retrospective and prospective study. *J Pediatr*. 1990;117:22-31.

42. Harris GD, Fiordalisi I. Physiologic management of diabetic ketoacidemia. A 5-year prospective pediatric experience in 231 episodes. *Arch Pediatr Adolesc Med*. 1994;148:1046-1052.

43. Hale PM, Rezvani I, Braunstein AW, et al. Factors predicting cerebral edema in young children with diabetic ketoacidosis and new onset type I diabetes. *Acta Paediatr*. 1997;86:626-631.

44. Carlotti AP, Bohn D, Mallie JP, et al. Tonicity balance, and not electrolyte-free water calculations, more accurately guides therapy for acute changes in natremia. *Intensive Care Med*. 2001;27:921-924.

45. Fort P, Waters SM, Lifshitz F. Low-dose insulin infusion in the treatment of diabetic ketoacidosis: bolus versus no bolus. *J Pediatr*. 1980;96:36-40.

46. Lindsay R, Bolte RG. The use of an insulin bolus in low-dose insulin infusion for pediatric diabetic ketoacidosis. *Pediatr Emerg Care*. 1989;5:77-79.

47. Hoorn EJ, Carlotti AP, Costa LA, et al. Preventing a drop in effective plasma osmolality to minimize the likelihood of cerebral edema during treatment of children with diabetic ketoacidosis. *J Pediatr*. 2007;150:467-473.

48. Edge JA, Jakes RW, Roy Y, et al. The UK case-control study of

cerebral oedema complicating diabetic ketoacidosis in children. *Diabetologia*. 2006;49:2002-2009.

49. Muir AB, Quisling RG, Yang MC, et al. Cerebral edema in childhood diabetic ketoacidosis: natural history, radiographic findings, and early identification. *Diabetes Care*. 2004;27:1541-1546.

50. Wolfsdorf J, Craig ME, Daneman D, et al; for the International Society for Pediatric and Adolescent Diabetes. Diabetic ketoacidosis. *Pediatr Diabetes*. 2007;8:28-43.

51. National Advisory Committee on Immunization. *Canadian Immunization Guide*. 7th ed. Ottawa, ON: Public Health Agency of Canada; 2006.

52. Infectious Diseases and Immunization Committee, Canadian Paediatric Society. Pneumococcal vaccine for children. *Paediatr Child Health*. 2002;6:214-217.

53. Infectious Diseases and Immunization Committee, Canadian Paediatric Society. Recommendations for the use of influenza vaccine for children. *Paediatr Child Health*. 2004;9:283-284.

54. Davies P, Nwokoro C, Leigh M. Vaccinations against influenza and pneumococcus in children with diabetes: telephone questionnaire survey. *BMJ*. 2004;328:203.

55. Irwin DE, Weatherby LB, Huang WY, et al. Impact of patient characteristics on the risk of influenza/ILI-related complications. *BMC Health Serv Res*. 2001;I:8.

56. Scott LJ, Warram JH, Hanna LS, et al. A nonlinear effect of hyperglycemia and current cigarette smoking are major determinants of the onset of microalbuminuria in type 1 diabetes. *Diabetes*. 2001;50:2842-2849.

57. Ray JG, O'Brien TE, Chan WS. Preconception care and the risk of congenital anomalies in the offspring of women with diabetes mellitus: a meta-analysis. *QJM*. 2001;94:435-444.

58. Kovacs M, Goldston D, Obrosky DS, et al. Psychiatric disorders in youths with IDDM: rates and risk factors. *Diabetes Care*. 1997;20:36-44.

59. Landolt MA, Vollrath M, Laimbacher J, et al. Prospective study of posttraumatic stress disorder in parents of children with newly diagnosed type 1 diabetes. *J Am Acad Child Adolesc Psychiatry*. 2005;44:682-689.

60. Grey M, Cameron ME, Lipman TH, et al. Psychosocial status of children with diabetes in the first 2 years after diagnosis. *Diabetes Care*. 1995;18:1330-1336.

61. Jacobson AM, Hauser ST, Lavori P, et al. Family environment and glycemic control: a four-year prospective study of children and adolescents with insulin-dependent diabetes mellitus. *Psychosom Med*. 1994;56:401-409.

62. Seiffge-Krenke I, Stemmler M. Coping with everyday stress and links to medical and psychosocial adaptation in diabetic adolescents. *J Adolesc Health*. 2003;33:180-188.

63. Skinner TC, Hampson SE. Social support and personal models of diabetes in relation to self-care and well-being in adolescents with type I diabetes mellitus. *J Adolesc*. 1998;21:703-715.

64. Anderson BJ, Vangsness L, Connell A, et al. Family conflict, adherence, and glycaemic control in youth with short duration type 1 diabetes. *Diabet Med*. 2002;19:635-642.

65. Graue M, Wentzel-Larsen T, Bru E, et al. The coping styles of adolescents with type 1 diabetes are associated with degree of metabolic control. *Diabetes Care.* 2004;27:1313-1317.

66. Northam EA, Matthews LK, Anderson PJ, et al. Psychiatric morbidity and health outcome in type 1 diabetes—perspectives from a prospective longitudinal study. *Diabet Med.* 2005; 22:152-157.

67. Wysocki T, Buckloh LM, Lochrie AS, et al. The psychologic context of pediatric diabetes. *Pediatr Clin North Am.* 2005;52: 1755-1778.

68. Wysocki T. Behavioural assessment and intervention in pediatric diabetes. *Behav Modif.* 2006;30:72-92.

69. Jones JM, Lawson ML, Daneman D, et al. Eating disorders in adolescent females with and without type 1 diabetes: cross sectional study. *BMJ.* 2000;320:1563-1566.

70. Rydall AC, Rodin GM, Olmsted MP, et al. Disordered eating behavior and microvascular complications in young women with insulin-dependent diabetes mellitus. *N Engl J Med.* 1997; 336:1849-1854.

71. Crow SJ, Keel PK, Kendall D. Eating disorders and insulin-dependent diabetes mellitus. *Psychosomatics.* 1998;39:233-243.

72. Barker JM. Clinical review: Type 1 diabetes-associated autoimmunity: natural history, genetic associations, and screening. *J Clin Endocrinol Metab.* 2006;91:1210-1217.

73. Glastras SJ, Craig ME, Verge CF, et al. The role of autoimmunity at diagnosis of type 1 diabetes in the development of thyroid and celiac disease and microvascular complications. *Diabetes Care.* 2005;28:2170-2175.

74. Marks SD, Girgis R, Couch RM. Screening for adrenal antibodies in children with type 1 diabetes and autoimmune thyroid disease. *Diabetes Care.* 2003;26:3187-3188.

75. Cerutti F, Bruno G, Chiarelli F, et al. Younger age at onset and sex predict celiac disease in children and adolescents with type 1 diabetes: an Italian multicenter study. *Diabetes Care.* 2004; 27:1294-1298.

76. Mayer M, Greco L, Troncone R, et al. Compliance of adolescents with celiac disease with a gluten-free diet. *Gut.* 1991; 32:881-885.

77. Holmes GK, Prior P, Lane MR, et al. Malignancy in coeliac disease—effect of a gluten free diet. *Gut.* 1989;30:333-338.

78. Lang-Muritano M, Molinari L, Dommann-Scherrer C, et al. Incidence of enteropathy-associated T-cell lymphoma in celiac disease: implications for children and adolescents with type 1 diabetes. *Pediatr Diabetes.* 2002;3:42-45.

79. Rami B, Sumnik Z, Schober E, et al. Screening detected celiac disease in children with type 1 diabetes mellitus: effect on the clinical course (a case control study). *J Pediatr Gastroenterol Nutr.* 2005;41:317-321.

80. Gatling W, Knight C, Hill RD. Screening for early diabetic nephropathy: which sample to detect microalbuminuria? *Diabet Med.* 1985;2:451-455.

81. Shield JP, Hunt LP, Baum JD, et al. Screening for diabetic microalbuminuria in routine clinical care: which method? *Arch Dis Child.* 1995;72:524-525.

82. Donaghue KC, Craig ME, Chan AK. Prevalence of diabetes complications 6 years after diagnosis in an incident cohort of childhood diabetes. *Diabet Med.* 2005;22:711-718.

83. Schultz CJ, Konopelska-Bahu T, Dalton RN, et al. Microalbuminuria prevalence varies with age, sex, and puberty in children with type 1 diabetes followed from diagnosis in a longitudinal study. Oxford Regional Prospective Study Group. *Diabetes Care.* 1999;22:495-502.

84. Stone ML, Craig ME, Chan AK, et al. Natural history and risk factors for microalbuminuria in adolescents with type 1 diabetes: a longitudinal study. *Diabetes Care.* 2006;29:2072-2077.

85. Cook J, Daneman D, Spino M, et al. Angiotensin converting enzyme inhibitor therapy to decrease microalbuminuria in normotensive children with insulin-dependent diabetes mellitus. *J Pediatr.* 1990;117:39-45.

86. ACE Inhibitors in Diabetic Nephropathy Trialist Group. Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta-analysis of individual patient data. *Ann Intern Med.* 2001; 134:370-379.

87. Maguire A, Chan A, Cusumano J, et al. The case for biennial retinopathy screening in children and adolescents. *Diabetes Care.* 2005;28:509-513.

88. Huo B, Steffen AT, Swan K, et al. Clinical outcomes and cost-effectiveness of retinopathy screening in youth with type 1 diabetes. *Diabetes Care.* 2007;30:362-363.

89. Karavanaki K, Baum JD. Coexistence of impaired indices of autonomic neuropathy and diabetic nephropathy in a cohort of children with type 1 diabetes mellitus. *J Pediatr Endocrinol Metab.* 2003;16:79-90.

90. Olsen BS, Sjølie A-K, Hougaard P, et al. A 6-year nationwide cohort study of glycaemic control in young people with type 1 diabetes. Risk markers for the development of retinopathy, nephropathy, and neuropathy. *J Diabetes Complications.* 2000; 14:295-300.

91. Donaghue KC, Fung ATW, Fairchild JM, et al. Prospective assessment of autonomic and peripheral nerve function in adolescents with diabetes. *Diabet Med.* 1996;13:65-71.

92. Nelson D, Mah JK, Adams C, et al. Comparison of conventional and non-invasive techniques for the early identification of diabetic neuropathy in children and adolescents with type 1 diabetes. *Pediatr Diabetes.* 2006;7:305-310.

93. Celermajer DS, Ayer JGJ. Childhood risk factors for adult cardiovascular disease and primary prevention in childhood. *Heart.* 2006;92:1701-1706.

94. Arambepola C, Farmer AJ, Perera R, et al. Statin treatment for children and adolescents with heterozygous familial hypercholesterolaemia: a systematic review and meta-analysis. *Atherosclerosis.* 2007;195:339-347.

95. Eppens MC, Craig ME, Cusumano J, et al. Prevalence of diabetes complications in adolescents with type 2 compared with type 1 diabetes. *Diabetes Care.* 2006;29:1300-1306.

96. Lurbe E, Redon J, Kesani A, et al. Increase in nocturnal blood pressure and progression to microalbuminuria in type 1 dia-

betes. *N Engl J Med*. 2002;347:797-805.

97. National Heart, Lung and Blood Institute. *Blood Pressure Tables for Children and Adolescents from the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents.* 2004. Available at: http://www.nhlbi.nih.gov/guidelines/hypertension/child_tbl.htm. Accessed September 1, 2008.

98. Frank M. Factors associated with non-compliance with a medical follow-up regimen after discharge from a pediatric diabetes clinic. *Can J Diabetes.* 1996;20:13-20.

99. Pacaud D, Yale JF, Stephure D, et al. Problems in transition from pediatric care to adult care for individuals with diabetes. *Can J Diabetes.* 2005;29:13-18.

100. Kipps S, Bahu T, Ong K, et al. Current methods of transfer of young people with type 1 diabetes to adult services. *Diabet Med.* 2002;19:649-654.

101. Hershey T, Perantie DC, Warren SL, et al. Frequency and timing of severe hypoglycemia affects spatial memory in children with type 1 diabetes. *Diabetes Care.* 2005;28:2372-2377.

102. Winkley K, Ismail K, Landau S, et al. Psychological interventions to improve glycaemic control in patients with type 1 diabetes: systematic review and meta-analysis of randomised controlled trials. *BMJ*. 2006;333:65.

103. Armour TA, Norris SL, Jack L Jr, et al. The effectiveness of family interventions in people with diabetes mellitus: a systematic review. *Diabet Med.* 2005;22:1295-1305.

104. McMahon SK, Airey FL, Marangou DA, et al. Insulin pump therapy in children and adolescents: improvements in key parameters of diabetes management including quality of life. *Diabet Med.* 2005;22:92-96.

105. Houlihan CA, Tsalamandris C, Akdeniz A, et al. Albumin to creatinine ratio: a screening test with limitations. *Am J Kidney Dis.* 2002;39:1183-1189.

106. Klein R, Klein BEK, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. IX. Four-year incidence and progression of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch Ophthalmol.* 1989;107:237-243.

107. Rocchini AP, Katch V, Anderson J, et al. Blood pressure in obese adolescents: effect of weight loss. *Pediatrics*. 1988;82:16-23.

Type 2 Diabetes in Children and Adolescents

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee
The initial draft of this chapter was prepared by Elizabeth A.C. Sellers MD MSc FRCPC, Constadina Panagiotopoulos MD FRCPC and Margaret L. Lawson MD MSc FRCPC

KEY MESSAGES

- Anticipatory guidance regarding healthy eating and active lifestyle is recommended to prevent obesity.

- Regular targeted screening for type 2 diabetes is recommended in children at risk.

- Children with type 2 diabetes should receive care in consultation with an interdisciplinary pediatric diabetes healthcare team.

- Early screening, intervention and optimization of glycemic control are essential, as onset of type 2 diabetes during childhood is associated with severe and early onset of microvascular complications.

Unless otherwise specified, the term "child" is used for individuals 0 to 18 years of age, and the term "adolescent" for those 13 to 18 years of age.

INTRODUCTION

Type 2 diabetes in children has increased in frequency in North America over the past 2 decades (1). Most of these children are from ethnic groups at high risk for type 2 diabetes, namely of Aboriginal, African, Hispanic or Asian descent. Limited Canadian prevalence data are available. The prevalence of type 2 diabetes in Canadian Aboriginal children 5 to 18 years of age is as high as 1%, with the highest prevalence in the Plains Cree of Central Canada (2,3). Data from the United States suggest a 10- to 30-fold increase in the number of children with type 2 diabetes over the past 10 to 15 years (4).

PREVENTION

Breastfeeding has been shown to reduce the risk of youth-onset type 2 diabetes in some populations (5).

Obesity is a major modifiable risk factor for the development of type 2 diabetes. In 2004, 18% of Canadian children and adolescents were overweight and 8% were obese (6). Studies on prevention of obesity in children are limited and have generally not been demonstrated to be successful (7). In obese children, standard lifestyle interventions in the form of dietary recommendations and regular clinic visits have been shown to have little benefit (7). However, lifestyle intervention trials that included dietary and exercise interventions, intensive counselling and family involvement have demonstrated long-term (5 to 10 years) weight maintenance (7).

The role of pharmacotherapy in the treatment of childhood obesity is controversial, as there are few controlled trials and no long-term safety or efficacy data (8). Several studies suggest that lifestyle changes plus pharmacotherapy may act synergistically when lifestyle intervention is aggressively pursued (8). Orlistat may be considered to aid in weight reduction and weight maintenance when added to a regimen of lifestyle intervention in adolescents (9-11). Metformin, orlistat and sibutramine each have potential for short-term positive effects on weight, glycemia, insulin sensitivity and/or lipids, but no pediatric studies have been performed to assess prevention of diabetes or long-term complications. In addition, safety concerns exist for sibutramine and possibly orlistat. In obese adolescents with evidence of severe insulin resistance, pharmacologic therapy with metformin or orlistat should only be considered after a comprehensive evaluation of the child's metabolic status, family history, and review of lifestyle intervention. Due to a lack of data in prepubertal children, the use of antiobesity drugs should only be considered within the context of a supervised clinical trial. Bariatric surgery in adolescents should be limited to exceptional cases and be performed only by experienced teams.

SCREENING AND DIAGNOSIS

Although not proven in children, it is generally assumed that earlier diagnosis of diabetes will lead to interventions that will improve glycemia and reduce the related short- and long-term complications (12). Children with type 2 diabetes from high-risk ethnic groups (Hispanic, African and Asian) have been identified in school-based screening studies in the United States (1) and Japan (13), but most have been reported as part of case series (4).

Risk factors for the development of type 2 diabetes in children include history of type 2 diabetes in a first- or second-degree relative (14), being a member of a high-risk population (e.g. people of Aboriginal, Hispanic, South Asian, Asian or African descent) (1), overweight (14-17), impaired glucose tolerance (IGT) (18), polycystic ovary syndrome (PCOS) (19), exposure to diabetes in utero (20,21), acanthosis nigricans (1,22), hypertension and dyslipidemia (23), and nonalcoholic fatty liver disease (NAFLD) (24). Atypical antipsychotic medications may cause significant weight gain and insulin resistance in children (25). Neuropsychiatric disorders and use of neuropsychiatric medications are more common in obese children at diagnosis of type 2 diabetes

compared to the general pediatric population (26).

While a fasting plasma glucose (FPG) is the recommended routine screening test for children, the oral glucose tolerance test (OGTT) may have a higher detection rate (15,27) in children who are very obese (body mass index [BMI] ≥99th percentile for age and gender) and who have multiple risk factors for type 2 diabetes. An OGTT may also be more sensitive in less obese children who have multiple risk factors.

The diagnostic criteria for diabetes in children are the same as for adults.

CLASSIFICATION

In most children, the presence of clinical risk factors, mode of presentation and early course of the disease indicate whether the child has type 1 or type 2 diabetes. However, differentiation may be difficult in some. Children with type 2 diabetes can present with diabetic ketoacidosis (DKA) (28,29). Testing for the absence of islet autoantibodies may be useful (30-32). Fasting insulin levels are not helpful at diagnosis, as levels may be low due to glucose toxicity (33). DNA diagnostic testing for genetic defects in beta cell function should be considered in children who have a strong family history suggestive of autosomal-dominant inheritance and who are lacking features of insulin resistance. This may be helpful when diabetes classification is unclear, and may lead to more appropriate management (34,35).

MANAGEMENT

Children with type 2 diabetes should receive care in conjunction or consultation with an interdisciplinary pediatric diabetes healthcare team. To be effective, treatment programs for adolescents with type 2 diabetes need to address the lifestyle and health habits of the entire family, emphasizing healthy eating and physical activity (36). In addition, psychological issues, such as depression, self-destructive behaviour patterns and smoking cessation, need to be addressed and interventions offered as required. In Aboriginal children, lifestyle intervention has improved glycemic control to within the normal range in <2 weeks (37). Insulin is required in those with severe metabolic decompensation at diagnosis (e.g. DKA, glycated hemoglobin [A1C] ≥9.0%, symptoms of severe hyperglycemia), but may be successfully weaned once glycemic targets are achieved, particularly if lifestyle changes are effectively adopted (38). There are limited data about the safety or efficacy of oral antihyperglycemic agents in the pediatric population. Metformin has been shown to be safe in adolescents for up to 16 weeks, reducing A1C by 1.0 to 2.0% and lowering FPG with similar side effects as seen in adults (39).

IMMUNIZATION

The recommendations for influenza and pneumococcal immunization in Canada do not address the issue of type 2 diabetes in children, and there are no studies evaluating the usefulness of the influenza or pneumococcal vaccine in this population.

There is no reason not to manage these children in a similar fashion to those with type 1 diabetes. Some children with type 2 diabetes may, however, have other factors (e.g. Aboriginal heritage) that may place them at higher risk of increased influenza- and pneumococcal-related morbidity (40,41).

COMPLICATIONS

Short-term complications of type 2 diabetes in children include DKA and hyperglycemic hyperosmolar state (HHS). High morbidity and mortality rates have been reported in youth presenting with combined DKA and HHS at onset of type 2 diabetes (42-44).

Evidence suggests that early-onset type 2 diabetes in adolescence is associated with severe and early-onset microvascular complications (including retinopathy, neuropathy, nephropathy) (12,45,46). Although neither retinopathy nor neuropathy has been described in adolescents with type 2 diabetes at diagnosis, 1 study found that 1 in 5 youth with type 2 diabetes had peripheral nerve abnormalities and more than half had autonomic neuropathy after a median duration of diabetes of 1.3 years (46). Therefore, it is prudent to consider screening for these complications at diagnosis and yearly thereafter until the natural history is better understood (Table 1). As well, Aboriginal youth in Canada are at increased risk of renal diseases not associated with diabetes (47). Given that the documentation of persistent albuminuria may indicate 1 of several possible diagnoses, including underlying primary renal disease, diabetic nephropathy or focal sclerosing glomerulosclerosis (a comorbid condition associated with obesity), referral to a pediatric nephrologist for assessment of etiology and treatment is recommended.

COMORBID CONDITIONS

Children with type 2 diabetes have an increased prevalence of dyslipidemia (46,48). Screening for dyslipidemia at diagnosis and every 1 to 3 years as clinically indicated thereafter is recommended. In children with familial dyslipidemia and a positive family history of early cardiovascular events, a statin should be started if the low-density lipoprotein cholesterol level remains >4.2 mmol/L after a 3- to 6-month trial of dietary intervention (49). A similar approach seems reasonable in the absence of evidence to recommend a specific intervention in children with type 2 diabetes.

Similarly, as up to 36% of adolescents with type 2 diabetes have hypertension (46), screening should begin at diagnosis of diabetes and continue at every diabetes-related clinical encounter thereafter (50). (See "Type 1 Diabetes in Children and Adolescents," p. S150, for additional discussion on treatment of dyslipidemia and hypertension.)

Since most adolescents with type 2 diabetes show clinical evidence of obesity and insulin resistance, surveillance should occur for comorbid complications associated with insulin resistance, including PCOS (51) and NAFLD (52) (Table 1).

Table 1. Screening for diabetes complications and comorbidities in children with type 2 diabetes		
Complication/ Comorbid condition	*Indications and intervals for screening*	*Screening test*
Dyslipidemia	Screening should commence at diagnosis of diabetes and every 1–3 years thereafter as clinically indicated	Fasting TC, HDL-C, TG, calculated LDL-C
Hypertension	At diagnosis of diabetes and at every diabetes-related clinical encounter thereafter (at least twice annually)	BP measurement using appropriate size cuff
NAFLD	Yearly screening commencing at diagnosis of diabetes	ALT
Nephropathy	Yearly screening commencing at diagnosis of diabetes	• First morning (preferred) or random ACR • Abnormal ACR requires confirmation at least 1 month later with a first morning ACR and if abnormal, follow-up with timed, overnight or 24-hour split urine collections for albumin excretion rate • Repeated sampling should be done every 3–4 months over a 6- to 12-month period to demonstrate persistence
Neuropathy	Yearly screening commencing at diagnosis of diabetes	Questioned and examined for: • symptoms of numbness, pain, cramps, and paresthesia • skin sensation • vibration sense • light touch, and • ankle reflexes
PCOS	Yearly screening commencing at puberty in females with oligo/ amenorrhea, acne and/or hirsutism	Androgen levels, including DHEAS and free testosterone
Retinopathy	Yearly screening commencing at diagnosis of diabetes	• 7-standard field, stereoscopic-colour fundus photography with interpretation by a trained reader (gold standard); or • Direct ophthalmoscopy or indirect slit-lamp fundoscopy through dilated pupil; or • Digital fundus photography

ACR = albumin to creatinine ratio
ALT = alanine aminotransferase
BP = blood pressure
DHEAS = dehydroepiandrosterone sulfate
HDL-C = high-density lipoprotein cholesterol
LDL-C = low-density lipoprotein cholesterol
NAFLD = nonalcoholic fatty liver disease
PCOS = polycystic ovary syndrome
TC = total cholesterol
TG = triglycerides

RECOMMENDATIONS

1. Anticipatory guidance promoting healthy eating, the maintenance of a healthy weight and regular physical activity is recommended as part of routine pediatric care [Grade D, Consensus].

2. Intensive lifestyle intervention, including dietary and exercise interventions, family counselling and family-oriented behaviour therapy, should be undertaken for obese children in order to achieve and maintain a healthy body weight [Grade D, Consensus].

3. Children 10 years of age, or younger if puberty is established, should be screened for type 2 diabetes every 2 years using an FPG test if they have ≥2 of the following risk factors [Grade D, Consensus]:
   • Obesity (BMI ≥95th percentile for age and gender)
   • Member of high-risk ethnic group and/or family history of type 2 diabetes and/or exposure to diabetes in utero
   • Signs or symptoms of insulin resistance (including acanthosis nigricans, hypertension, dyslipidemia, NAFLD)
   • IGT
   • Use of antipsychotic medications/atypical neuroleptics

4. Very obese children (BMI ≥99th percentile for age and gender) who meet the criteria in recommendation 3 should have an OGTT performed annually [Grade D, Consensus].

5. Commencing at the time of diagnosis of type 2 diabetes, all children should receive intensive counselling, including lifestyle modification, from an interdisciplinary pediatric healthcare team [Grade D, Consensus].

6. The target A1C for most children with type 2 diabetes should be ≤7.0% [Grade D, Consensus].

7. In children with type 2 diabetes and an AIC ≥9.0%, and in those with severe metabolic decompensation (e.g. DKA), insulin therapy should be initiated, but may be successfully weaned once glycemic targets are achieved, particularly if lifestyle changes are effectively adopted [Grade D, Level 4 (38)].

8. In children with type 2 diabetes, if glycemic targets are not achieved within 3 to 6 months using lifestyle modifications alone, 1 of the following should be initiated: metformin [Grade B, Level 2 (39)] or insulin [Grade D, Consensus]. Metformin may be used at diagnosis in those children presenting with an A1C >7.0% [Grade B, Level 2 (39)].

9. Children with type 2 diabetes should be screened annually for microvascular complications (nephropathy, neuropathy, retinopathy) beginning at diagnosis of diabetes [Grade D, Level 4 (46)].

10. All children with type 2 diabetes and persistent albuminuria (2 abnormal of 3 samples over a 6- to 12-month period) should be referred to a pediatric nephrologist for assessment of etiology and treatment [Grade D, Consensus].

11. Children with type 2 diabetes should have a fasting lipid profile measured at diagnosis of diabetes and every 1 to 3 years thereafter as clinically indicated [Grade D, Consensus].

12. Children with type 2 diabetes should be screened for hypertension beginning at diagnosis of diabetes and at every diabetes-related clinical encounter thereafter (at least biannually) [Grade D, Consensus].

DIABETES IN CHILDREN AND ADOLESCENTS

OTHER RELEVANT GUIDELINES

REFERENCES

1. Fagot-Campagna A, Pettitt DJ, Engelgau MM, et al. Type 2 diabetes among North American children and adolescents: an epidemiologic review and a public health perspective. J Pediatr. 2000;136:664-672.

2. Dean HJ, Young TK, Flett B, et al. Screening for type-2 diabetes in aboriginal children in northern Canada [letter]. Lancet. 1998;352:1523-1524.

3. Harris SB, Perkins BA, Whalen-Brough E. Non-insulin dependent diabetes mellitus among First Nations children. New entity among First Nations people of north western Ontario. Can Fam Physician. 1996;42:869-876.

4. Fagot-Campagna A. Emergence of type 2 diabetes mellitus in children: epidemiological evidence. J Pediatr Endocrinol Metab. 2000;13(suppl 6):1395-1402.

5. Taylor JS, Kacmar JE, Nothnagle M, et al. A systematic review of the literature associating breastfeeding with type 2 diabetes and gestational diabetes. J Am Coll Nutr. 2005;24:320-326.

6. Shields M. Measured Obesity: Overweight Canadian Children and Adolescents. Nutrition: Findings from the Canadian Community Health Survey. Ottawa, ON: Statistics Canada; 2005(1). Catalogue no. 82-620-MWE2005001.

7. Summerbell CD, Waters E, Edmunds LD, et al. Interventions for preventing obesity in children. Cochrane Database Syst Rev. 2005;(3):CD001871.

8. Freemark M. Pharmacotherapy of childhood obesity: an evidence-based conceptual approach. Diabetes Care. 2007;30:395-402.

9. McDuffie JR, Calis KA, Uwaifo GI, et al. Efficacy of orlistat as an adjunct to behavioral treatment in overweight African American and Caucasian adolescents with obesity-related co-morbid conditions. J Pediatr Endocrinol Metab. 2004;17:307-319.

10. Ozkan B, Bereket A, Turan S, et al. Addition of orlistat to conventional treatment in adolescents with severe obesity. Eur J

Pediatr. 2004;163:738-741.

11. Chanoine JP, Hampl S, Jensen C, et al. Effect of orlistat on weight and body composition in obese adolescents: a randomized controlled trial. *JAMA.* 2005;293:2873-2883.

12. Krakoff J, Lindsay RS, Looker HC, et al. Incidence of retinopathy and nephropathy in youth-onset compared with adult-onset type 2 diabetes. *Diabetes Care.* 2003;26:76-81.

13. Owada M, Hanaoka Y, Tanimoto Y, et al. Descriptive epidemiology of non-insulin dependent diabetes mellitus detected by urine glucose screening in school children in Japan. *Acta Paediatr Jpn.* 1990;32:716-724.

14. Pinhas-Hamiel O, Dolan LM, Daniels SR, et al. Increased incidence of non-insulin-dependent diabetes mellitus among adolescents. *J Pediatr.* 1996;128:608-615.

15. Sinha R, Fisch G, Teague B, et al. Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. *N Engl J Med.* 2002;346:802-810.

16. McCance DR, Pettitt DJ, Hanson RL, et al. Glucose, insulin concentrations and obesity in childhood and adolescence as predictors of NIDDM. *Diabetologia.* 1994;37:617-623.

17. Hanley AJ, Harris SB, Gittelsohn J, et al. Overweight among children and adolescents in a Native Canadian community: prevalence and associated factors. *Am J Clin Nutr.* 2000;71: 693-700.

18. Weiss R, Taksali SE, Tamborlane WV, et al. Predictors of changes in glucose tolerance status in obese youth. *Diabetes Care.* 2005;28:902-909.

19. Palmert MR, Gordon CM, Kartashov AI, et al. Screening for abnormal glucose tolerance in adolescents with polycystic ovary syndrome. *J Clin Endocrinol Metab.* 2002;87:1017-1023.

20. Dabelea D, Hanson RL, Lindsay RS, et al. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. *Diabetes.* 2000;49:2208-2211.

21. Young TK, Martens PJ, Taback SP, et al. Type 2 diabetes mellitus in children: prenatal and early infancy risk factors among Native Canadians. *Arch Pediatr Adolesc Med.* 2002;156:651-655.

22. Stoddart ML, Blevins KS, Lee ET, et al. Association of acanthosis nigricans with hyperinsulinemia compared with other selected risk factors for type 2 diabetes in Cherokee Indians: the Cherokee Diabetes Study. *Diabetes Care.* 2002;25:1009-1014.

23. Weiss R, Dziura J, Burgert TS, et al. Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med.* 2004; 350:2362-2374.

24. Perseghin G, Bonfanti R, Magni S, et al. Insulin resistance and whole body energy homeostasis in obese adolescents with fatty liver disease. *Am J Physiol Endocrinol Metab.* 2006;291:E697-703.

25. Stigler KA, Potenza MN, Posey DJ, et al. Weight gain associated with atypical antipsychotic use in children and adolescents: prevalence, clinical relevance, and management. *Pediatr Drugs.* 2004;6:33-44.

26. Levitt Katz LE, Swami S, Abraham M, et al. Neuropsychiatric disorders at the presentation of type 2 diabetes mellitus in chil-

dren. *Pediatr Diabetes.* 2005;6:84-89.

27. Reinehr T, Andler W, Kapellen T, et al. Clinical characteristics of type 2 diabetes mellitus in overweight European Caucasian adolescents. *Exp Clin Endocrinol Diabetes.* 2005;113:167-170.

28. Pinhas-Hamiel O, Dolan LM, Zeitler PS. Diabetic ketoacidosis among obese African-American adolescents with NIDDM. *Diabetes Care.* 1997;20:484-486.

29. Sellers EA, Dean HJ. Diabetic ketoacidosis: a complication of type 2 diabetes in Canadian aboriginal youth [letter]. *Diabetes Care.* 2000;23:1202-1204.

30. Dabelea D, Palmer JP, Bennett PH, et al. Absence of glutamic acid decarboxylase antibodies in Pima Indian children with diabetes mellitus [letter]. *Diabetologia.* 1999;42:1265-1266.

31. Sellers E, Eisenbarth G, Young TK, et al. Diabetes-associated autoantibodies in aboriginal children [letter]. *Lancet.* 2000; 355:1156.

32. Hathout EH, Thomas W, El-Shahawy M, et al. Diabetic autoimmune markers in children and adolescents with type 2 diabetes. *Pediatrics.* 2001;107:E102. Available at: http://www.pediatrics.org/cgi/content/full/107/6/e102. Accessed September 1, 2008.

33. Ferrannini E. Insulin resistance versus insulin deficiency in non-insulin dependent diabetes mellitus: problems and prospects. *Endocr Rev.* 1998;19:477-490.

34. Sellers EA, Triggs-Raine B, Rockman-Greenberg C, et al. The prevalence of the HNF-1alpha G319S mutation in Canadian aboriginal youth with type 2 diabetes. *Diabetes Care.* 2002;25: 2202-2206.

35. Hattersley AT. Molecular genetics goes to the diabetes clinic. *Clin Med.* 2005;5:476-481.

36. Pinhas-Hamiel O, Standiford D, Hamiel D, et al. The type 2 family: a setting for development and treatment of adolescent type 2 diabetes mellitus. *Arch Pediatr Adolesc Med.* 1999;153: 1063-1067.

37. Anderson KA, Dean HJ. The effect of diet and exercise on a native youth with poorly controlled non-insulin dependent diabetes mellitus. *Beta Release.* 1990;14:105-106.

38. Sellers EA, Dean HJ. Short-term insulin therapy in adolescents with type 2 diabetes mellitus. *J Pediatr Endocrinol Metab.* 2004; 17:1561-1564.

39. Jones KL, Arslanian S, Peterokova VA, et al. Effect of metformin in pediatric patients with type 2 diabetes: a randomized controlled trial. *Diabetes Care.* 2002;25:89-94.

40. Advisory Committee on Immunization Practices. Preventing pneumococcal disease among infants and children. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2000; 49:1-35.

41. Crighton EJ, Elliott SJ, Moineddin R, et al. A spatial analysis of the determinants of pneumonia and influenza hospitalizations in Ontario (1992-2001). *Soc Sci Med.* 2007;64:1636-1650.

42. Morales AE, Rosenbloom AL. Death caused by hyperglycemic hyperosmolar state at the onset of type 2 diabetes. *J Pediatr.* 2004;144:270-273.

43. Bhowmick SK, Levens KL, Rettig KR. Hyperosmolar hyper-

glycemic crisis: an acute life-threatening event in children and adolescents with type 2 diabetes mellitus. *Endocr Pract*. 2005; 11:23-29.

44. Carchman RM, Dechert-Zeger M, Calikoglu AS, et al. A new challenge in pediatric obesity: pediatric hyperglycemic hyperosmolar syndrome. *Pediatr Crit Care Med*. 2005;6:20-24.

45. Yokoyama H, Okudaira M, Otani T, et al. Existence of early-onset NIDDM Japanese demonstrating severe diabetic complications. *Diabetes Care*. 1997;20:844-847.

46. Eppens MC, Craig ME, Cusumano J, et al. Prevalence of diabetes complications in adolescents with type 2 compared with type 1 diabetes. *Diabetes Care*. 2006;29:1300-1306.

47. Bulloch B, Postl BD, Ogborn MR. Excess prevalence of non diabetic renal disease in native American children in Manitoba. *Pediatr Nephrol*. 1996;10:702-704.

48. Kershnar AK, Daniels SR, Imperatore G, et al. Lipid abnormalities are prevalent in youth with type 1 and type 2 diabetes: the SEARCH for Diabetes in Youth Study. *J Pediatr*. 2006; 149:314-319.

49. National Cholesterol Education Program (NCEP): highlights of the report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatrics*. 1992;89:495-501.

50. Ettinger LM, Freeman K, DiMartino-Nardi JR, et al. Microalbuminuria and abnormal ambulatory blood pressure in adolescents with type 2 diabetes mellitus. *J Pediatr*. 2005; 147:67-73.

51. Norris AW, Svoren BM. Complications and comorbidities of type 2 diabetes. *Pediatr Ann*. 2005;34:710-718.

52. Nadeau KJ, Klingensmith G, Zeitler P. Type 2 diabetes in children is frequently associated with elevated alanine aminotransferase. *J Pediatr Gastroenterol Nutr*. 2005;41:94-98.

DIABETES IN CHILDREN AND ADOLESCENTS

Diabetes and Pregnancy

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by David Thompson MD FRCPC, Sarah Capes MD MSc FRCPC, Denice S. Feig MD MSc FRCPC, Tina Kader MD FRCPC CDE, Erin Keely MD FRCPC, Sharon Kozak BSN and Edmond A. Ryan MD FRCPC

KEY MESSAGES

Pregestational diabetes

- All women with pre-existing type 1 or type 2 diabetes should receive preconception care to optimize glycemic control, assess complications, review medications and begin folate supplementation.

- Care by an interdisciplinary diabetes healthcare team composed of diabetes nurse educators, dietitians, obstetricians and endocrinologists, both prior to conception and during pregnancy, has been shown to minimize maternal and fetal risks in women with pre-existing type 1 or type 2 diabetes.

Gestational diabetes mellitus (GDM)

- The suggested screening test for GDM is the Gestational Diabetes Screen – a 50-g glucose load followed by a plasma glucose test measured 1 h later.

- Untreated GDM leads to increased maternal and perinatal morbidity, while intensive treatment is associated with outcomes similar to control populations.

INTRODUCTION

This chapter covers both pregnancy in pre-existing diabetes (pregestational diabetes) and gestational diabetes; as outlined in the text that follows, some of the management principles are common to all types of diabetes in pregnancy, including monitoring and lifestyle factors.

Blood glucose targets during pregnancy

Normal maternal blood glucose (1) and glycated hemoglobin (A1C) (2) levels during pregnancy are considerably lower than in nonpregnant adults: fasting and preprandial (mean±SD) 4.3±0.7 mmol/L; 1h postprandial 6.1±0.9 mmol/L; 2h postprandial 5.4±0.6 mmol/L; and 24-h mean 5.3 mmol/L. Values are higher in obese women (1).

While there is uncertainty about the precise levels of maternal plasma glucose (PG) required to prevent complications, there appears to be a glycemic threshold that identifies the majority of fetuses at risk. A mean PG <6.0 mmol/L is associated with a lower incidence of macrosomia, while rates of other complications increase at higher PG levels (3). Even in women without diabetes, fetal abdominal circumference correlates with postprandial PG levels (4). Current treatment of diabetes in pregnancy often results in higher mean

blood glucose levels than those in nondiabetic pregnancy (5). Recommended glycemic targets for preconception and during pregnancy are shown in Table 1.

Table 1. Recommended glycemic targets for preconception and during pregnancy*	
Pre-pregnancy A1C	**≤7.0%***
During pregnancy	
Fasting and preprandial PG	3.8–5.2 mmol/L
1h postprandial PG	5.5–7.7 mmol/L
2h postprandial PG	5.0–6.6 mmol/L
A1C	≤6.0% (normal)

*A1C ≤6.0% if this can be safely achieved. In some women, particularly those with type 1 diabetes, higher targets may be necessary to avoid excessive hypoglycemia

A1C = glycated hemoglobin
PG = plasma glucose

PREGESTATIONAL DIABETES

Recent large studies of women with pregestational diabetes continue to show higher rates of complications compared to the general population, including perinatal mortality, congenital malformations, hypertension, preterm delivery, large-for-gestational-age infants, cesarean delivery and neonatal morbidities (6-20). Adverse outcomes in pregnancies in women with type 2 diabetes, including congenital anomalies (8) and perinatal mortality (6), may be worse than in those with type 1 diabetes and may have actually increased over the past decade (9,21).

Preconception care

Preconception care for women with pregestational diabetes is associated with better outcomes, but <50% of women receive such care, and it is less common in women with type 2 diabetes (8,14). Higher A1C levels are associated with poorer outcomes (14), but even women who achieve tight glycemic control (A1C <7.0%) have an increased rate of complications (16). By discussing pregnancy prior to conception, healthcare providers may be able to improve out-

comes by educating women about the importance of strict glycemic control and encouraging them to participate in pre-pregnancy care.

Assessment and management of complications
Retinopathy
Women with type 1 (22,23) and type 2 diabetes (24) should have ophthalmologic assessments before conception, during the first trimester, as needed during pregnancy and within the first year postpartum (25). The risk of progression of retinopathy is increased with poor glycemic control during pregnancy, and such progression may occur up to 1 year postpartum (24,25). Additional risk factors for retinopathy progression include chronic and pregnancy-induced hypertension, pre-eclampsia and more severe pre-existing retinopathy (22,26-28). Pregnancy does not affect the long-term outcome of mild to moderate retinopathy (25).

Hypertension
The incidence of hypertension complicating pregnancy is 40 to 45% in women with type 1 and type 2 diabetes (28). Type 1 diabetes is more often associated with pre-eclampsia; type 2 diabetes with chronic hypertension. Of the risk factors for hypertension, poor glycemic control in early pregnancy is potentially modifiable. Some (29,30) but not all (31) studies have found that increased urinary protein excretion in early pregnancy raises the risk of developing hypertension.

Any type of hypertension is strongly associated with adverse outcomes. A number of antihypertensive medications are known to be safe and effective in pregnancy, including calcium channel blockers, beta-blockers, labetalol, hydralazine and methyldopa (32).

Chronic kidney disease
Prior to conception, women should be screened for chronic kidney disease (CKD) according to the guidelines (see "Chronic Kidney Disease in Diabetes," p. S126). In the presence of early CKD, monitoring of renal function using a random albumin-to-creatinine ratio (ACR) and estimated glomerular filtration rate (eGFR) from serum creatinine should occur each trimester. Microalbuminuria and overt nephropathy are associated with increased risk of maternal and fetal complications (33-37). Proteinuria increases during pregnancy, but in women with a normal GFR, pregnancy has no adverse effects on long-term renal function as long as blood pressure and blood glucose are well controlled (33-36,38). In women with elevated serum creatinine, however, pregnancy can lead to a permanent deterioration in renal function (39,40).

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are associated with an increased risk of congenital malformations and fetopathy, and their use should be avoided throughout pregnancy (41,42).

Cardiovascular disease
Although rare, cardiovascular disease (CVD) can occur in women of reproductive age with diabetes. Myocardial infarction in pregnancy is associated with poor maternal and fetal outcomes (43,44). Women with known CVD should be evaluated and counselled about the significant risks associated with pregnancy.

Management
Care by an interdisciplinary diabetes healthcare (DHC) team composed of diabetes nurse educators, dietitians, obstetricians and endocrinologists, both prior to conception and during pregnancy, has been shown to minimize maternal and fetal risks in women with diabetes (20,45-47). An early working relationship should be established between the woman and DHC team to optimize care, facilitate planning of pregnancy, ensure adequate self-care practices and discuss the need for social support during pregnancy.

Women should begin supplementing their diet with multivitamins containing 5 mg folic acid at least 3 months pre-conception and continue until 12 weeks postconception. From this time and continuing through the pregnancy, the first 6 weeks postpartum and as long as breastfeeding continues, supplementation should consist of a multivitamin with 0.4 to 1.0 mg folic acid (48).

Glycemic control
Hyperglycemia has adverse effects on the fetus throughout pregnancy: at conception and during the first trimester, it increases the risk of fetal malformations; later in pregnancy, it increases the risk of macrosomia and metabolic complications at birth (49). As a result, meticulous glycemic control is required for optimal maternal and fetal outcomes. Glycemic targets recommended for pregnancy are outlined in Table 1 (1,3,45,50-52).

During pregnancy there is a blunting of the normal counter-regulatory hormone responses to hypoglycemia (53,54). This and the risk of recurrent hypoglycemic episodes as a result of striving to reach glycemic targets may lead to hypoglycemia unawareness. Women with type 1 diabetes may, therefore, be at high risk of severe hypoglycemia, especially during the first trimester before relative insulin resistance from the placental hormones develops, and care should be taken to counsel these patients about the risks. There do not appear to be significant adverse effects on the neonate from maternal hypoglycemia (55); however, in the presence of hypoglycemia unawareness, there may be an increased risk of macrosomia related to erratic glycemic control, as well as an increased risk of maternal seizures (56,57).

Monitoring
Self-monitoring of blood glucose (SMBG) is essential during pregnancy (6). Both preprandial and postprandial testing are recommended to guide therapy in order to achieve glycemic

RECOMMENDATIONS

1. Women with type 1 or type 2 diabetes of reproductive age should:
   a. Use reliable birth control if sexually active and if glycemic control is not optimal [Grade D, Consensus].
   b. Be counselled about the necessity of pregnancy planning, including the importance of good glycemic control and the need to stop potentially embryopathic drugs prior to pregnancy [Grade D, Consensus].

2. Before attempting to become pregnant, women with type 1 or type 2 diabetes should:
   a. Receive preconception counselling regarding optimal diabetes management and nutrition, preferably in consultation with an interdisciplinary pregnancy team, to optimize maternal and neonatal outcomes [Grade C, Level 3 (47,88,89)].
   b. Strive to attain a preconception A1C ≤7.0% (<6.0% if safely achievable) to decrease the risk of:
      • Spontaneous abortions [Grade C, Level 3 (90), for type 1 diabetes; Grade D, Consensus, for type 2 diabetes]
      • Congenital malformations [Grade C, Level 3 (47,91,92)]
      • Pre-eclampsia [Grade C, Level 3 (93,94)]
      • Progression of retinopathy in pregnancy [Grade A, Level 1A (24), for type 1 diabetes; Grade D, Consensus, for type 2 diabetes].
   c. Supplement their diet with multivitamins containing 5 mg folic acid at least 3 months preconception and continuing until at least 12 weeks postconception [Grade D, Consensus]. From 12 weeks postconception and throughout the pregnancy, the first 6 weeks postpartum and as long as breastfeeding continues, supplementation should consist of a multivitamin with 0.4 to 1.0 mg folic acid [Grade D, Consensus].
   d. Discontinue medications considered to be potentially embryopathic, including any from the following classes:
      • ACE inhibitors and ARBs [Grade C, Level 3 (42)]. In the setting of hypertension, these may be replaced with antihypertensives that are known to be safe in pregnancy (calcium channel blockers, beta-blockers, labetalol, hydralazine and methyldopa) [Grade D, Consensus].
      • Statins [Grade D, Level 4 (95)].
   e. Undergo an ophthalmologic evaluation by an eye care specialist. Repeat assessments should be performed during the first trimester, as needed during the rest of pregnancy and within the first year postpartum [Grade A, Level 1, for type 1 diabetes (24,96); Grade D, Consensus, for type 2 diabetes].
   f. Be screened for nephropathy [Grade D, Consensus]. If microalbuminuria or overt nephropathy is found, glycemic and blood pressure control should be optimized to minimize maternal and fetal complications and progression of nephropathy [Grade C, Level 3 (33,37)].

3. Women with type 2 diabetes who are planning a pregnancy or become pregnant should:
   a. Switch from oral antihyperglycemic agents to insulin [Grade D, Consensus]. This should preferably be done prepregnancy, except in the setting of PCOS, where metformin can be safely used for ovulation induction [Grade D, Consensus]. The safety of metformin beyond ovulation induction in women with type 2 diabetes remains unknown [Grade D, Consensus].
   b. Receive an individualized insulin regimen to achieve glycemic targets, with consideration given to intensive insulin therapy [Grade A, Level 1 (65)].

4. Pregnant women with type 1 or type 2 diabetes should:
   a. Strive to achieve target glucose values:
      • Fasting/preprandial PG: 3.8 to 5.2 mmol/L
      • 1h postprandial PG: 5.5 to 7.7 mmol/L
      • 2h postprandial PG I: 5.0 to 6.6 mmol/L
   b. Perform SMBG, both pre- and postprandially (≥4 times/day if needed) to achieve glycemic targets and improve pregnancy outcomes [Grade C, Level 3 (47)].
   c. Receive nutrition counselling from a registered dietitian who is part of the DHC team during pregnancy [Grade C, Level 3 (89)] and postpartum [Grade D, Consensus]. Recommendations for weight gain during pregnancy should be based on pregravid body mass index (BMI) [Grade D, Consensus].
   d. Avoid ketosis during pregnancy [Grade C, Level 3 (97)].

5. Women with type 1 diabetes in pregnancy should receive intensive insulin therapy with multiple daily injections or an insulin pump to attain glycemic targets during pregnancy [Grade A, Level 1A (20,65)].

Postpartum
6. Women with type 1 diabetes in pregnancy should be screened for postpartum thyroiditis with a thyroid-stimulating hormone test at 6 weeks postpartum [Grade D, Consensus].

targets (50). Due to the increased risk of nocturnal hypoglycemia during pregnancy, testing during the night is often necessary in patients receiving insulin (56). Because starvation ketosis is common in pregnancy and may have detrimental effects on the fetus, urine and/or blood monitoring of ketones is warranted to confirm that the diet is adequate (58,59).

Lifestyle
During pregnancy, women should be evaluated and followed by a registered dietitian to ensure that nutrition therapy promotes euglycemia, appropriate weight gain and adequate nutritional intake (60,61). Meal planning should emphasize moderate carbohydrate restriction and distribution over 3 meals and 3 snacks, 1 of which should be at bedtime. Hypocaloric diets are not recommended, as they result in weight loss and significant ketosis and are likely inadequate in required nutrients such as protein and calcium (62). Pre-pregnancy body mass is a potent predictor of birth weight and should be considered when making recommendations about energy intake and rate of weight gain (62). Physical activity should be encouraged, unless obstetrical contraindications exist or glycemic control is worsened by the activity (63).

Pharmacologic interventions

Insulin

Insulin therapy must be individualized and regularly adapted to the changing needs of pregnancy (20,46,50,64,65). Intensive insulin therapy with multiple daily injections or continuous subcutaneous insulin infusion (CSII or the insulin pump) is recommended to achieve glycemic targets prior to pregnancy. Women using CSII should be educated about the increased risk of diabetic ketoacidosis (DKA) in the event of insulin pump failure, because DKA is a potentially fatal complication for the fetus (66). Short-acting analogues aspart and lispro can be safely used in pregnancy (67-70). However, although aspart and lispro can help women achieve postprandial targets without severe hypoglycemia (71,72), no significant improvements in A1C or in fetal or maternal outcomes have been demonstrated compared with regular insulin in pregnant women with pregestational diabetes (73). There is insufficient evidence on the use of detemir or glargine in pregnancy, but in women who cannot tolerate NPH because of nocturnal hypoglycemia, consideration may be given to the use of detemir following a discussion of the risks and benefits. While there are case series of patients using glargine in pregnancy with no adverse effects (74), theoretical considerations would suggest that patients should avoid glargine use in pregnancy (75).

Oral antihyperglycemic agents and type 2 diabetes

A meta-analysis of first-trimester use of either glyburide or metformin did not show an increased incidence of congenital anomalies (76). However, studies have found increased perinatal mortality and pre-eclampsia in women treated with metformin and/or glyburide compared to those treated with insulin, despite similar glycemic control (77,78). As a result, oral agents are not recommended for glycemic control in women with type 2 diabetes during pregnancy.

Metformin and polycystic ovary syndrome

Women with polycystic ovary syndrome (PCOS), some of whom also had type 2 diabetes, have been treated with metformin to increase fertility and decrease miscarriage rates. Treatment of PCOS with metformin reduces testosterone levels and improves insulin levels and insulin resistance both before and during pregnancy (79,80). Although metformin crosses the placenta, 1 small study found no increase in the rate of congenital malformations, neonatal hypoglycemia or abnormal growth and motor development at 18 months (81).

Postpartum

Breastfeeding

All women should be encouraged to breastfeed, since this may reduce offspring obesity, especially in the setting of maternal obesity (82).

Few studies have examined breastfeeding and use of oral agents. Three case series (83-85) found metformin in the milk and plasma of breastfeeding women who were taking metformin 500 mg BID or TID, but infant exposure was well below the 10% "level of concern" (0.18 to 0.65%). A study looking at weight, height and motor-social development up to 6 months of age in children of mothers taking metformin while breastfeeding showed normal development and no difference from formula-fed infants (81). One case series that looked at women taking glyburide or glipizide while breastfeeding found neither drug in the breast milk, and the maximum theoretical infant dose again was well below 10% (<1.5%), with no hypoglycemia found in the 3 infants tested (86). There are no studies to date looking at thiazolidinedione (TZD) use while breastfeeding. As a result, metformin and glyburide can be considered for use during breastfeeding, although further long-term studies are needed to better clarify the safety of these drugs.

Postpartum thyroiditis

Women with type 1 diabetes have a high risk of autoimmune thyroid disease (87) and should be screened for postpartum thyroiditis with a thyroid-stimulating hormone test at 6 weeks postpartum.

GESTATIONAL DIABETES MELLITUS

Definition and prevalence

Gestational diabetes mellitus (GDM) is defined as hyperglycemia with onset or first recognition during pregnancy (98). The prevalence of GDM is population-specific and reflects the underlying incidence of diabetes in that population (99). In Canada, the prevalence of GDM is higher than previously thought, varying from 3.7% in the non-Aboriginal (but probably multiethnic) population to 8–18% in Aboriginal populations (99-101).

Screening and diagnosis

Given conclusive evidence demonstrating that treatment of GDM is worthwhile (102), it is important to make the diagnosis of this generally asymptomatic condition. The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study was designed to determine whether hyperglycemia during pregnancy was associated with increased risk of maternal or fetal complications compared to overt diabetes. This large study (N=23 316) confirms that an increase in the glucose level during the oral glucose tolerance test (OGTT) of 1 standard deviation in pregnancy is associated with fetal hyperinsulinemia, increased birth weight, higher rates of cesarian deliveries and more neonatal hypoglycemia (103). However, the international approach to the diagnosis of GDM remains fragmented (104).

The suggested screening test is the Gestational Diabetes Screen (GDS) – a 50-g glucose load, with a PG measured 1 h later. The 2003 Canadian Diabetes Association guidelines (as well as these current guidelines) recommend diagnosing GDM if the glucose level 1 h after the GDS is ≥10.3 mmol/L.

Continuing to use the cutoff of 10.3 mmol/L postscreen is reasonable to presume the presence of GDM. Retrospective studies published since the 2003 guidelines indicate a threshold of 11.1 mmol/L would give a false positive rate of 7% for GDM diagnosis (105) and be 79% predictive of GDM (106). There were increased cesarean delivery or shoulder dystocia rates once the screening result was ≥11.1 mmol/L, even if GDM was not diagnosed (106). A1C testing remains too insensitive (107), and the GDS is a better screening test than the FPG test (108). A large retrospective cohort study confirmed that the 7.8 mmol/L cutoff is valid for white people, but there are minor racial differences (109). These guidelines for diagnosing GDM are robust in terms of predicting macrosomia or the need for cesarian delivery (110). In the presence of a screening value of 7.8 to 10.2 mmol/L, a 75-g OGTT is indicated, with samples at 0, 1 and 2 h. Normal PG levels are fasting plasma glucose (FPG) <5.3 mmol/L, 1-hour PG <10.6 mmol/L and 2-hour PG <8.9 mmol/L. If 2 of the 3 values are met or exceeded, a diagnosis of GDM is established. Two large retrospective studies found that 1 abnormal value on the OGTT had a worse outcome (111,112). Thus, if only 1 value is met or exceeded,

the diagnosis is impaired glucose tolerance (IGT) of pregnancy (see Figure 1).

All pregnant women should be screened for GDM between 24 and 28 weeks' gestation. Women with multiple risk factors should be screened during the first trimester (Figure 1). Risk factors include previous diagnosis of GDM or delivery of a macrosomic infant, member of a high-risk population (Aboriginal, Hispanic, South Asian, Asian, African), age ≥35 years, BMI ≥30 kg/m², PCOS, acanthosis nigricans and corticosteroid use. Universal screening is better than a risk factor-based approach; an observational study demonstrated a 2-fold increase in the rate of large-for-gestational-age neonates and their admission rate to the pediatric unit in the risk factor alone versus the universally screened group (113). Another study showed that a risk factor approach would miss half the cases of GDM (114). Both these studies confirm the findings of an earlier large prospective, randomized study (115).

An international consensus meeting is planned for the summer of 2008 with the goal of standardizing the criteria for diagnosing GDM; the guidelines for diagnosing GDM presented here will remain unaltered pending the outcome of that meeting.

Figure 1. Screening for and diagnosis of GDM
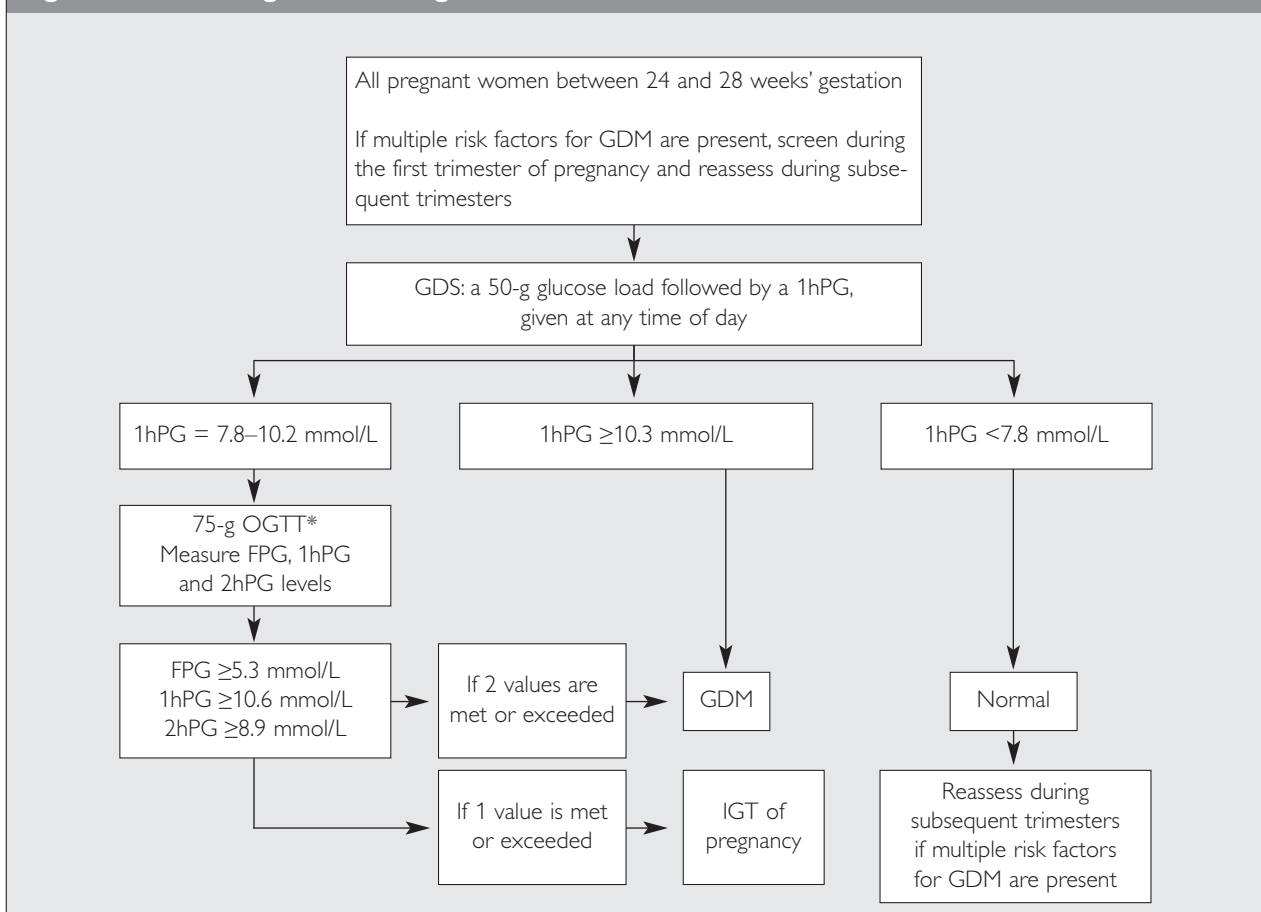
*In view of the controversies about diagnostic tests, other accepted methods may be used.

1hPG = 1-hour plasma glucose
2hPG = 2-hour plasma glucose
FPG = fasting plasma glucose

GDM = gestational diabetes mellitus
GDS = Gestational Diabetes Screen

IGT = impaired glucose tolerance
OGTT = oral glucose tolerance test

Management

Untreated GDM (116) or IGT (102) leads to increased maternal and perinatal morbidity, while intensive treatment is associated with outcomes similar to control populations (52,117,118). Some women with GDM actually have undiagnosed type 2 diabetes, and this group has an increased risk of offspring having congenital malformations (101,119,120). Women at high risk of type 2 diabetes (advanced maternal age, strong family history, previous GDM, ethnic predisposition, marked obesity) should be assessed for diabetes at the first prenatal visit if this has not been done in the 6 months before pregnancy. The recommended glycemic targets (Table 1), use of SMBG and lifestyle interventions are similar for all types of diabetes in pregnancy. Since many women of different high-risk ethnic backgrounds have GDM, it is important to have culturally relevant educational materials available. Use of 1-hour or 2-hour postprandial glucose levels appears to be equally effective in therapy (121).

Monitoring

SMBG is essential during pregnancy (6). Both preprandial and postprandial testing are recommended to guide therapy in order to achieve glycemic targets (50,116). Due to the increased risk of nocturnal hypoglycemia during pregnancy, testing during the night is often necessary in patients receiving insulin (56). Because starvation ketosis is common in pregnancy and may have detrimental effects on the fetus, urine and/or blood monitoring of ketones is warranted to confirm that the diet is adequate (58,59).

Lifestyle

During pregnancy, women should be evaluated and followed by a registered dietitian to ensure that nutrition therapy promotes euglycemia, appropriate weight gain and adequate nutritional intake (60,61,122,123). Meal planning should emphasize moderate carbohydrate restriction and distribution over 3 meals and 3 snacks, 1 of which should be at bedtime. Hypocaloric diets are not recommended, as they result in weight loss and significant ketosis and are likely inadequate in required nutrients, such as protein and calcium. Prepregnancy body mass is a potent predictor of birth weight and should be considered when making recommendations about energy intake and rate of weight gain (62). Detailed recommendations for nutritional management of GDM are available (123). Physical activity should be encouraged unless obstetrical contraindications exist or glycemic control is worsened by the activity (63,124).

Pharmacologic interventions

Insulin

If women with GDM or IGT do not achieve glycemic targets within 2 weeks from nutrition therapy alone, insulin therapy should be initiated (125,126). In some cases, assessment of fetal growth by early third-trimester ultrasound can be used to guide therapy (127,128). The use of insulin to achieve glycemic targets has been shown to reduce fetal and maternal morbidities (52,126). A variety of protocols can be used, with multiple injections being the most effective (65). Insulin usually needs to be continuously adjusted to achieve target glucose values. Although short-acting analogues aspart and lispro can help achieve postprandial glucose targets without severe hypoglycemia (71,72), improvements in fetal outcomes or in fetal growth parameters have not been demonstrated with the use of lispro compared to regular insulin in clinical trials in women with GDM (73).

Glyburide

Glyburide is safe and effective at controlling glucose levels in over 80% of patients with GDM (129-131) and does not cross the placenta (132). Women with higher fasting and postprandial glucose values on their OGTT (133), or while on diet therapy (132), are less likely to respond to glyburide. Despite good glucose levels, however, some studies report more adverse perinatal outcomes in women treated with glyburide than with insulin (134,135). Glyburide can be considered for women in whom insulin cannot be used.

Metformin

In a recent study (136), 751 women with GDM were randomly assigned to open treatment with metformin (with supplemental insulin if required) or insulin. Of the women assigned to metformin, 46.3% received supplemental insulin. Metformin (alone or with supplemental insulin) was not associated with increased perinatal complications compared with insulin. There was less severe hypoglycemia in neonates receiving metformin, but more spontaneous preterm delivery (i.e. <37 weeks' gestation). While metformin appears to be a safe alternative to insulin therapy, it does cross the placenta. Results of the offspring follow-up of the Metformin in Gestational Diabetes trial (MiG TOFU), expected in several years, will provide more data on its long-term safety.

As the use of metformin or glyburide during pregnancy is currently not an approved indication in Canada, such use would be considered off-label and would therefore require the appropriate discussion with patients.

Postpartum

Breastfeeding

All women should be encouraged to breastfeed, since this may reduce offspring obesity, especially in the setting of maternal obesity, and prevent the development of type 2 diabetes (82,137,138).

Long-term maternal risks

With the diagnosis of GDM, there is evidence of both impairment of insulin secretion and action (139,140). These defects persist postpartum and increase the risk of impaired fasting

glucose, IGT and type 2 diabetes (141,142). The cumulative incidence increases markedly in the first 5 years postpartum and more slowly after 10 years (143,144). At 3 to 6 months postpartum, risks of dysglycemia are in the 16 to 20% range, and the cumulative risks increase to a 30 to 60% range, depending on time since the index pregnancy and the population studied. The strongest predictor of early postpartum development of diabetes is elevated FPG during pregnancy (145,146).

Some women with GDM, especially lean women <30 years of age who require insulin during pregnancy, progress to type 1 diabetes (147,148). Women with positive autoantibodies (anti-GAD, IA-2) are more likely to have diabetes by 6 months postpartum (149).

Postpartum testing is essential to identify women who continue to have diabetes, those who develop diabetes after temporary normalization and those at risk, including those with IGT. However, many women do not receive adequate postpartum follow-up (150,151), and it is essential that the importance of follow-up be explicitly communicated with the woman and her caregivers who are responsible for postpartum testing.

Women should be screened postpartum to determine their glucose status. Postnatal FPG has been the most consistently found variable in determining women at high risk for early postpartum diabetes (152). A FPG alone, however, will miss many women with some degree of abnormal glucose tolerance (153), and therefore, a 75-g OGTT should be done between 6 weeks and 6 months postpartum.

Metabolic syndrome has been shown to be more prevalent in women with GDM, especially those who are obese and non-Caucasian in some (154-156) but not all studies (157). Given the increased risk of CVD with metabolic syndrome, consideration should be given to screening for all components of metabolic syndrome in the postpartum care of women with GDM. Education on lifestyle modification to prevent diabetes and CVD should begin in pregnancy and continue postpartum. Emphasis on targeted strategies that incorporate women's exercise beliefs may increase participation rates (158) (see "Prevention of Diabetes," p. S17).

RECOMMENDATIONS

7. All pregnant women should be screened for GDM *[Grade C, Level 3 (113,115)]*. For most women, screening should be performed between 24 and 28 weeks' gestation *[Grade D, Consensus]*. Women with multiple risk factors should be screened during the first trimester and, if negative, should be reassessed during subsequent trimesters *[Grade D, Consensus]*.

8. Screening for GDM should be conducted using the GDS – a 50-g glucose load followed by a PG test measured 1 h later *[Grade D, Level 4 (108)]*. If GDM is strongly suspected, an OGTT can be performed without an initial GDS *[Grade D, Consensus]*.

9. Women who have a positive screening test (a 1hPG of 7.8 to 10.2 mmol/L on the GDS) should undergo an OGTT in order to diagnose GDM. A value of ≥10.3 mmol/L is considered diagnostic of GDM, in which case an OGTT does not need to be performed *[Grade D, Consensus]*.

10. GDM is diagnosed when at least 2 of the following values on the OGTT are met or exceeded. If 1 value is met or exceeded, a diagnosis of IGT of pregnancy is made *[Grade D, Consensus]*:
    • FPG: ≥5.3 mmol/L
    • 1hPG: ≥10.6 mmol/L
    • 2hPG: ≥8.9 mmol/L

11. Women with GDM should:
    a. Strive to achieve target glucose values:
       • Fasting/preprandial PG: 3.8 to 5.2 mmol/L
       • 1h postprandial PG: 5.5 to 7.7 mmol/L
       • 2h postprandial PG: 5.0 to 6.6 mmol/L
    b. Perform SMBG both pre- and postprandially (≥4 times per day, if needed) to achieve glycemic targets and improve pregnancy outcomes *[Grade C, Level 3 (47)]*.
    c. Receive nutrition counselling from a registered dietitian during pregnancy *[Grade C, Level 3 (89)]* and postpartum *[Grade D, Consensus]*. Recommendations for weight gain during pregnancy should be based on pregravid BMI *[Grade D, Consensus]*.
    d. Avoid ketosis during pregnancy *[Grade C, Level 3 (97)]*.

12. If women with GDM do not achieve glycemic targets within 2 weeks using nutrition therapy alone, insulin therapy should be initiated *[Grade D, Consensus]*, with up to 4 injections/day considered *[Grade A, Level 1A (65)]*.

13. Glyburide *[Grade B, Level 2 (130,134,135)]* or metformin *[Grade B, Level 2 (136)]* may be considered as second-line agents in women with GDM who are nonadherent to or who refuse insulin. Glyburide may be preferred, as metformin use is more likely to need supplemental insulin for glycemic control and metformin crosses the placenta with unknown long-term effects. Use of oral agents in pregnancy is off-label and should be discussed with the patient *[Grade D, Consensus]*.

Postpartum

14. As women who have had GDM are defined as high risk of developing subsequent type 2 diabetes, they should be re-evaluated postpartum *[Grade D, Consensus]*. A 75-g OGTT should be performed between 6 weeks and 6 months postpartum to establish their glucose status. Women who are suspected of having had pre-existing diabetes should be monitored more closely postpartum. All women with GDM should be counselled on a healthy lifestyle.

15. Women with previous GDM should follow the screening and prevention guidelines for other high-risk groups screened for type 2 diabetes *[Grade D, Consensus]* and should be screened for type 2 diabetes when planning another pregnancy *[Grade D, Consensus]*.

Long-term risks in offspring

There is compelling evidence that offspring exposed to GDM are at increased risk of obesity and IGT, especially if large for gestational age and born to obese mothers (58,159-162). In a Canadian cohort of children exposed to GDM, 7% had IGT at age 7 to 11 years (162). In the Pima Indian population, as many as 70% of offspring exposed to diabetes in utero had type 2 diabetes at age 25 to 35 years (163). Breastfeeding may lower the risk (82,138,164). The importance of tight glycemic control during pregnancy to prevent these outcomes is not clearly established. The need for increased surveillance of these children requires further study.

Planning subsequent pregnancies

Women with previous GDM should plan future pregnancies in consultation with their healthcare providers (165,166). Glucose tolerance should be assessed prior to conception to assure normoglycemia at the time of conception, and any glucose abnormality should be treated. In an effort to reduce the risk of congenital anomalies and optimize pregnancy outcomes, all women should take a folic acid supplement of 0.4 to 1.0 mg (48).

OTHER RELEVANT GUIDELINES

Screening for Type 1 and Type 2 Diabetes, p. S14
Targets for Glycemic Control, p. S29
Chronic Kidney Disease in Diabetes, p. S126
Type 1 Diabetes in Children and Adolescents, p. S150

REFERENCES

1. Yogev Y, Ben-Haroush A, Chen R, et al. Diurnal glycemic profile in obese and normal weight nondiabetic pregnant women. *Am J Obstet Gynecol.* 2004;191:949-953.

2. Nielsen LR, Ekbom P, Damm P, et al. HbA1c levels are significantly lower in early and late pregnancy. *Diabetes Care.* 2004; 27:1200-1201.

3. Langer O, Conway DL. Level of glycemia and perinatal outcome in pregestational diabetes. *J Matern Fetal Med.* 2000;9:35-41.

4. Parretti E, Mecacci F, Papini M, et al. Third-trimester maternal glucose levels from diurnal profiles in nondiabetic pregnancies: correlation with sonographic parameters of fetal growth. *Diabetes Care.* 2001;24:1319-1323.

5. Ben-Haroush A, Yogev Y, Chen R, et al. The postprandial glucose profile in the diabetic pregnancy. *Am J Obstet Gynecol.* 2004;191:576-581.

6. Cundy T, Gamble G, Townend K, et al. Perinatal mortality in type 2 diabetes mellitus. *Diabet Med.* 2000;17:33-39.

7. Wylie BR, Kong J, Kozak SE, et al. Normal perinatal mortality in type 1 diabetes mellitus in a series of 300 consecutive pregnancy outcomes. *Am J Perinatol.* 2002;19:169-176.

8. Roland JM, Murphy HR, Ball V, et al. The pregnancies of women with type 2 diabetes: poor outcomes but opportunities for improvement. *Diabet Med.* 2005;22:1774-1777.

9. Clausen TD, Mathiesen E, Ekbom P, et al. Poor pregnancy outcome in women with type 2 diabetes. *Diabetes Care.* 2005;28: 323-328.

10. Gunton JE, Morris J, Boyce S, et al. Outcome of pregnancy complicated by pre-gestational diabetes – improvement in outcomes. *Aust N Z J Obstet Gynaecol.* 2002;42:478-481.

11. Hadden DR, Cull CA, Croft DJ, et al. Poor pregnancy outcome for women with type 2 diabetes. *Diabetic Med.* 2003;20: 506-507.

12. Dunne F, Brydon P, Smith K, et al. Pregnancy in women with type 2 diabetes: 12 years outcome data 1990-2002. *Diabet Med.* 2003;20:734-738.

13. Farrell T, Neale L, Cundy T. Congenital anomalies in the offspring of women with type 1, type 2 and gestational diabetes. *Diabetic Med.* 2002;19:322-326.

14. Boulot P, Chabbert-Buffet N, d'Ercole C, et al; Diabetes and Pregnancy Group, France. French multicentric survey of outcome of pregnancy in women with pregestational diabetes. *Diabetes Care.* 2003;26:2990-2993.

15. dos Santos Silva I, Higgins C, Swerdlow AJ, et al. Birthweight and other pregnancy outcomes in a cohort of women with pregestational insulin-treated diabetes mellitus, Scotland, 1979-95. *Diabet Med.* 2005;22:440-447.

16. Evers IM, de Valk HW, Visser GH. Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. *BMJ.* 2004;328:915.

17. Jensen DM, Damm P, Moelsted-Pedersen L, et al. Outcomes in type 1 diabetic pregnancies: a nationwide, population-based study. *Diabetes Care.* 2004;27:2819-2823.

18. Penney GC, Mair G, Pearson DW; Scottish Diabetes in Pregnancy Group. Outcomes of pregnancies in women with type 1 diabetes in Scotland: a national population-based study. *BJOG.* 2003;110:315-318.

19. Platt MJ, Stanisstreet M, Casson IF, et al. St Vincent's Declaration 10 years on: outcomes of diabetic pregnancies. *Diabet Med.* 2002;19:216-220.

20. The Diabetes Control and Complications Trial Research Group. Pregnancy outcomes in the Diabetes Control and Complications Trial. *Am J Obstet Gynecol.* 1996;174:1343-1353.

21. McIntosh M, ed. *Pregnancy in Women with Type 1 and Type 2 Diabetes: 2002–2003. England, Wales and Northern Ireland.* London, UK: Confidential Enquiry into Maternal and Child Health; 2005.

22. Klein BE, Moss SE, Klein R. Effect of pregnancy on progression of diabetic retinopathy. *Diabetes Care.* 1990;13:34-40.

23. Omori Y, Minei S, Testuo T, et al. Current status of pregnancy in diabetic women. A comparison of pregnancy in IDDM and NIDDM mothers. *Diabetes Res Clin Pract.* 1994;24(suppl): S273-S278.

24. The Diabetes Control and Complications Trial Research Group. Effect of pregnancy on microvascular complications in the Diabetes Control and Complications Trial. *Diabetes Care.* 2000;23:1084-1091.

25. Chew EY, Mills JL, Metzger BE, et al. Metabolic control and

progression of retinopathy. The Diabetes in Early Pregnancy Study. National Institute of Child Health and Human Development Diabetes in Early Pregnancy Study. *Diabetes Care.* 1995;18:631-637.

26. Lövestam-Adrian M, Agardh CD, Aberg A, et al. Pre-eclampsia is a potent risk factor for deterioration of retinopathy during pregnancy in type 1 diabetic patients. *Diabetic Med.* 1997; 14:1059-1065.

27. Rosenn B, Miodovnik M, Kranias G, et al. Progression of diabetic retinopathy in pregnancy: association with hypertension in pregnancy. *Am J Obstet Gynecol.* 1992;166:1214-1218.

28. Cundy T, Slee F, Gamble G, et al. Hypertensive disorders of pregnancy in women with type 1 and type 2 diabetes. *Diabet Med.* 2002;19:482-489.

29. Sibai BM, Caritis S, Hauth J, et al. Risks of preeclampsia and adverse neonatal outcomes among women with pregestational diabetes mellitus. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *Am J Obstet Gynecol.* 2000;182:364-369.

30. Schröder W, Heyl W, Hill-Grasshoff B, et al. Clinical value of detecting microalbuminuria as a risk factor for pregnancy-induced hypertension in insulin-treated diabetic pregnancies. *Eur J Obstet Gynecol Reprod Biol.* 2000;91:155-158.

31. How HY, Sibai B, Lindheimer M, et al. Is early-pregnancy proteinuria associated with an increased rate of preeclampsia in women with pregestational diabetes mellitus? *Am J Obstet Gynecol.* 2004;190:775-778.

32. Chobanian AV, Bakris GL, Black HR, et al; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension.* 2003; 42:1206-1252.

33. Ekbom P, Damm P, Feldt-Rasmussen B, et al. Pregnancy outcome in type 1 diabetic women with microalbuminuria. *Diabetes Care.* 2001;24:1739-1744.

34. Dunne FP, Chowdhury TA, Hartland A, et al. Pregnancy outcome in women with insulin-dependent diabetes mellitus complicated by nephropathy. *QJM.* 1999;92:451-454.

35. Bagg W, Neale L, Henley P, et al. Long-term maternal outcome after pregnancy in women with diabetic nephropathy. *N Z Med J.* 2003;116:U566.

36. Rossing K, Jacobsen P, Hommel E, et al. Pregnancy and progression of diabetic nephropathy. *Diabetologia.* 2002;45:36-41.

37. Reece EA, Leguizamon G, Homko C. Stringent controls in diabetic nephropathy associated with optimization of pregnancy outcomes. *J Matern Fetal Med.* 1998;7:213-216.

38. Leguizamon G, Reece EA. Effect of medical therapy on progressive nephropathy: influence of pregnancy, diabetes and hypertension. *J Matern Fetal Med.* 2000;9:70-78.

39. Biesenbach G, Grafinger P, Stöger H, et al. How pregnancy influences renal function in nephropathic type 1 diabetic women depends on their pre-conceptional creatinine clearance. *J Nephrol.* 1999;12:41-46.

40. Gordon M, Landon MB, Samuels P, et al. Perinatal outcome and long-term follow-up associated with modern management of diabetic nephropathy. *Obstet Gynecol.* 1996;87:401-409.

41. Quan A. Fetopathy associated with exposure to angiotensin converting enzyme inhibitors and angiotensin receptor antagonists. *Early Hum Dev.* 2006;82:23-28.

42. Cooper WO, Hernandez-Diaz S, Arbogast PG, et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. *N Engl J Med.* 2006;354:2443-2451.

43. Silfen SL, Wapner RJ, Gabbe SG. Maternal outcome in class H diabetes mellitus. *Obstet Gynecol.* 1980;55:749-751.

44. Bagg W, Henley PG, Macpherson P, et al. Pregnancy in women with diabetes and ischemic heart disease. *Aust N Z J Obstet Gynaecol.* 1999;39:99-102.

45. Howorka K, Pumprla J, Gabriel M, et al. Normalization of pregnancy outcome in pregestational diabetes through functional insulin treatment and modular out-patient education adapted for pregnancy. *Diabet Med.* 2001;18:965-972.

46. Quevedo SF, Coustan DR. Diabetes and pregnancy. Use of an integrated "team" approach provides the necessary comprehensive care. *R I Med J.* 1989;72:129-132.

47. Ray JG, O'Brien TE, Chan WS. Preconception care and the risk of congenital anomalies in the offspring of women with diabetes mellitus: a meta-analysis. *QJM.* 2001;94:435-444.

48. Wilson RD. Pre-conception vitamin/folic acid supplementation 2007: the use of folic acid in combination with a multivitamin supplement for the prevention of neural tube defects and other congenital anomalies. *J Obstet Gynaecol Can.* 2007;29: 1003-1026.

49. Langer O. A spectrum of glucose thresholds may effectively prevent complications in the pregnant diabetic patient. *Semin Perinatol.* 2002;26:196-205.

50. Combs CA, Gunderson E, Kitzmiller JL, et al. Relationship of fetal macrosomia to maternal postprandial glucose control during pregnancy. *Diabetes Care.* 1992;15:1251-1257.

51. de Veciana M, Major CA, Morgan MA, et al. Postprandial versus preprandial blood glucose monitoring in women with gestational diabetes mellitus requiring insulin therapy. *N Engl J Med.* 1995;333:1237-1241.

52. Langer O, Rodriguez DA, Xenakis EM, et al. Intensified versus conventional management of gestational diabetes. *Am J Obstet Gynecol.* 1994;170:1036-1046.

53. Rosenn BM, Miodovnik M, Khoury JC, et al. Counterregulatory hormonal responses to hypoglycemia during pregnancy. *Obstet Gynecol.* 1996;87:568-574.

54. Diamond MP, Reece EA, Caprio S, et al. Impairment of counterregulatory hormone responses to hypoglycemia in pregnant women with insulin-dependent diabetes mellitus. *Am J Obstet Gynecol.* 1992;166:70-77.

55. Reece EA, Hagay Z, Roberts AB, et al. Fetal Doppler and behavioral responses during hypoglycemia induced with the insulin clamp technique in pregnant diabetic women. *Am J*

Obstet Gynecol. 1995;172:151-155.

56. Egger M, Davey Smith G, Stettler C, et al. Risk of adverse effects of intensified treatment in insulin-dependent diabetes mellitus: a meta-analysis. *Diabet Med.* 1997;14:919-928.

57. Rosenn BM, Miodovnik M, Khoury JC, et al. Deficient counterregulation: a possible risk factor for excessive fetal growth in IDDM pregnancies. *Diabetes Care*. 1997;20:872-874.

58. Silverman BL, Rizzo TA, Cho NH, et al. Long-term effects of the intrauterine environment. The Northwestern University Diabetes in Pregnancy Center. *Diabetes Care.* 1998;21(suppl 2): B142-B149.

59. Ornoy A. Growth and neurodevelopmental outcome of children born to mothers with pregestational and gestational diabetes. *Pediatr Endocrinol Rev.* 2005;3:104-113.

60. Franz MJ, Bantle JP, Beebe CA, et al. Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. *Diabetes Care.* 2002;25:148-198.

61. Jovanovic L. Medical nutritional therapy in pregnant women with pregestational diabetes mellitus. *J Matern Fetal Med.* 2000;9:21-28.

62. Knopp RH, Magee MS, Raisys V, et al. Metabolic effects of hypocaloric diets in management of gestational diabetes. *Diabetes.* 1991;40(suppl 2):165-171.

63. Sternfeld B, Quesenberry CP Jr, Eskenazi B, et al. Exercise during pregnancy and pregnancy outcome. *Med Sci Sports Exerc*. 1995;27:634-640.

64. Jovanovic L, Druzin M, Peterson CM. Effect of euglycemia on the outcome of pregnancy in insulin-dependent diabetic women as compared with normal control subjects. *Am J Med.* 1981;71:921-927.

65. Nachum Z, Ben-Shlomo I, Weiner E, et al. Twice daily versus four times daily insulin dose regimens for diabetes in pregnancy: randomised controlled trial. *BMJ.* 1999;319:1223-1227.

66. Chauhan SP, Perry KG Jr, McLaughlin BN, et al. Diabetic ketoacidosis complicating pregnancy. *J Perinatol.* 1996;16:173-175.

67. Boskovic R, Feig DS, Derewlany L, et al. Transfer of insulin lispro across the human placenta: in vitro perfusion studies. *Diabetes Care.* 2003;26:1390-1394.

68. Persson B, Swahn ML, Hjertberg R, et al. Insulin lispro therapy in pregnancies complicated by type 1 diabetes mellitus. *Diabetes Res Clin Pract.* 2002;58:115-121.

69. Wyatt JW, Frias JL, Hoyme HE, et al; IONS study group. Congenital anomaly rate in offspring of mothers with diabetes treated with insulin lispro during pregnancy. *Diabet Med.* 2005;22:803-807.

70. Mathiesen ER, Kinsley B, Amiel SA, et al; Insulin Aspart Pregnancy Study Group. Maternal glycemic control and hypoglycemia in type 1 diabetic pregnancy: a randomized trial of insulin aspart versus human insulin in 322 pregnant women. *Diabetes Care.* 2007;30:771-776.

71. Mecacci F, Carignani L, Cioni R, et al. Maternal metabolic control and perinatal outcome in women with gestational diabetes treated with regular or lispro insulin: comparison with non-diabetic pregnant women. *Eur J Obstet Gynecol Reprod Biol.* 2003;111:19-24.

72. Pettitt DJ, Ospina P, Kolaczynski JW, et al. Comparison of an insulin analog, insulin aspart, and regular human insulin with no insulin in gestational diabetes mellitus. *Diabetes Care.* 2003; 26:183-186.

73. Plank J, Siebenhofer A, Berghold A, et al. Systematic review and meta-analysis of short-acting insulin analogues in patients with diabetes mellitus. *Arch Intern Med.* 2005;165:1337-1344.

74. Gallen IW, Jaap A, Roland JM, et al. Survey of glargine use in 115 pregnant women with type 1 diabetes. *Diabet Med.* 2008; 25:165-169.

75. Kurtzhals P, Schaffer L, Sorensen A, et al. Correlations of receptor binding and metabolic and mitogenic potencies of insulin analogs designed for clinical use. *Diabetes.* 2000;49: 999-1005.

76. Gutzin SJ, Kozer E, Magee LA, et al. The safety of oral hypoglycemic agents in the first trimester of pregnancy: a meta-analysis. *Can J Clin Pharmacol.* 2003;10:179-183.

77. Hellmuth E, Damm P, Molsted-Pedersen L. Oral hypoglycaemic agents in 118 diabetic pregnancies. *Diabet Med.* 2000; 17:507-511.

78. Ekpebegh CO, Coetzee EJ, van der Merwe L, et al. A 10-year retrospective analysis of pregnancy outcome in pregestational type 2 diabetes: comparison of insulin and oral glucose-lowering agents. *Diabet Med.* 2007;24:253-258.

79. Glueck CJ, Wang P, Kobayashi S, et al. Metformin therapy throughout pregnancy reduces the development of gestational diabetes in women with polycystic ovary syndrome. *Fertil Steril.* 2002;77:520-525.

80. Glueck CJ, Goldenberg N, Pranikoff J, et al. Height, weight, and motor-social development during the first 18 months of life in 126 infants born to 109 mothers with polycystic ovary syndrome who conceived on and continued metformin through pregnancy. *Hum Reprod.* 2004;19:1323-1330.

81. Glueck CJ, Salehi M, Sieve L, et al. Growth, motor, and social development in breast- and formula-fed infants of metformin-treated women with polycystic ovary syndrome. *J Pediatr.* 2006;148:628-632.

82. Mayer-Davis EJ, Rifas-Shiman SL, Zhou L, et al. Breast-feeding and risk for childhood obesity: does maternal diabetes or obesity status matter? *Diabetes Care.* 2006;29:2231-2237.

83. Gardiner SJ, Kirkpatrick CM, Begg EJ, et al. Transfer of metformin into human milk. *Clin Pharmacol Ther.* 2003;73:71-77.

84. Briggs GG, Ambrose PJ, Nageotte MP, et al. Excretion of metformin into breast milk and the effect on nursing infants. *Obstet Gynecol.* 2005;105:1437-1441.

85. Hale TW, Kristensen JH, Hackett LP, et al. Transfer of metformin into human milk. *Diabetologia.* 2002;45:1509-1514.

86. Feig DS, Briggs GG, Kraemer JM, et al. Transfer of glyburide and glipizide into breast milk. *Diabetes Care.* 2005;28:1851-1855.

87. Umpierrez GE, Latif KA, Murphy MB, et al. Thyroid dysfunc-

tion in patients with type 1 diabetes: a longitudinal study. *Diabetes Care.* 2003;26:1181-1185.

88. Kitzmiller JL, Gavin LA, Gin GD, et al. Preconception care of diabetes. Glycemic control prevents congenital anomalies. *JAMA.* 1991;265:731-736.

89. McElvy SS, Miodovnik M, Rosenn B, et al. A focused preconceptional and early pregnancy program in women with type 1 diabetes reduces perinatal mortality and malformation rates to general population levels. *J Matern Fetal Med.* 2000;9:14-20.

90. Jovanovic L, Knopp RH, Kim H, et al. Elevated pregnancy losses at high and low extremes of maternal glucose in early normal and diabetic pregnancy: evidence for a protective adaptation in diabetes. *Diabetes Care.* 2005;28:1113-1117.

91. Suhonen L, Hiilesmaa V, Teramo K. Glycaemic control during early pregnancy and fetal malformations in women with type I diabetes mellitus. *Diabetologia.* 2000;43:79-82.

92. Guerin A, Nisenbaum R, Ray JG. Use of maternal GHb concentration to estimate the risk of congenital anomalies in the offspring of women with pre-pregnancy diabetes. *Diabetes Care.* 2007;30:1920-1925.

93. Hiilesmaa V, Suhonen L, Teramo K. Glycaemic control is associated with pre-eclampsia but not with pregnancy-induced hypertension in women with type I diabetes mellitus. *Diabetologia.* 2000;43:1534-1539.

94. Hsu CD, Tan HY, Hong SF, et al. Strategies for reducing the frequency of preeclampsia in pregnancies with insulin-dependent diabetes mellitus. *Am J Perinatol.* 1996;13:265-268.

95. Edison RJ, Muenke M. Central nervous system and limb anomalies in case reports of first-trimester statin exposure. *N Engl J Med.* 2004;350:1579-1582.

96. The Diabetes Control and Complications Trial Research Group. Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. *Arch Ophthalmol.* 1998;116:874-886.

97. Rizzo T, Metzger BE, Burns WJ, et al. Correlations between antepartum maternal metabolism and child intelligence. *N Engl J Med.* 1991;325:911-916.

98. Metzger BE, Coustan DR. Summary and recommendations of the Fourth International Workshop – Conference on Gestational Diabetes Mellitus. *Diabetes Care.* 1998;21(suppl 2): B161-B167.

99. Dyck R, Klomp H, Tan LK, et al. A comparison of rates, risk factors, and outcomes of gestational diabetes between aboriginal and non-aboriginal women in the Saskatoon Health District. *Diabetes Care.* 2002;25:487-493.

100. Godwin M, Muirhead M, Huynh J, et al. Prevalence of gestational diabetes mellitus among Swampy Cree women in Moose Factory, James Bay. *CMAJ.* 1999;160:1299-1302.

101. Harris SB, Caulfield LE, Sugamori ME, et al. The epidemiology of diabetes in pregnant Native Canadians. A risk profile. *Diabetes Care.* 1997;20:1422-1425.

102. Crowther CA, Hiller JE, Moss JR, et al; Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group. Effect of treatment of gestational dia-

betes mellitus on pregnancy outcomes. *N Engl J Med.* 2005; 352:2477-2486.

103. HAPO Study Cooperative Research Group; Metzger BE, Lowe LP, Dyer AR, et al. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med.* 2008;358:1991-2002.

104. Cutchie WA, Cheung NW, Simmons D. Comparison of international and New Zealand guidelines for the care of pregnant women with diabetes. *Diabet Med.* 2006;23:460-468.

105. Lanni S, Barrett D. The predictive value of the 1-h 50-g glucose screen for diagnosing gestational diabetes mellitus in a high-risk population. *J Matern Fetal Neonatal Med.* 2004;15:375-379.

106. Cheng YW, Esakoff TF, Block-Kurbisch I, et al. Screening or diagnostic: markedly elevated glucose loading test and perinatal outcomes. *J Matern Fetal Neonatal Med.* 2006;19:729-734.

107. Agarwal MM, Dhatt GS, Punnose J, et al. Gestational diabetes: a reappraisal of HBA1c as a screening test. *Acta Obstet Gynecol Scand.* 2005;84:1159-1163.

108. Rey E, Hudon L, Michon N, et al. Fasting plasma glucose versus glucose challenge test: screening for gestational diabetes and cost effectiveness. *Clin Biochem.* 2004;37:780-784.

109. Esakoff TF, Cheng YW, Caughey AB. Screening for gestational diabetes: different cut-offs for different ethnicities? *Am J Obstet Gynecol.* 2005;193:1040-1044.

110. Agarwal MM, Dhatt GS, Punnose J, et al. Gestational diabetes: dilemma caused by multiple international diagnostic criteria. *Diabet Med.* 2005;22:1731-1736.

111. Chico A, Lopez-Rodo V, Rodriguez-Vaca D, et al. Features and outcome of pregnancies complicated by impaired glucose tolerance and gestational diabetes diagnosed using different criteria in a Spanish population. *Diabetes Res Clin Pract.* 2005;68: 141-146.

112. McLaughlin GB, Cheng YW, Caughey AB. Women with one elevated 3-hour glucose tolerance test value: are they at risk for adverse perinatal outcomes? *Am J Obstet Gynecol.* 2006;194: e16-e19.

113. Cosson E, Benchimol M, Carbillon L, et al. Universal rather than selective screening for gestational diabetes mellitus may improve fetal outcomes. *Diabetes Metab.* 2006;32:140-146.

114. Pöyhönen-Alho MK, Teramo KA, Kaaja RJ, et al. 50gram oral glucose challenge test combined with risk factor-based screening for gestational diabetes. *Eur J Obstet Gynecol Reprod Biol.* 2005;121:34-37.

115. Griffin ME, Coffey M, Johnson H, et al. Universal vs. risk factor-based screening for gestational diabetes mellitus: detection rates, gestation at diagnosis and outcome. *Diabet Med.* 2000;17: 26-32.

116. Langer O, Yogev Y, Most O, et al. Gestational diabetes: the consequences of not treating. *Am J Obstet Gynecol.* 2005;192: 989-997.

117. Thompson DM, Dansereau J, Creed M, et al. Tight glucose control results in normal perinatal outcomes in 150 patients with gestational diabetes. *Obstet Gynecol.* 1994;83:362-366.

118. Salim R, Hasanein J, Nachum Z, et al. Anthropometric parameters in infants of gestational diabetic women with

strict glycemic control. *Obstet Gynecol.* 2004;104:1021-1024.

119. Martínez-Frías ML, Frías JP, Bermejo E, et al. Pre-gestational maternal body mass index predicts an increased risk of congenital malformations in infants of mothers with gestational diabetes. *Diabet Med.* 2005;22:775-781.

120. García-Patterson A, Erdozain L, Ginovart G, et al. In human gestational diabetes mellitus congenital malformations are related to pre-pregnancy body mass index and to severity of diabetes. *Diabetologia*. 2004;47:509-514.

121. Weisz B, Shrim A, Homko CJ, et al. One hour versus two hours postprandial glucose measurement in gestational diabetes: a prospective study. *J Perinatol.* 2005;25:241-244.

122. Dornhorst A, Frost G. The principles of dietary management of gestational diabetes: reflection on current evidence. *J Hum Nutr Diet.* 2002;15:145-156.

123. Anderson K, Barbeau M-C, Blagrave P, et al. Recommendations for nutrition best practice in the management of gestational diabetes mellitus. *Can J Diet Pract Res*. 2006;67:206-208.

124. Bung P, Bung C, Artal R, et al. Therapeutic exercise for insulin-requiring gestational diabetics: effects on the fetus – results of a randomized prospective longitudinal study. *J Perinat Med.* 1993;21:125-137.

125. McFarland MB, Langer O, Conway DL, et al. Dietary therapy for gestational diabetes: how long is long enough? *Obstet Gynecol*. 1999;93:978-982.

126. Hadden DR. When and how to start insulin treatment in gestational diabetes: a UK perspective. *Diabet Med.* 2001;18:960-964.

127. Rossi G, Somigliana E, Moschetta M, et al. Adequate timing of fetal ultrasound to guide metabolic therapy in mild gestational diabetes mellitus. Results from a randomized study. *Acta Obstet Gynecol Scand.* 2000;79:649-654.

128. Kjos SL, Schaefer-Graf U, Sardesi S, et al. A randomized controlled trial using glycemic plus fetal ultrasound parameters versus glycemic parameters to determine insulin therapy in gestational diabetes with fasting hyperglycemia. *Diabetes Care.* 2001;24:1904-1910.

129. Kremer CJ, Duff P. Glyburide for the treatment of gestational diabetes. *Am J Obstet Gynecol.* 2004;190:1438-1439.

130. Langer O, Conway DL, Berkus MD, et al. A comparison of glyburide and insulin in women with gestational diabetes mellitus. *N Engl J Med.* 2000;343:1134-1138.

131. Chmait R, Dinise T, Moore T. Prospective observational study to establish predictors of glyburide success in women with gestational diabetes mellitus. *J Perinatol.* 2004;24:617-622.

132. Elliott BD, Schenker S, Langer O, et al. Comparative placental transport of oral hypoglycemic agents in humans: a model of human placental drug transfer. *Am J Obstet Gynecol.* 1994; 171:653-660.

133. Conway DL, Gonzales O, Skiver D. Use of glyburide for the treatment of gestational diabetes: the San Antonio experience. *J Matern Fetal Neonatal Med.* 2004;15:51-55.

134. Bertini AM, Silva JC, Taborda W, et al. Perinatal outcomes and the use of oral hypoglycemic agents. *J Perinat Med.* 2005; 33:519-523.

135. Jacobson GF, Ramos GA, Ching JY, et al. Comparison of glyburide and insulin for the management of gestational diabetes in a large managed care organization. *Am J Obstet Gynecol.* 2005;193:118-124.

136. Rowan JA, Hague WM, Gao W, et al; MiG Trial Investigators. Metformin versus insulin for the treatment of gestational diabetes. *N Engl J Med.* 2008;358:2003-2015.

137. Schaefer-Graf UM, Hartmann R, Pawliczak J, et al. Association of breast-feeding and early childhood overweight in children from mothers with gestational diabetes mellitus. *Diabetes Care.* 2006;29:1105-1107.

138. Stuebe AM, Rich-Edwards JW, Willett WC, et al. Duration of lactation and incidence of type 2 diabetes. *JAMA.* 2005;294: 2601-2610.

139. Catalano PM, Drago NM, Amini SB. Longitudinal changes in pancreatic beta-cell function and metabolic clearance rate of insulin in pregnant women with normal and abnormal glucose tolerance. *Diabetes Care.* 1998;21:403-408.

140. Ergin T, Lembet A, Duran H, et al. Does insulin secretion in patients with one abnormal glucose tolerance test value mimic gestational diabetes mellitus? *Am J Obstet Gynecol.* 2002;186:204-209.

141. Kjos SL, Peters RK, Xiang A, et al. Predicting future diabetes in Latino women with gestational diabetes. Utility of early postpartum glucose tolerance testing. *Diabetes*. 1995;44:586-591.

142. Pallardo F, Herranz L, Garcia-Ingelmo T, et al. Early postpartum metabolic assessment in women with prior gestational diabetes. *Diabetes Care.* 1999;22:1053-1058.

143. O'Sullivan JB. Diabetes mellitus after GDM. *Diabetes*. 1991;40(suppl 2):131-135.

144. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. *Diabetes Care*. 2002;25:1862-1868.

145. Kaufmann RC, Schleyhahn FT, Huffman DG, et al. Gestational diabetes diagnostic criteria: long-term maternal follow-up. *Am J Obstet Gynecol.* 1995;172:621-625.

146. Schaefer-Graf UM, Buchanan TA, Xiang AH, et al. Clinical predictors for a high risk for the development of diabetes mellitus in the early puerperium in women with recent gestational diabetes mellitus. *Am J Obstet Gynecol.* 2002;186:751-756.

147. Järvelä IY, Juutinen J, Koskela P, et al. Gestational diabetes identifies women at risk for permanent type 1 and type 2 diabetes in fertile age: predictive role of autoantibodies. *Diabetes Care.* 2006;29:607-612.

148. Dozio N, Beretta A, Belloni C, et al. Low prevalence of islet autoantibodies in patients with gestational diabetes mellitus. *Diabetes Care.* 1997;20:81-83.

149. Löbner K, Knopff A, Baumgarten A, et al. Predictors of postpartum diabetes in women with gestational diabetes mellitus. *Diabetes*. 2006;55:792-797.

150. Smirnakis KV, Chasan-Taber L, Wolf M, et al. Postpartum diabetes screening in women with a history of gestational dia-

betes. *Obstet Gynecol.* 2005;106:1297-1303.

151. Clark HD, van Walraven C, Code C, et al. Did publication of a clinical practice guideline recommendation to screen for type 2 diabetes in women with gestational diabetes change practice? *Diabetes Care*. 2003;26:265-268.

152. Holt RI, Goddard JR, Clarke P, et al. A postnatal fasting plasma glucose is useful in determining which women with gestational diabetes should undergo a postnatal oral glucose tolerance test. *Diabet Med.* 2003;20:594-598.

153. Reinblatt SL, Morin L, Meltzer SJ. The importance of a postpartum 75 g oral glucose tolerance test in women with gestational diabetes. *J Obstet Gynaecol Can.* 2006;28:690-694.

154. Kousta E, Efstathiadou Z, Lawrence NJ, et al. The impact of ethnicity on glucose regulation and the metabolic syndrome following gestational diabetes. *Diabetologia*. 2006;49:36-40.

155. Bo S, Monge L, Macchetta C, et al. Prior gestational hyperglycemia: a long-term predictor of the metabolic syndrome. *J Endocrinol Invest.* 2004;27:629-635.

156. Lauenborg J, Mathiesen E, Hansen T, et al. The prevalence of the metabolic syndrome in a Danish population of women with previous gestational diabetes mellitus is three-fold higher than in the general population. *J Clin Endocrinol Metab.* 2005;90:4004-4010.

157. Albareda M, Caballero A, Badell G, et al. Metabolic syndrome at follow-up in women with and without gestational diabetes mellitus in index pregnancy. *Metabolism*. 2005;54:1115-1121.

158. Symons Downs D, Ulbrecht JS. Understanding exercise beliefs and behaviors in women with gestational diabetes mellitus. *Diabetes Care.* 2006;29:236-240.

159. Boney CM, Verma A, Tucker R, et al. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. *Pediatrics*. 2005;115:e290-e296.

160. Krishnaveni GV, Hill JC, Leary SD, et al. Anthropometry, glucose tolerance, and insulin concentrations in Indian children: relationships to maternal glucose and insulin concentrations during pregnancy. *Diabetes Care.* 2005;28:2919-2925.

161. Gillman MW, Rifas-Shiman S, Berkey CS, et al. Maternal gestational diabetes, birth weight, and adolescent obesity. *Pediatrics*. 2003;111:e221-e226.

162. Malcolm JC, Lawson ML, Gaboury I, et al. Glucose tolerance of offspring of mother with gestational diabetes mellitus in a low-risk population. *Diabet Med.* 2006;23:565-570.

163. Dabelea D, Knowler WC, Pettitt DJ. Effect of diabetes in pregnancy on offspring: follow-up research in the Pima Indians. *J Matern Fetal Med.* 2000;9:83-88.

164. Plagemann A, Harder T, Franke K, et al. Long-term impact of neonatal breast-feeding on body weight and glucose tolerance in children of diabetic mothers. *Diabetes Care*. 2002;25:16-22.

165. MacNeill S, Dodds L, Hamilton DC, et al. Rates and risk factors for recurrence of gestational diabetes. *Diabetes Care.* 2001;24:659-662.

166. Gaudier FL, Hauth JC, Poist M, et al. Recurrence of gestational diabetes mellitus. *Obstet Gynecol.* 1992;80:755-758.

Diabetes in the Elderly

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee
The initial draft of this chapter was prepared by Graydon Meneilly MD FRCPC and Daniel Tessier MD MSc

DIABETES IN SPECIAL POPULATIONS

KEY MESSAGES

- Diabetes in the elderly is metabolically distinct from and the approach to therapy should be different than in people <60 years of age.

- Sulfonylureas should be used with caution because the risk of hypoglycemia increases exponentially with age.

- In elderly people, the use of premixed insulins as an alternative to mixing insulins minimizes dose errors.

INTRODUCTION

The definition of "elderly" varies, with some studies defining the elderly population as ≥60 years of age. Administrative guidelines frequently classify people >65 years of age as elderly. Although there is no uniformly agreed-upon definition of elderly, it is generally accepted that this is a concept that reflects an age continuum starting sometime after age 60 and is characterized by a slow, progressive frailty that continues until the end of life (1).

PREVENTION OF DIABETES

Lifestyle interventions are effective in the prevention of diabetes in elderly people at high risk for the development of the disease (2,3). Acarbose (4) and rosiglitazone (5) are also effective in the prevention of diabetes in elderly people at high risk, but metformin is not (3).

MANAGEMENT

Glycemic control

As interdisciplinary interventions have been shown to improve glycemic control in elderly individuals with diabetes, these people should be referred to a diabetes healthcare team (6,7). The same glycemic targets apply to otherwise healthy elderly as to younger people with diabetes (8-18). In people with multiple comorbidities, a high level of functional dependency and limited life expectancy, the goal should be less stringent, and clinicians should try to avoid symptoms of hyperglycemia and prevent hypoglycemia.

Nutrition and physical activity

Nutrition education programs can improve metabolic control in ambulatory older people with diabetes (19). Physical training programs can be successfully implemented in older people with diabetes, although comorbid conditions may prevent aerobic physical training in many patients, and increased activity levels may be difficult to sustain. While the effects of aerobic exercise programs on glucose and lipid metabolism are inconsistent (20-23), resistance training has been shown to result in modest improvements in glycemic control, as well as improvements in strength, body composition and mobility (24-28). However, it appears difficult to maintain these changes outside of a supervised setting (29).

Oral antihyperglycemic agents

In lean elderly people with type 2 diabetes, the principal metabolic defect is impairment in glucose-induced insulin secretion (30). Therefore, initial therapy for these individuals should involve agents that stimulate insulin secretion. In obese elderly people with type 2 diabetes, the principal metabolic defect is resistance to insulin-mediated glucose disposal, with insulin secretion being relatively preserved (31-33). Initial therapy for obese older people with diabetes should involve agents that improve insulin resistance.

Alpha-glucosidase inhibitors are modestly effective in older people with diabetes, but a substantial percentage of individuals cannot tolerate them because of gastrointestinal side effects (34-38).

Thiazolidinediones are effective agents, but are associated with an increased incidence of edema and congestive heart failure (CHF) in older people and should be used with caution in individuals with cardiovascular disease (CVD) (39-43). When used as monotherapy, they are less likely to fail than metformin or glyburide (43).

Sulfonylureas should be used with caution because the risk of hypoglycemia increases exponentially with age (44) and appears to be higher with glyburide (45,46). Gliclazide and glimepiride are preferred over glyburide in the elderly because they are associated with a lower frequency of hypoglycemic and CV events (47-49). A long-acting formulation of gliclazide resulted in equivalent glycemic control and the same frequency of hypoglycemic events as regular gliclazide in the elderly (50), and appears to result in a lower frequency of hypoglycemic events than glimepiride (51).

Meglitinides (repaglinide and nateglinide) are associated with a lower frequency of hypoglycemia in the elderly compared to glyburide (52,53), and would be preferred in individuals with irregular eating habits.

Insulin therapy

Insulin regimens in the elderly should be individualized and selected to promote patient safety. In elderly people, the use of premixed insulins as an alternative to mixing insulins (54) and prefilled insulin pens as an alternative to conventional syringes (55,56) minimizes dose errors and may improve glycemic control. Rapid-acting insulin analogue mixtures can be used and be administered after meals (57-59), although recent data suggest that the kinetics of regular and rapid-acting insulin are similar in the elderly (60). Multiple daily injections (MDI) may be associated with greater improvements in glycemic control, health status and mood than twice-daily injections of long-acting insulin (61). In older people with poorly controlled type 2 diabetes requiring insulin, both continuous subcutaneous insulin infusion (CSII) and MDI can result in excellent glycemic control, with good safety and patient satisfaction (62). One study demonstrated equivalent glycemic control in older people treated with either twice-daily insulin injections or a combination of a single injection of NPH insulin with an oral antihyperglycemic agent (63). Another study demonstrated that once-daily glargine with continuation of an oral antihyperglycemic agent resulted in better glycemic control and a reduced rate of hypoglycemia when compared to twice-daily injections of 30/70 insulin (64).

Prevention and treatment of complications

Hypertension

Treatment of isolated systolic hypertension or combined systolic and diastolic hypertension in elderly people with diabetes is associated with a significant reduction in CV morbidity and mortality (65-68). Treatment of isolated systolic hypertension may also preserve renal function in elderly people with diabetes (69).

Several different classes of antihypertensive agents have been shown to be effective in reducing the risk of CV events and end-stage renal disease, including thiazide-like diuretics, long-acting calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists (65-75). Any of these agents is a reasonable first choice (70-72), although the calcium channel blocker amlodipine may be associated with an increased risk of CHF (72). Cardioselective beta blockers and alpha-adrenergic blockers are less likely to reduce CV risk than the above agents (70-74). ACE inhibitors may be particularly valuable for people with diabetes and ≥1 other CV risk factor (76,77).

Recent data suggest there has been a significant improvement in the last decade in the number of older people treated for hypertension, and therapies being used are more consistent with current clinical practice guidelines (78).

Dyslipidemia

The treatment of hypercholesterolemia with statins for both primary and secondary prevention of CV events has been shown in most, although not all, studies to significantly reduce CV morbidity and mortality in older people with diabetes (79-88). The data on the use of fibrates in this patient population are equivocal (89,90).

Erectile dysfunction

Type 5 phosphodiesterase inhibitors appear to be effective for the treatment of erectile dysfunction in carefully selected elderly people with diabetes (91-93).

DIABETES IN NURSING HOMES

Diabetes is often undiagnosed in nursing home patients (94-96), and individuals frequently have established macro- and microvascular complications (97,98). In observational studies, the degree of glycemic control varies between different centres (94,98). Undernutrition is a major problem in people with diabetes living in nursing homes (98).

There are very few intervention studies on diabetes in nursing homes. The short-term substitution of a regular diet

---

RECOMMENDATIONS

1. In elderly individuals with impaired glucose tolerance, a structured program of lifestyle modification that includes moderate weight loss and regular physical activity should be considered to reduce the risk of type 2 diabetes *[Grade A, Level 1A (2)]*.

2. Otherwise healthy elderly people with diabetes should be treated to achieve the same glycemic, blood pressure and lipid targets as younger people with diabetes *[Grade D, Consensus]*. In people with multiple comorbidities, a high level of functional dependency or limited life expectancy, the goals should be less stringent *[Grade D, Consensus]*.

3. Elderly people with diabetes living in the community should be referred for interdisciplinary interventions involving education and support *[Grade C, Level 3 (6,7,19)]*.

4. Aerobic exercise and/or resistance training may benefit elderly people with type 2 diabetes and should be recommended for those individuals in whom it is not contraindicated *[Grade B, Level 2 (20,23-25)]*.

5. In elderly people with type 2 diabetes, sulfonylureas should be used with caution because the risk of hypoglycemia increases exponentially with age *[Grade D, Level 4 (44)]*. In general, initial doses of sulfonylureas in the elderly should be half those used for younger people, and doses should be increased more slowly *[Grade D, Consensus]*. Gliclazide and gliclazide MR *[Grade B, Level 2 (48,51)]* and glimepiride *[Grade C, Level 3 (49)]* are the preferred sulfonylureas, as they are associated with a reduced frequency of hypoglycemic events. Meglitinides (repaglinide and nateglinide) should be considered in patients with irregular eating habits *[Grade D, Consensus]*.

6. In elderly people, the use of premixed insulins and prefilled insulin pens as alternatives to mixing insulins should be considered to reduce dose errors, and to potentially improve glycemic control *[Grade B, Level 2 (54-56)]*.

or a standard nutritional formula for a "diabetic diet" or a diabetic nutritional formula did not modify the level of glycemic control (99-101). For selected nursing home residents with type 2 diabetes, substitution of regular insulin by multiple injections with lispro insulin may improve glycemic control and glycated hemoglobin (A1C) levels with a reduced number of hypoglycemic episodes (102).

Screening for diabetes may be warranted in selected individuals. In the absence of positive intervention studies on morbidity or mortality in this population, the decision about screening for diabetes should be made on an individual basis.

OTHER RELEVANT GUIDELINES

Screening for Type 1 and Type 2 Diabetes, p. S14
Prevention of Diabetes, p. S17
Organization of Diabetes Care, p. S20
Self-management Education, p. S25
Targets for Glycemic Control, p. S29
Insulin Therapy in Type 1 Diabetes, p. S46
Pharmacologic Management of Type 2 Diabetes, p. S53
Hypoglycemia, p. S62
Screening for the Presence of Coronary Artery Disease, p. S99
Dyslipidemia, p. S107
Treatment of Hypertension, p. S115
Erectile Dysfunction, p. S147

REFERENCES

1. Tessier D, Meneilly GS. Diabetes management in the elderly. In: Gerstein HC, Haynes RB, eds. *Evidence-based Diabetes Care.* Hamilton, ON: BC Decker Inc.; 2001:370-379.

2. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med.* 2002;346:393-403.

3. Diabetes Prevention Program Research Group; Crandall J, Schade D, Ma Y, et al. The influence of age on the effects of lifestyle modification and metformin in prevention of diabetes. *J Gerontol A Biol Med Sci.* 2006;61:1075-1081.

4. Chiasson JL, Josse RG, Gomis R, et al; STOP-NIDDM Trial Research Group. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet.* 2002; 359:2072-2077.

5. DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators; Gerstein HC, Yusuf S, Bosch J, et al. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet.* 2006;368:1096-1105.

6. Kronsbein P, Jörgens V, Mühlhauser I, et al. Evaluation of a structured treatment and teaching programme on non-insulin-dependent diabetes. *Lancet.* 1988;2:1407-1411.

7. Wilson W, Pratt C. The impact of diabetes education and peer support upon weight and glycemic control of elderly persons with noninsulin dependent diabetes mellitus (NIDDM). *Am J Public Health.* 1987;77:634-635.

8. Kuusisto J, Mykkänen L, Pyörälä K, et al. Non-insulin-dependent diabetes and its metabolic control are important predictors of stroke in elderly subjects. *Stroke.* 1994;25:1157-1164.

9. Kuusisto J, Mykkänen L, Pyörälä K, et al. NIDDM and its metabolic control predict coronary heart disease in elderly subjects. *Diabetes.* 1994;43:960-967.

10. Nathan DM, Singer DE, Godine JE, et al. Retinopathy in older type II diabetics. Association with glucose control. *Diabetes.* 1986;35:797-801.

11. Morisaki N, Watanabe S, Kobayashi J, et al. Diabetic control and progression of retinopathy in elderly patients: five-year follow-up study. *J Am Geriatr Soc.* 1994;42:142-145.

12. Tanaka Y, Atsumi Y, Matsuoka K, et al. Role of glycemic control and blood pressure in the development and progression of nephropathy in elderly Japanese NIDDM patients. *Diabetes Care.* 1998;21:116-120.

13. Stolk RP, Vingerling JR, de Jong PT, et al. Retinopathy, glucose, and insulin in an elderly population. The Rotterdam Study. *Diabetes.* 1995;44:11-15.

14. Beks PJ, Mackaay AJ, de Neeling JN, et al. Peripheral arterial disease in relation to glycaemic level in an elderly Caucasian population: the Hoorn study. *Diabetologia.* 1995;38:86-96.

15. The DECODE study group, on behalf of the European Diabetes Epidemiology Group. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. *Lancet.* 1999;354:617-621.

16. The DECODE study group, on behalf of the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. *Arch Intern Med.* 2001;161:397-405.

17. Kanaya AM, Grady D, Barrett-Connor E. Explaining the sex difference in coronary heart disease mortality among patients with type 2 diabetes mellitus: a meta-analysis. *Arch Intern Med.* 2002;162:1737-1745.

18. Barzilay JI, Spiekerman CF, Wahl PW, et al. Cardiovascular disease in older adults with glucose disorders: comparison of American Diabetes Association criteria for diabetes mellitus with WHO criteria. *Lancet.* 1999;354:622-625.

19. Miller CK, Edwards L, Kissling G, et al. Nutrition education improves metabolic outcomes among older adults with diabetes mellitus: results from a randomized controlled trial. *Prev Med.* 2002;34:252-259.

20. Tessier D, Ménard J, Fülöp T, et al. Effects of aerobic physical exercise in the elderly with type 2 diabetes mellitus. *Arch Gerontol Geriatr.* 2000;31:121-132.

21. Skarfors ET, Wegener TA, Lithell H, et al. Physical training as treatment for type 2 (non-insulin-dependent) diabetes in elderly men. A feasibility study over 2 years. *Diabetologia.* 1987; 30:930-933.

22. Ligtenberg PC, Godaert GLR, Hillenaar EF, et al. Influence of a physical training program on psychological well-being in elderly type 2 diabetes patients. Psychological well-being, physical training, and type 2 diabetes [letter]. *Diabetes Care.* 1998; 21:2196-2197.

23. Ligtenberg PC, Hoekstra JBL, Bol E, et al. Effects of physical training on metabolic control in elderly type 2 diabetes mellitus patients. *Clin Sci (Lond)*. 1997;93:127-135.

24. Dunstan DW, Daly RM, Owen N, et al. High-intensity resistance training improves glycemic control in older patients with type 2 diabetes. *Diabetes Care*. 2002;25:1729-1736.

25. Castaneda C, Layne JE, Munoz-Orians L, et al. A randomized controlled trial of resistance exercise training to improve glycemic control in older adults with type 2 diabetes. *Diabetes Care*. 2002;25:2335-2341.

26. Brandon LJ, Gaasch DA, Boyette LW, et al. Effects of long-term resistive training on mobility and strength in older adults with diabetes. *J Gerontol A Biol Sci Med Sci*. 2003;58:740-745.

27. Cuff DJ, Meneilly GS, Martin A, et al. Effective exercise modality to reduce insulin resistance in women with type 2 diabetes. *Diabetes Care*. 2003;26:2977-2982.

28. Ibanez J, Izquierdo M, Argüelles I, et al. Twice-weekly progressive resistance training decreases abdominal fat and improves insulin sensitivity in older men with type 2 diabetes. *Diabetes Care*. 2005;28:662-667.

29. Dunstan DW, Daly RM, Owen N, et al. Home-based resistance training is not sufficient to maintain improved glycemic control following supervised training in older individuals with type 2 diabetes. *Diabetes Care*. 2005;28:3-9.

30. Meneilly GS, Elahi D. Metabolic alterations in middle-aged and elderly lean patients with type 2 diabetes. *Diabetes Care*. 2005; 28:1498-1499.

31. Meneilly GS, Elliott T. Metabolic alterations in middle-aged and elderly obese patients with type 2 diabetes. *Diabetes Care*. 1999;22:112-118.

32. Meneilly GS, Elliott T, Tessier D, et al. NIDDM in the elderly. *Diabetes Care*. 1996;19:1320-1325.

33. Arner P, Pollare T, Lithell H. Different aetiologies of type 2 (non-insulin-dependent) diabetes mellitus in obese and non-obese subjects. *Diabetologia*. 1991;34:483-487.

34. Spengler M, Cagatay M. Evaluation of efficacy and tolerability of acarbose by postmarketing surveillance. *Diabetes und Stoffwechsel*. 1992;1:218-222.

35. Johnston PS, Lebovitz HE, Coniff RF, et al. Advantages of alpha-glucosidase inhibition as monotherapy in elderly type 2 diabetic patients. *J Clin Endocrinol Metab*. 1998;83:1515-1522.

36. Orimo H, Akiguchi I, Shiraki M. Usefulness of acarbose in the management of non-insulin-dependent diabetes in the aged. In: Creutzfeldt W, ed. *Acarbose*. New York, NY: Excerpta Medica; 1982:348-352.

37. Johansen K. Acarbose treatment of sulfonylurea-treated non-insulin dependent diabetics. A double-blind cross-over comparison of an alpha-glucosidase inhibitor with metformin. *Diabete Metab*. 1984;10:219-223.

38. Josse RG, Chiasson JL, Ryan EA, et al. Acarbose in the treatment of elderly patients with type 2 diabetes. *Diabetes Res Clin Pract*. 2003;59:37-42.

39. Delea TE, Edelsberg JS, Hagiwara M, et al. Use of thiazolidinediones and risk of heart failure in people with type 2 diabetes: a retrospective cohort study. *Diabetes Care*. 2003;26: 2983-2989.

40. Chilcott J, Tappenden P, Jones ML, et al. A systematic review of the clinical effectiveness of pioglitazone in the treatment of type 2 diabetes mellitus. *Clin Ther*. 2001;23:1792-1823.

41. Rajagopalan R, Perez A, Ye Z, et al. Pioglitazone is effective therapy for elderly patients with type 2 diabetes mellitus. *Drugs Aging*. 2004;21:259-271.

42. Kreider M, Heise M. Rosiglitazone in the management of older patients with type 2 diabetes mellitus. *Int J Clin Pract*. 2002;56:538-541.

43. Kahn SE, Haffner SM, Heise MA, et al; ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med*. 2006;355:2427-2443.

44. Asplund K, Wiholm BE, Lithner F. Glibenclamide-associated hypoglycaemia: a report on 57 cases. *Diabetologia*. 1983;24: 412-417.

45. Shorr RI, Ray WA, Daugherty JR, et al. Individual sulfonylureas and serious hypoglycemia in older people. *J Am Geriatr Soc*. 1996; 44:751-755.

46. Shorr RI, Ray WA, Daugherty JR, et al. Incidence and risk factors for serious hypoglycemia in older persons using insulin or sulfonylureas. *Arch Intern Med*. 1997;157:1681-1686.

47. Johnsen SP, Monster TB, Olsen ML, et al. Risk and short-term prognosis of myocardial infarction among users of antidiabetic drugs. *Am J Ther*. 2006;13:134-140.

48. Tessier D, Dawson K, Tétrault JP, et al. Glibenclamide vs gliclazide in type 2 diabetes of the elderly. *Diabet Med*. 1994; 11:974-980.

49. Holstein A, Plaschke A, Egberts EH. Lower incidence of severe hypoglycaemia in patients with type 2 diabetes treated with glimepiride versus glibenclamide. *Diabetes Metab Res Rev*. 2001; 17:467-473.

50. DiamicronMR Study Group, Drouin P. DiamicronMR once daily is effective and well tolerated in type 2 diabetes: a double-blind, randomized, multinational study. *J Diabetes Complications*. 2000;14:185-191.

51. Schernthaner G, Grimaldi A, Di Mario U, et al. GUIDE study: double-blind comparison of once-daily gliclazide MR and glimepiride in type 2 diabetic patients. *Eur J Clin Invest*. 2004; 34:535-542.

52. Del Prato S, Heine RJ, Keilson L, et al. Treatment of patients over 64 years of age with type 2 diabetes: experience from nateglinide pooled database retrospective analysis. *Diabetes Care*. 2003;26:2075-2080.

53. Papa G, Fedele V, Rizzo MR, et al. Safety of type 2 diabetes treatment with repaglinide compared with glibenclamide in elderly people: a randomized, open-label, two-period, cross-over trial. *Diabetes Care*. 2006;29:1918-1920.

54. Coscelli C, Calabrese G, Fedele D, et al. Use of premixed insulin among the elderly. Reduction of errors in patient preparation of mixtures. *Diabetes Care*. 1992;15:1628-1630.

55. Corsi A, Torre E, Coronel GA, et al. Pre-filled insulin pen in newly insulin-treated diabetic patients over 60 years old. *Diab*

Nutr Metab. 1997;10:78-81.

56. Coscelli C, Lostia S, Lunetta M, et al. Safety, efficacy, acceptability of a pre-filled insulin pen in diabetic patients over 60 years old. *Diabetes Res Clin Pract*. 1995;28:173-177.

57. Herz M, Sun B, Milicevic Z, et al. Comparative efficacy of preprandial or postprandial Humalog Mix75/25 versus glyburide in patients 60 to 80 years of age with type 2 diabetes mellitus. *Clin Ther*. 2002;24:73-86.

58. Warren ML, Conway MJ, Klaff LJ, et al. Postprandial versus preprandial dosing of biphasic insulin aspart in elderly type 2 diabetes patients. *Diabetes Res Clin Pract*. 2004;66:23-29.

59. Galic E, Vrtovec M, Bozikov V, et al. The impact of the timing of Humalog Mix25 injections on blood glucose fluctuations in the postprandial period in elderly patients with type 2 diabetes. *Med Sci Monit*. 2005;11:P187-P192.

60. Meneilly GS. A comparison of insulin aspart and regular insulin in elderly patients with type 2 diabetes. *Diabetes Obes Metab*. 2007;9:754-755.

61. Hendra TJ, Taylor CD. A randomised trial of insulin on well-being and carer strain in elderly type 2 diabetic subjects. *J Diabetes Complications*. 2004;18:148-154.

62. Herman WH, Ilag LL, Johnson SL, et al. A clinical trial of continuous subcutaneous insulin infusion versus multiple daily injections in older adults with type 2 diabetes. *Diabetes Care*. 2005;28:1568-1573.

63. Wolffenbuttel BH, Sels JP, Rondas-Colbers GJ, et al. Comparison of different insulin regimens in elderly patients with NIDDM. *Diabetes Care*. 1996;19:1326-1332.

64. Janka HU, Plewe G, Busch K. Combination of oral antidiabetic agents with basal insulin versus premixed insulin alone in randomized elderly patients with type 2 diabetes mellitus. *J Am Geriatr Soc*. 2007;55:182-188.

65. Curb JD, Pressel SL, Cutler JA, et al. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. Systolic Hypertension in the Elderly Program Cooperative Research Group. *JAMA*. 1996;276:1886-1892.

66. Wang JG, Staessen JA, Gong L, et al. Chinese trial on isolated systolic hypertension in the elderly. Systolic Hypertension in China (Syst-China) Collaborative Group. *Arch Intern Med*. 2000;160:211-220.

67. Tuomilehto J, Rastenyte D, Birkenhäger WH, et al. Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *N Engl J Med*. 1999;340:677-684.

68. Lindholm LH, Hansson L, Ekbom T, et al. Comparison of antihypertensive treatments in preventing cardiovascular events in elderly diabetic patients: results from the Swedish Trial in Old Patients with Hypertension-2. STOP Hypertension-2 Study Group. *J Hypertens*. 2000;18:1671-1675.

69. Voyaki SM, Staessen JA, Thijs L, et al; Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Follow-up of renal function in treated and untreated older patients with isolated systolic hypertension. *J Hypertens*. 2001;19:511-519.

70. Barzilay JI, Davis BR, Bettencourt J, et al; ALLHAT Collaborative Research Group. Cardiovascular outcomes using doxazosin vs. chlorthalidone for the treatment of hypertension in older adults with and without glucose disorders: a report from the ALLHAT study. *J Clin Hypertens (Greenwich)*. 2004; 6:116-125.

71. Rahman M, Pressel S, Davis BR, et al. Renal outcomes in high-risk hypertensive patients treated with an angiotensin-converting enzyme inhibitor or a calcium channel blocker vs a diuretic: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med*. 2005;165:936-946.

72. Whelton PK, Barzilay J, Cushman WC, et al; ALLHAT Collaborative Research Group. Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med*. 2005;165:1401-1409.

73. Kjeldsen SE, Dahlöf B, Devereux RB, et al; LIFE (Losartan Intervention for Endpoint Reduction) Study Group. Effects of losartan on cardiovascular morbidity and mortality in patients with isolated systolic hypertension and left ventricular hypertrophy: a Losartan Intervention for Endpoint Reduction (LIFE) substudy. *JAMA*. 2002;288:1491-1498.

74. Dahlöf B, Sever PS, Poulter NR, et al; ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet*. 2005;366:895-906.

75. Ferrari R; Perindopril and Remodeling in Elderly with Acute Myocardial Infarction Investigators. Effects of angiotensin-converting enzyme inhibition with perindopril on left ventricular remodeling and clinical outcome: results of the randomized Perindopril and Remodeling in Elderly with Acute Myocardial Infarction (PREAMI) Study. *Arch Intern Med*. 2006;166:659-666.

76. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet*. 2000;355:253-259.

77. Fox KM; EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet*. 2003;362:782-788.

78. McAlister FA, Campbell NR, Duong-Hua M, et al. Antihypertensive medication prescribing in 27,822 elderly Canadians with diabetes over the past decade. *Diabetes Care*. 2006;29:836-841.

79. Baigent C, Keech A, Kearney PM, et al; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data

from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005;366:1267-1278.

80. Collins R, Armitage J, Parish S, et al; Heart Protection Study Collaborative Group. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. *Lancet*. 2004;363:757-767.

81. Collins R, Armitage J, Parish S, et al; Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet*. 2003; 361:2005-2016.

82. Heart Protection Study Collaborative Group. The effects of cholesterol lowering with simvastatin on cause-specific mortality and on cancer incidence in 20,536 high-risk people: a randomised placebo-controlled trial (ISRCTN48489393). *BMC Med*. 2005;3:6.

83. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *JAMA*. 1999;282:2340-2346.

84. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7-22.

85. Keech A, Colquhoun D, Best J, et al; LIPID Study Group. Secondary prevention of cardiovascular events with long-term pravastatin in patients with diabetes or impaired fasting glucose: results from the LIPID trial. *Diabetes Care*. 2003;26: 2713-2721.

86. Neil HA, DeMicco DA, Luo D, et al; CARDS Study Investigators. Analysis of efficacy and safety in patients aged 65-75 years at randomization: Collaborative Atorvastatin Diabetes Study (CARDS). *Diabetes Care*. 2006;29:2378-2384.

87. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA*. 2002;288:2998-3007.

88. Sever PS, Poulter NR, Dahlöf B, et al. Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial – lipid-lowering arm (ASCOT-LLA). *Diabetes Care*. 2005;28:1151-1157.

89. Rubins HB, Robins SJ, Collins D, et al. Diabetes, plasma insulin, and cardiovascular disease: subgroup analysis from the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). *Arch Intern Med*. 2002;162:2597-2604.

90. Keech A, Simes RJ, Barter P, et al; FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet*. 2005; 366:1849-1861.

91. Wagner G, Montorsi F, Auerbach S, et al. Sildenafil citrate (VIAGRA) improves erectile function in elderly patients with erectile dysfunction: a subgroup analysis. *J Gerontol A Biol Sci Med Sci*. 2001;56A:M113-M119.

92. Sáenz de Tejada I, Anglin G, Knight JR, et al. Effects of tadalafil on erectile dysfunction in men with diabetes. *Diabetes Care*. 2002;25:2159-2164.

93. Goldstein I, Young JM, Fischer J, et al; Vardenafil Diabetes Study Group. Vardenafil, a new phosphodiesterase type 5 inhibitor, in the treatment of erectile dysfunction in men with diabetes: a multicenter double-blind placebo-controlled fixed-dose study. *Diabetes Care*. 2003;26:777-783.

94. Hauner H, Kurnaz AA, Haastert B, et al. Undiagnosed diabetes mellitus and metabolic control assessed by HbA(1c) among residents of nursing homes. *Exp Clin Endocrinol Diabetes*. 2001;109:326-329.

95. Sinclair AJ, Gadsby R, Penfold S, et al. Prevalence of diabetes in care home residents. *Diabetes Care*. 2001;24:1066-1068.

96. Aspray TJ, Nesbit K, Cassidy TP, et al. Diabetes in British nursing and residential homes: a pragmatic screening study. *Diabetes Care*. 2006;29:707-708.

97. Wolffenbuttel BH, van Vliet S, Knols A, et al. Clinical characteristics and management of diabetic patients residing in a nursing home. *Diabetes Res Clin Pract*. 1991;13:199-206.

98. Mooradian AD, Osterweil D, Petrasek D, et al. Diabetes mellitus in elderly nursing home patients. A survey of clinical characteristics and management. *J Am Geriatr Soc*. 1988;36:391-396.

99. Coulston AM, Mandelbaum D, Reaven GM. Dietary management of nursing home residents with non-insulin-dependent diabetes mellitus. *Am J Clin Nutr*. 1990;51:67-71.

100. Tariq SH, Karcic E, Thomas DR, et al. The use of a no-concentrated-sweets diet in the management of type 2 diabetes in nursing homes. *J Am Diet Assoc*. 2001;101:1463-1466.

101. Levinson Y, Epstein A, Adler B, et al. Successful use of a sucrose-containing enteral formula in diabetic nursing home elderly. *Diabetes Care*. 2006;29:698-700.

102. Velussi M. Lispro insulin treatment in comparison with regular human insulin in type 2 diabetic patients living in nursing homes. *Diabetes Nutr Metab*. 2002;15:96-100.

Type 2 Diabetes in Aboriginal Peoples

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by David Dannenbaum MD CCFP, Keith G. Dawson MD PhD FRCPC, Stewart B. Harris MD MPH FCPC FACPM and Jay Wortman MD

KEY MESSAGES

- Efforts to prevent diabetes should focus on all diabetes risk factors, including pregravid obesity, to reduce gestational diabetes mellitus, macrosomia and diabetes risk in offspring; promotion of breast-feeding; and prevention of childhood, adolescent and adult obesity.

- Routine medical care in Aboriginal peoples should include identification of modifiable risk factors (e.g. lack of physical activity, unhealthy eating habits, obesity resulting in elevated waist circumference and/or body mass index) in order to identify higher-risk individuals who would benefit from diabetes prevention strategies and counselling.

- Screening for diabetes in adults should be considered every 1 to 2 years in Aboriginal individuals with ≥1 additional risk factor(s). Screening every 2 years should also be considered from age 10 or established puberty in Aboriginal children with ≥1 additional risk factor(s).

- Treatment of diabetes in Aboriginal peoples should follow current clinical practice guidelines using Aboriginal-specific community diabetes management programs developed and delivered in partnership with the target communities.

INTRODUCTION

Canadian Aboriginal peoples are a heterogeneous population comprised of individuals of First Nations, Inuit and Métis heritage living in a range of environments from large cities to small, isolated communities. As in other countries, type 2 diabetes has reached epidemic proportions among Aboriginal peoples in Canada, with the national age-adjusted prevalence 3 to 5 times higher than that of the general population (1) and as high as 26% in individual communities (2). Aboriginal peoples are diagnosed with type 2 diabetes at a much younger age (1), with high rates of diabetes in children and adolescents (3). As well, Aboriginal women are at more than twice the risk of gestational diabetes mellitus (GDM) compared to non-Aboriginal women (4) and have high rates of pre-existing type 2 diabetes in pregnancy (5). Prediabetes and metabolic syndrome are also more common in these populations (6).

The high rate of type 2 diabetes is associated with increased rates of cardiovascular disease (CVD), peripheral arterial disease, neuropathy and renal disease in this population (7). In Manitoba, it is estimated that between the years 1996 and 2016, there will be a 10-fold increase in CVD, a 10-fold increase in lower-extremity amputations, a 10-fold increase in dialysis starts and a 5-fold increase in blindness among Aboriginal peoples (8).

High rates of diabetes are likely the result of the interaction of genetic susceptibility and local genetic mutations with numerous social stressors and lifestyle factors (9-11). Decreased rates of physical activity and the replacement of traditional foods with highly refined foods have resulted in high rates of obesity and diabetes risk factors in children (12) and adults (13).

Indicators of insulin resistance and hyperinsulinemia (e.g. elevated body mass index [BMI] and waist circumference [WC], and metabolic syndrome) are strong predictors of risk for developing type 2 diabetes in Aboriginal peoples (14-16). Other predisposing factors include positive family history and maternal pregnancy complicated by frank diabetes or GDM (which lead to increased incidence of diabetes in the offspring) (17,18). As well, pregravid maternal obesity in Aboriginal populations is associated with increased risk of GDM and infant macrosomia (5). Rates of macrosomia continue to rise in northern communities (19), and infant macrosomia has been associated with increased rates of childhood obesity (20), and hence adolescent and adult obesity.

SCREENING

Due to the high prevalence of risk factors for diabetes in specific Aboriginal groups (6,12,13,20), routine medical care in Aboriginal peoples of all ages (starting in early childhood) should include identification of these modifiable risk factors (e.g. obesity, elevated WC or BMI, lack of physical activity, unhealthy eating habits), impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), to identify higher-risk individuals who would benefit from diabetes prevention strategies and individualized counselling. While WC is a more reliable predictor than BMI for development of diabetes (14), the standard cut-offs for BMI and WC should be used in Aboriginal populations.

As part of routine medical care provided to Aboriginal people, screening for diabetes with a fasting plasma glucose test should be considered every 1 to 2 years in individuals with ≥1 additional risk factor(s). Screening every 2 years should also be considered from age 10 or established puberty

(21) in Aboriginal children with ≥1 additional risk factor(s) (e.g. obesity, family history of type 2 diabetes, exposure to diabetes in utero, acanthosis nigricans, polycystic ovary syndrome [PCOS], hypertension, dyslipidemia and use of antipsychotic medications/atypical neuroleptics). An oral glucose tolerance test (OGTT) should be done annually in children who are very obese (BMI ≥99.5 percentile) (see "Type 2 Diabetes in Children and Adolescents," p. S162).

Those individuals with normal results but with diabetes risk factors (in addition to Aboriginal heritage) should receive post-test counselling on promotion of healthy lifestyles for diabetes prevention. Annual OGTT testing in individuals with prediabetes (IFG and/or IGT) or PCOS should be encouraged, as 20 to 50% of high-risk individuals with IFG may have a 2-hour plasma glucose ≥11.1 mmol/L (22).

PRIMARY PREVENTION

Efforts to prevent diabetes should focus on all diabetes risk factors, including pregravid obesity to reduce GDM, macrosomia and diabetes risk in offspring; promotion of breast-feeding; and prevention of childhood, adolescent and adult obesity.

Primary prevention of diabetes requires collaboration between community leaders, healthcare professionals and funding agencies. Several initiatives with community-researcher partnerships are ongoing, and include programs to mobilize entire communities, promote environmental changes and prevent GDM (23-27). These partnerships share the common values of incorporating traditions and local culture to promote empowerment, increased physical activity, balanced eating and healthy body weights. Such programs reinforce to individuals and families that they have some control over their risk for diabetes. This can impact positively on the approach to self-care and to the philosophy around family or community activities, all of which affect family members who already have the disease or are at risk for diabetes. However, there remains a lack of published evidence that these interventions result in a reduction in the incidence of diabetes in the target communities (27).

Prevention of childhood obesity through moderate interventions starting in infancy has been shown to be effective (28). In Zuni First Nations children, an educational component targeting decreased consumption of sugared beverages, knowledge of diabetes risk factors and a youth-oriented fitness centre significantly decreased insulin resistance (29). These types of interventions aimed at decreasing childhood obesity, as well as efforts to promote breast-feeding in the first year of life (30), may help to reduce the risk for diabetes. As well, strategies aimed at the prevention of maternal obesity prior to first conception or subsequent pregnancy may be important tools to decrease the incidence of GDM and type 2 diabetes in pregnancy, thereby potentially decreasing the incidence of diabetes in subsequent generations of Aboriginal Canadians (5,18,26).

MANAGEMENT

Treatment of diabetes in Aboriginal peoples should follow current clinical practice guidelines, with Aboriginal-specific community diabetes management programs developed and delivered in partnership with the target communities, reflecting a population health approach. Ideally, multidisciplinary teams should include community members with local knowledge and expertise. Diabetes education programs should consider various learning styles, incorporate local traditions and culture, promote traditional activities and foods (provided they are safe, acceptable and accessible) and, ideally, be taught in the language of the individual.

In Aboriginal communities, much of the responsibility for diabetes care falls to community health representatives (local lay healthcare providers), who are often already overburdened. These individuals are able to provide better care when they have appropriate additional training and can focus on diabetes. A number of communities have provided comprehensive diabetes training to local lay people, who can then combine their knowledge of diabetes with sensitivity to the culture and issues in their community.

Weight loss associated with a temporary return to a traditional hunter-gatherer lifestyle was shown to significantly improve glycemic control among adult male volunteers in an Australian Aboriginal community (31). A number of recent American studies have demonstrated that carbohydrate-restricted diets, which resemble traditional Aboriginal diets, have a salutary effect on diabetes and metabolic syndrome (32-37). A focus on dietary change to a more carbohydrate-restricted diet may be warranted in both the prevention and treatment of diabetes in Aboriginal populations.

Comprehensive management of diabetes in small remote communities remains difficult, due to discontinuities in staffing, lack of work-practice support and individuals' acceptance of services (38). In some communities, mobile teams of nurses, technicians and in some cases physicians assess and treat community members with diagnosed diabetes (39). Use of a nurse-directed hypertension treatment protocol has been shown to be effective in Aboriginal peoples in Northern Canada (40). Use of a nurse case manager in large urban centres (caring for a mean of 365 Aboriginal patients) was shown to be somewhat more effective than usual care when assessing diabetes care on multiple parameters, and may be an effective strategy for remote and poorly serviced communities (41). Retinal photography has been shown to be another effective strategy for screening for diabetic retinopathy in remote communities (42). Due to the heterogeneous settings of different high-risk groups, each community or region must determine the most cost-effective strategy to provide comprehensive diabetes care to best suit their reality.

In the United States, federally funded on-reserve programs include diabetes registries, use of flow charts, annual chart audits with continuous quality assurance, full-time

dedicated diabetes clinical staff (e.g. nurses) and funding for community initiatives. These programs have conclusively demonstrated improvements in conventional diabetes measures (e.g. decreased glycated hemoglobin, improved lipid profiles, reductions in blood pressure) (43). A similar national program should be established in Canada for on- and off-reserve Aboriginal communities.

RECOMMENDATIONS

1. Starting in early childhood, Aboriginal people should be routinely assessed for modifiable risk factors of diabetes (e.g. obesity, elevated WC, lack of physical activity, unhealthy eating habits), IFG or IGT in order to identify higher-risk individuals who would benefit from diabetes prevention strategies [Grade D, Consensus].

2. Screening for diabetes in Aboriginal children and adults should follow guidelines for high-risk populations (i.e. earlier and at more frequent intervals depending on presence of additional risk factors) [Grade D, Consensus].

3. Culturally appropriate primary prevention programs for children and adults should be initiated in and by Aboriginal communities to increase awareness of diabetes, increase physical activity, improve eating habits and achieve healthy body weights, and to promote an environment supportive of a healthy lifestyle [Grade D, Consensus].

4. Management of prediabetes and diabetes in Aboriginal people should follow the same clinical practice guidelines as those for the general population with recognition of, respect for and sensitivity to the unique language, cultural and geographic issues as they relate to diabetes care and education in Aboriginal communities across Canada [Grade D, Consensus].

5. Aboriginal peoples in Canada should have access in their communities to a diabetes management program that would include the hiring of diabetes healthcare professionals, the establishment of diabetes registries, and ongoing quality assurance programs [Grade D, Consensus].

OTHER RELEVANT GUIDELINES
Screening for Type 1 and Type 2 Diabetes, p. S14
Prevention of Diabetes, p. S17
Management of Obesity in Diabetes, p. S77
Type 2 Diabetes in Children and Adolescents, p. S162

RELATED WEBSITES
Aboriginal Diabetes Initiative, First Nations and Inuit Health Branch. Available at: http://www.hc-sc.gc.ca/fnihb/cp/adi/index.htm. Accessed September 1, 2008.
National Aboriginal Diabetes Association. Available at: http://www.nada.ca. Accessed September 1, 2008.

REFERENCES
1. Green C, Blanchard J, Young TK, et al. The epidemiology of diabetes in the Manitoba-registered First Nation population: current patterns and comparative trends. Diabetes Care. 2003; 26:1993-1998.
2. Harris SB, Gittelsohn J, Hanley A, et al. The prevalence of NIDDM and associated risk factors in Native Canadians. Diabetes Care. 1997;20:185-187.
3. Fagot-Campagna A, Pettitt DJ, Engelgau MM, et al. Type 2 diabetes among North American children and adolescents: an epidemiologic review and a public health perspective. J Pediatr. 2000;136:664-672.
4. Dyck R, Klomp H, Tan LK, et al. A comparison of rates, risk factors, and outcomes of gestational diabetes between aboriginal and non-aboriginal women in the Saskatoon health district. Diabetes Care. 2002;25:487-493.
5. Brennand EA, Dannenbaum D, Willows ND. Pregnancy outcomes of First Nation women in relation to pregravid weight and pregnancy weight gain. J Obstet Gynaecol Can. 2005;27: 936-944.
6. Pollex RL, Hanley JG, Zinman B, et al. Synergism between mutant HNF1A and the metabolic syndrome in Oji Cree Type 2 diabetes. Diabet Med. 2005;22;1510-1515.
7. Hanley AJ, Harris SB, Mamakeesick M, et al. Complications of type 2 diabetes among Aboriginal Canadians: prevalence and associated risk factors. Diabetes Care. 2005;28:2054-2057.
8. Diabetes in Canada. 2nd ed. Ottawa, ON: Centre for Chronic Disease Prevention and Control, Population and Public Health Branch, Health Canada; 2002.
9. Dowse G, Zimmet P. The thrifty genotype in non-insulin dependent diabetes. BMJ. 1993;306:532-533.
10. Hegele RA, Cao H, Harris SB, et al. The hepatocyte nuclear factor-1alpha G319S. A private mutation in Oji-Cree associated with type 2 diabetes. Diabetes Care. 1999;22:524.
11. Valencia ME, Weil EJ, Nelson RG, et al. Impact of lifestyle on prevalence of kidney disease in Pima Indians in Mexico and the United States. Kidney Int Suppl. 2005:97:S141-S144.
12. Hanley AJ, Harris SB, Gittelsohn J, et al. Overweight among children and adolescents in a Native Canadian community: prevalence and associated factors. Am J Clin Nutr. 2000;71: 693-700.
13. Young TK. Obesity among Aboriginal peoples in North America: epidemiological patterns, risk factors and metabolic consequences. In: Angel A, Anderson H, Bouchard C, et al, eds. Progress in Obesity Research. London, UK: John Libby; 1996:337-342.
14. Wang Z, Hoy WE. Body size measurements as predictors of type 2 diabetes in Aboriginal people. Int J Obes Relat Metab Disord. 2004;28:1580-1584.
15. Hanson RL, Imperatore G, Bennett PH, et al. Components of the "metabolic syndrome" and incidence of type 2 diabetes. Diabetes. 2002;51:3120-3127.
16. Resnick HE, Jones K, Ruotolo G, et al. Insulin resistance, the metabolic syndrome, and risk of incident cardiovascular disease in nondiabetic American Indians: the Strong Heart Study. Diabetes Care. 2003;26:861-867.

17. Franks PW, Looker HC, Kobes S, et al. Gestational glucose tolerance and risk of type 2 diabetes in young Pima Indian offspring. *Diabetes.* 2006;55:460-465.

18. Dean H, Flett B. Natural history of type 2 diabetes diagnosed in childhood: long-term follow-up in young adult years [abstract]. *Diabetes.* 2002;51(suppl 2):A24. Abstract 99-OR.

19. Dyck RF, Tan L. Differences in high birthweight rates between Northern and Southern Saskatchewan: implications for Aboriginal peoples. *Chronic Dis Canada.* 1995. Available at: http://www.phac-aspc.gc.ca/publicat/cdic-mcc/16-3/a_e.html. Accessed September 1, 2008.

20. Whitaker RC, Wright JA, Pepe MS, et al. Predicting obesity in young adulthood from children and parental obesity. *N Engl J Med.* 1997;337:899-873.

21. Gahagan S, Silverstein J; American Academy of Pediatrics Committee on Native American Child Health. Prevention and treatment of type 2 diabetes mellitus in children, with special emphasis on American Indian and Alaska Native children. *Pediatrics.* 2003;112:328-347.

22. Perry RC, Shankar RR, Fineberg N, et al. HbA1c measurement improved the detection of type 2 diabetes in high-risk individuals with nondiagnostic levels of fasting plasma glucose. *Diabetes Care.* 2001;24:465-471.

23. Macaulay AC, Paradis G, Potvin L, et al. The Kahnawake Schools Diabetes Prevention Project: intervention, evaluation, and baseline results of a diabetes primary prevention program with a native community in Canada. *Prev Med.* 1997;26:779-790.

24. Macaulay AC, Harris SB, Lévesque L, et al. Primary prevention of type 2 diabetes: a tale of 2 Aboriginal communities in Canada. *Can J Diabetes.* 2003;27:464-475.

25. Daniel M, Green LW, Marion SA, et al. Effectiveness of community-directed diabetes prevention and control in a rural Aboriginal population in British Columbia, Canada. *Soc Sci Med.* 1999;48:815-832.

26. Dyck RF, Sheppard MS, Cassidy H, et al. Preventing NIDDM among Aboriginal people: is exercise the answer? Description of a pilot project using exercise to prevent gestational diabetes. *Int J Circumpolar Health.* 1998;57(suppl 1):375-378.

27. Paradis G, Levesque L, Macaulay AC, et al. Impact of a diabetes prevention program on body size, physical activity, and diet among Kanien'kehá:ka (Mohawk) children 6 to 11 years old: 8-year results from the Kahnawake Schools Diabetes Prevention Project. *Pediatrics.* 2005;115:333-339.

28. Hakanen M, Langstrom H, Kaitosaari T, et al. Development of overweight in an atherosclerosis prevention trial started in early childhood. The STRIP study. *Int J Obes (Lond).* 2006;30:618-626.

29. Ritenbaugh C, Teufel-Shone NI, Aickin MG, et al. A lifestyle intervention improves plasma insulin levels among Native American high school youth. *Prev Med.* 2003;36:309-319.

30. Young TK, Martens PJ, Taback SP, et al. Type 2 diabetes mellitus in children: prenatal and early infancy risk factors among native Canadians. *Arch Pediatr Adolesc Med.* 2002;156:651-655.

31. O'Dea K. Marked improvement in carbohydrate and lipid metabolism in diabetic Australian Aborigines after temporary reversion to traditional lifestyle. *Diabetes.* 1984;33:596-603.

32. Boden G, Sargrad K, Homko C, et al. Effect of a low-carbohydrate diet on appetite, blood glucose levels, and insulin resistance in obese patients with type 2 diabetes. *Ann Intern Med.* 2005;142:403-411.

33. Gannon MC, Nuttall FQ. Effect of a high-protein, low-carbohydrate diet on blood glucose control in people with type 2 diabetes. *Diabetes.* 2004;53:2375-2382.

34. Volek JS, Feinman RD. Carbohydrate restriction improves the features of Metabolic Syndrome. Metabolic Syndrome may be defined by the response to carbohydrate restriction. *Nutr Metab (Lond).* 2005;2:31. Available at: http://www.nutritionand metabolism.com/content/pdf/1743-7075-2-31.pdf. Accessed September 1, 2008.

35. Arora SK, McFarlane SI. The case for low carbohydrate diets in diabetes management. *Nutr Metab (Lond).* 2005,2:16. Available at: http://www.nutritionandmetabolism.com/content/pdf/1743-7075-2-16.pdf. Accessed September 1, 2008.

36. Sharman MJ, Kraemer WJ, Love DM, et al. A ketogenic diet favorably affects serum biomarkers for cardiovascular disease in normal-weight men. *J Nutr.* 2002;132:1879-1885.

37. Allick G, Bisschop PH, Ackermans MT, et al. A low-carbohydrate/high-fat diet improves glucoregulation in type 2 diabetes mellitus by reducing postabsorptive glycogenolysis. *J Clin Endocrinol Metab.* 2004,89:6193-6197.

38. Bailie RS, Si D, Robinson GW, et al. A multifaceted health-service intervention in remote Aboriginal communities: 3-year follow-up of the impact on diabetes care. *Med J Aust.* 2004; 181:195-200.

39. Jin AJ, Martin D, Maberley D, et al. Evaluation of a mobile diabetes care telemedicine clinic serving Aboriginal communities in Northern British Columbia, Canada. *Int J Circumpolar Health.* 2004;63(suppl 2):124-128.

40. Tobe SW, Pylypchuk G, Wentworth J, et al. Effect of nurse-directed hypertension treatment among First Nations people with existing hypertension and diabetes mellitus: the Diabetes Risk Evaluation and Microalbuminuria (DREAM 3) randomized controlled trial. *CMAJ.* 2006;174:1267-1271.

41. Wilson C, Curtis J, Lipke S, et al. Nurse case manager effectiveness and case load in a large clinical practice: implications for workforce development. *Diabet Med.* 2005;22:1116-1120.

42. Maberley D, Walker H, Koushik A, et al. Screening for diabetic retinopathy in James Bay, Ontario: a cost-effectiveness analysis. *CMAJ.* 2003;168:160-164.

43. Indian Health Service National Diabetes Program. Special Diabetes Program for Indians. Interim Report to Congress. 2004. Available at: http://www.ihs.gov/MedicalPrograms/diabetes/resources/r_rtc2004index.asp. Accessed September 1, 2008.

Type 2 Diabetes in High-risk Ethnic Populations

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

The initial draft of this chapter was prepared by Elisabeth Harvey RNEC MScN, Stewart B. Harris MD MPH FCFP FACPM and Parmjit Sohal MD PhD CCFP

KEY MESSAGES

- There is some evidence to support the use of ethnic-specific body mass index and waist circumference cutoffs to improve risk stratification and targeted risk management.

- The complex interplay between cultural context and lifestyle supports the use of ethnic-specific community-based diabetes prevention programs that focus on lifestyle modification.

- High-risk ethnic patients develop diabetes complications, particularly cardiovascular disease and renal failure, much earlier than other populations, warranting aggressive management of relevant risk factors, including hypertension and dyslipidemia.

INTRODUCTION

The increase in immigration to Canada over the last 50 years has created a very ethnically diverse population. The 2006 census enumerated over 6 million foreign-born people in Canada, accounting for 19.8% of the total population, the highest proportion in 75 years (1). Among the foreign-born population who reported a mother tongue other than French or English, most reported Chinese languages (18.6%), followed by Italian (6.6%), Punjabi (5.9%), Spanish (5.8%), German (5.4%), Tagalog (4.8%) and Arabic (4.7%). Recent immigrants born in Asia (including the Middle East) comprise the largest proportion (58.3%) of newcomers to Canada, compared to 12.1% in 1971 (1). Toronto, Montreal and Vancouver are home to 68.9% of recent immigrants. In contrast, only 27.1% of Canada's total population lives in these 3 cities (1).

Ethnic disparities in diabetes prevalence have been well documented in the United Kingdom and the United States where, compared with the general population, individuals of South Asian, Chinese, African and Latin ancestry have higher rates of metabolic syndrome, impaired glucose tolerance (IGT), abdominal (central) obesity, insulin resistance (2-7), type 2 diabetes in childhood (8-10), gestational diabetes mellitus (11), and diagnosed and undiagnosed type 2 diabetes with onset at a younger age (12). Those with type 2 diabetes have poorer metabolic control (13-15) and experience higher rates of microvascular and macrovascular complications, which occur at younger ages than the general population (1,16-19). Individuals of South Asian descent represent Canada's fastest-growing immigrant population. Of all expa-triate ethnic groups, they have the highest rates of morbidity and mortality from diabetes-related cardiovascular disease (CVD), with 40% higher age-standardized mortality from coronary artery disease than Caucasians (6,19-21).

Factors responsible for ethnic disparities in diabetes prevalence are multifactorial and include genetic susceptibility, insulin resistance, inadequate socioeconomic resources, self-care capacity challenges, degree of acculturation, health literacy, psychosocial stressors, differences in treatment response, and barriers to accessing healthcare. Traditional diabetes care systems designed for mainstream populations are often of limited relevance to culturally diverse populations, as these systems emphasize the reduction of behavioural risk factors and benefits of self-care behaviours, but ignore the social, cultural, economic and physical environments in which lifestyle practices are shaped and often constrained. There is growing evidence that diabetes prevention and management strategies that target the social determinants of health, offer group support, provide services of a multidisciplinary team that includes community members with local knowledge and expertise are designed with an affinity to the cultural traditions and socioeconomic realities of the target ethnic group, and are delivered in the language of the individual, are associated with improved clinical outcomes and reduced ethnic disparities (22-30).

SCREENING

As the relationship between body fat, waist circumference (WC) and disease varies between ethnic groups, there is some evidence to support the use of ethnic-specific body mass index (BMI) (31) and WC (32) cutoffs to improve risk stratification and targeted risk management in different ethnic groups. Asian-specific cutoffs for risk are BMI=22 to 25 kg/m² ("at risk"); and BMI ≥26 kg/m² ("at higher risk") (31), and WC ≥80 cm for women or ≥90 cm for men (32).

Opportunistic screening by family physicians is ideal but not always accessible to high-risk new immigrant groups. Targeted, ethnic-specific, stepped screening approaches offered in the community, and developed and delivered in partnership with the target communities may refine risk stratification and identification of those who would benefit most from a visit to a family physician (5).

In patients in whom a suspicion of prediabetes is high, a 2-hour 75-g oral glucose tolerance test may be considered.

PRIMARY PREVENTION

Several large primary prevention clinical trials published in the past 5 years have shown that progression of IGT can be prevented or delayed with lifestyle or pharmacological interventions. In the Da Qing study (with 577 Chinese subjects with IGT) and a Japanese study (with 458 Japanese subjects with IGT), lifestyle interventions were associated with 46 and 67% reductions, respectively, in the incidence of type 2 diabetes (33,34). The Diabetes Prevention Program, a large prospective randomized clinical trial in 3234 American adults with impaired fasting glucose (IFG) or IGT, demonstrated that lifestyle modifications reduced the incidence of type 2 diabetes in a variety of high-risk racial/ethnic groups (35). The recently published Indian Diabetes Prevention Program demonstrated a relative risk reduction of 28.5% with lifestyle intervention in native Asian Indians with IGT who were younger, leaner and more insulin resistant than the above populations (36). Progression of IGT to diabetes was 18.3% per year. In a 3-year follow-up, 55% of the nonobese yet highly insulin-resistant Indian population with IGT developed diabetes (23).

The complex interplay between cultural context and lifestyle supports the use of ethnic-specific, community diabetes prevention programs that focus on lifestyle modification. They should be developed and delivered in partnership with the target communities (5).

MANAGEMENT

The cultural dynamics influencing chronic illness management are complex and deeply rooted in the cultural traditions and fabric of ethnic communities. There is a growing body of evidence supporting the use of ethnic-specific community diabetes management programs that reflect the unique sociocultural dynamics of and are delivered in partnership with the target communities (5,24-26). Individuals from high-risk ethnic populations develop diabetes complications, particularly CVD and renal failure, much earlier than other populations. Given the high CV mortality in South Asians, aggressive management of risk factors, including hypertension and dyslipidemia, is warranted to reduce morbidity and mortality (6).

RECOMMENDATIONS

1. High-risk ethnic peoples should be screened for diabetes according to clinical practice guidelines *[Grade D, Consensus]*. Ethnic-specific BMI and WC cutoff points should be used for risk stratification *[Grade D, Consensus]*. Where access to screening by a family physician is not available, targeted community screening programs should be provided for those at high risk of diabetes *[Grade D, Consensus]*.

2. Community-based prevention and management programs aimed at high-risk ethnic peoples should be developed and delivered in partnership with target communities, and should reflect the local ethnocultural representation *[Grade D, Consensus]*.

OTHER RELEVANT GUIDELINES

Screening for Type 1 and Type 2 Diabetes, p. S14

Prevention of Diabetes, p. S17

Organization of Diabetes Care, p. S20

Self-management Education, p. S25

Identification of Individuals at High Risk of Coronary Events p. S95

Type 2 Diabetes in Children and Adolescents, p. S162

REFERENCES

1. Statistics Canada. *The Daily*. Ottawa, ON: Statistics Canada; December 4, 2007. Catalogue 11-001-XIE. Available at: http://www.statcan.ca/Daily/English/071204/d071204.pdf. Accessed September 1, 2008.

2. Oldroyd J, Banerjee M, Heald A, et al. Diabetes and ethnic minorities. *Postgrad Med J.* 2005;81:486-490.

3. Egede LE, Dagogo-Jack S. Epidemiology of type 2 diabetes: focus on ethnic minorities. *Med Clin North Am*. 2005;89:949-975.

4. Bajaj M, Banerji MA. Type 2 diabetes in South Asians: a pathophysiologic focus on the Asian-Indian epidemic. *Curr Diabetes Rep.* 2004;4:213-218.

5. Davachi S, Flynn MA, Edwards AL. A health region/community partnership for type 2 diabetes risk factor screening in Indo-Asian communities. *Can J Diabetes*. 2005;29:87-94.

6. Anand SS, Yusuf S, Vuksan V, et al. Differences in risk factors, arthrosclerosis, and cardiovascular disease between ethnic groups in Canada: the Study of Heath Assessments and Risk in Ethnic groups (SHARE). *Lancet*. 2000;356:279-284.

7. Lorenzo C, Williams K, Hunt KJ, et al. Trend in the prevalence of the metabolic syndrome and its impact on cardiovascular disease incidence: the San Antonio Heart Study. *Diabetes Care*. 2006;29:625-630.

8. Khunti K, Davies M. Primary prevention of type 2 diabetes in people of South Asian origin: potential roles of schools. *Br J Diabetes Vasc Dis*. 2003;3:432-433.

9. Ehtisham S, Crabtree N, Clark P, et al. Ethnic differences in insulin resistance and body composition in United Kingdom adolescents. *J Clin Endocrinol Metab*. 2005;90:3963-3969.

10. Zdravkovic V, Daneman D, Hamilton J. Presentation and course of type 2 diabetes in youth in a large multi-ethnic city. *Diabet Med*. 2004;21:1144-1148.

11. Ferrara A, Kahn HS, Quesenberry CP, et al. An increase in the incidence of gestational diabetes mellitus: Northern California, 1991–2000. *Obstet Gynecol*. 2004;103:526-533.

12. Razak F, Anand S, Vuksan V, et al. Ethnic differences in the relationships between obesity and glucose-metabolic abnormalities: a cross-sectional population-based study. *Int J Obes (Lond)*. 2005;29:656-667.

13. Hertz RP, Unger AN, Ferrario CM. Diabetes, hypertension, and dyslipidemia in Mexican Americans and non-Hispanic whites. *Am J Prev Med*. 2006;30:103-110.

14. Davis TM, Cull CA, Holman RR; UK Prospective Diabetes Study (UKPDS) Group. Relationship between ethnicity and

glycemic control, lipid profiles, and blood pressure during the first 9 years of type 2 diabetes: UK Prospective Diabetes Study (UKPDS 55). *Diabetes Care*. 2001;24:1167-1174.

15. Mukhopadhyay B, Forouhi NG, Fisher BM, et al. A comparison of glycaemic and metabolic control over time among South Asian and European patients with type 2 diabetes: results from follow-up in a routine diabetes clinic. *Diabet Med*. 2006;23:94-98.

16. McElduff P, Edwards R, Burns JA, et al. Comparison of processes and intermediate outcomes between South Asian and European patients with diabetes in Blackburn, north-west England. *Diabet Med*. 2005;22:1226-1233.

17. Karter AJ, Ferrara A, Liu JY, et al. Ethnic disparities in diabetic complications in an insured population. *JAMA*. 2002;287:2519-2527.

18. Baskar V, Kamalakannan D, Holland MR, et al. Does ethnic origin have an independent impact on hypertension and diabetic complications? *Diabetes Obes Metab*. 2006;8:214-219.

19. LaRosa JC, Brown CD. Cardiovascular risk factors in minorities. *Am J Med*. 2005;118:1314-1322.

20. Patel JV, Vyas A, Cruickshank JK, et al. Impact of migration on coronary heart disease risk factors: comparison of Gujaratis in Britain and their contemporaries in villages of origin in India. *Atherosclerosis*. 2006;185:297-306.

21. Gupta M, Brister S. Is South Asian ethnicity an independent cardiovascular risk factor? *Can J Cardiol*. 2006;22:193-197.

22. Bonds DE, Zaccaro DJ, Karter AJ, et al. Ethnic and racial differences in diabetes care: The Insulin Resistance Atherosclerosis Study. *Diabetes Care*. 2003;26:1040-1046.

23. O'Hare JP, Raymond NT, Mughal S, et al; UKADS Study Group. Evaluation of delivery of enhanced diabetes care to patients of South Asian ethnicity: the United Kingdom Asian Diabetes Study (UKADS). *Diabet Med*. 2004;21:1357-1365.

24. Baradaran H, Knill-Jones R. Assessing the knowledge, attitudes and understanding of type 2 diabetes amongst ethnic groups in Glasgow, Scotland. *Pract Diabetes Int*. 2004;21:143-148.

25. McDonald JT, Kennedy S. Is migration to Canada associated with unhealthy weight gain? Overweight and obesity among Canada's immigrants. *Soc Sci Med*. 2005;61:2469-2481.

26. Peyrot M, Rubin RR, Lauritzen T, et al. Psychosocial problems and barriers to improved diabetes management: results of the Cross-National Diabetes Attitudes, Wishes and Needs (DAWN) study. *Diabet Med*. 2005;22:1379-1385.

27. Raphael D, Anstice S, Raine K, et al. The social determinants of the incidence and management of type 2 diabetes mellitus: are we prepared to rethink our questions and redirect our research activities? *Leadership Health Serv*. 2003;16:10-20.

28. Jack L Jr, Liburd L, Spencer T, et al. Understanding the environmental issues in diabetes self-management education research: a reexamination of 8 studies in community-based settings. *Ann Intern Med*. 2004;140:964-971.

29. Bray P, Thompson D, Wynn JD, et al. Confronting disparities in diabetes care: the clinical effectiveness of redesigning care management for minority patients in rural primary care prac-

tices. *J Rural Health*. 2005;21:317-321.

30. Two Feathers J, Kieffer EC, Palmisano G, et al. Racial and Ethnic Approaches to Community Health (REACH) Detroit partnership: improving diabetes-related outcomes among African American and Latino adults. *Am J Public Health*. 2005;95:1552-1560.

31. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet*. 2004;363:157-163.

32. International Diabetes Federation (IDF). *The IDF Consensus Worldwide Definition of the Metabolic Syndrome*. Brussels, Belgium: IDF; 2006. Available at: http://www.idf.org. Accessed September 1, 2008.

33. Pan XR, Li GW, Hu YH, et al. Effect of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes study. *Diabetes Care*. 1997;20:537-544.

34. Kosaka K, Noda M, Kuzuya T. Prevention of type 2 diabetes by lifestyle interventions: a Japanese trial in IGT males. *Diabetes Res Clin Pract*. 2005;67:152-162.

35. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393-403.

36. Ramachandran A, Snehalatha C, Mary S, et al; Indian Diabetes Prevention Programme. The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). *Diabetologia*. 2006;49:289-297.

Appendix 1

*Etiologic Classification of Diabetes Mellitus**

Type 1 diabetes mellitus
Beta cell destruction, usually leading to absolute insulin deficiency • Immune-mediated • Idiopathic
Type 2 diabetes mellitus
May range from predominant insulin resistance with relative insulin deficiency to predominant secretory defect with insulin resistance
Gestational diabetes mellitus
Onset or first recognition of glucose intolerance during pregnancy
Other specific types

Genetic defects of beta cell function
  • Chromosome 20, HNF-4alpha (formerly MODY1)
  • Chromosome 7, glucokinase (formerly MODY2)
  • Chromosome 12, HNF-1alpha (formerly MODY3)
  • Chromosome 13, IPF-1 (formerly MODY4)
  • Chromosome 17, HNF-1beta (MODY5)
  • Chromosome 2, *NeuroD1* (MODY6)
  • Mitochondrial DNA
  • Neonatal diabetes (e.g. due to Kir6.2 mutation)
  • Others
 	
Genetic defects in insulin action
  • Leprechaunism
  • Lipoatrophic diabetes
  • Rabson-Mendenhall syndrome
  • Type A insulin resistance
  • Others
 	
Diseases of the pancreas
  • Cystic fibrosis
  • Fibrocalculous pancreatopathy
  • Hemochromatosis
  • Neoplasia
  • Pancreatitis
  • Trauma/pancreatectomy
  • Others
 	
Endocrinopathies
  • Acromegaly
  • Aldosteronoma
  • Cushing syndrome
  • Glucagonoma
  • Hyperthyroidism
  • Pheochromocytoma
  • Somatostatinoma
  • Others
	Infections
	  • Congenital rubella
	  • Cytomegalovirus
	  • Others
	
	Uncommon forms of immune-mediated diabetes
	  • Anti-insulin receptor antibodies
	  • "Stiff-man" syndrome
	  • Others
	
	Drug- or chemical-induced
	  • Atypical antipsychotics
	  • Beta-adrenergic agonists
	  • Cyclosporine
	  • Diazoxide
	  • Glucocorticoids
	  • Interferon alfa
	  • Nicotinic acid
	  • Pentamidine
	  • Phenytoin
	  • Protease inhibitors
	  • Thiazide diuretics
	  • Thyroid hormone
	  • Others
	
	Other genetic syndromes sometimes associated with diabetes
	  • Down syndrome
	  • Friedreich ataxia
	  • Huntington chorea
	  • Klinefelter syndrome
	  • Laurence-Moon-Bardet-Biedl syndrome
	  • Myotonic dystrophy
	  • Porphyria
	  • Prader-Willi syndrome
	  • Turner syndrome
	  • Wolfram syndrome
	  • Others

*Patients with any form of diabetes may require insulin treatment at some stage of their illness. Such use of insulin does not, of itself, classify the patient

HNF = hepatocyte nuclear factor   IPF = insulin promoter factor   MODY = maturity-onset diabetes of the young

Adapted with permission from: American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care.* 2007;30(suppl 1):S42-S47.

Appendix 2. Sample Diabetes Patient Care Flow Sheet for Adults

Name **Date of birth**	**Type 1** ❑ **Type 2** ❑ **Age at diagnosis**

Care objectives (risk factors, comorbidities)	*Self-management (discuss with patient)*
❑ Hypertension (target <130/80 mm Hg) ❑ Dyslipidemia ❑ CAD ❑ Smoking _____ (date stopped) ❑ PAD ❑ Alcohol _____ (assess/discussed) ❑ CKD ❑ Mental health diagnosis ❑ PCOS ❑ Foot disease ❑ ED ❑ Retinopathy	❑ Refer to diabetes teaching team _____ (date) ❑ Weight management: Wt: _____ Ht: _____ BMI: _____ (normal: 18.5–24.9 kg/m²) Target wt: _____ WC: _____ (M <102 cm; F <88 cm) ❑ Physical activity (≥150 min/week): _____ ❑ Glucose meter/lab comparison ❑ Patient care plan (including pregnancy planning)

Visits (3 to 6 months)

Date	BP	Wt	A1C (Target ≤7%)	Notes (goals, clinical status)	**Diabetes medication baseline:** Allergies, side effects, contraindications. Consider ACEI, ARB, statin ASA as indicated

Review SMBG records. Target: preprandial 4–7 mmol/L; 2-hour postprandial 5–10 mmol/L (5–8 mmol/L if not achieving A1C target)

Screen for diabetes complications annually, or as indicated

Nephropathy

Date	ACR target: M <2.0, F <2.8	eGFR/CrCl target: >60

Neuropathy
❑ Check feet for lesions and sensation (10-g monofilament, 128 Hz tuning fork)
❑ Check for pain, ED, GI symptoms

Date: _____ Findings: _____
Date: _____ Findings: _____
Date: _____ Findings: _____

Retinopathy
❑ Annual eye exam
Date: _____
Date: _____

Ophthalmologist/ optometrist:
_____

CAD assessment
❑ Not high risk ❑ High risk
Definition M ≥45 y, F ≥50 y
or has ≥1 of the following:
macrovascular disease; microvascular disease;
multiple risk factors (esp. family history);
1 extreme risk factor; duration of diabetes
>15 y and age >30 y

Resting ECG: _____

Exercise stress test: _____

Other: _____

Lipids Targets for those at high risk for CAD
Primary target: LDL-C ≤2.0 mmol/L
Secondary target: TC/HDL-C <4.0

Date	TC	LDL-C	TC/HDL-C	TG	Medications

Vaccinations

❑ Annual influenza

Date: _____

Date: _____

❑ Pneumococcus

Date: _____

SEE REVERSE FOR CARE OBJECTIVES AND TARGETS

APPENDICES

Care	Objective	Target
Self-monitoring of blood glucose	• Reinforce patient's responsibility for regular monitoring as appropriate • Ensure patient can use glucose meter, interpret SMBG results and modify treatment as needed • Develop an SMBG schedule with patient and review records	Preprandial (mmol/L) **4.0–7.0 for most patients** 2-hour postprandial (mmol/L) **5.0–10.0 for most patients** **5.0–8.0 if not achieving A1C target**
Blood glucose control	• Measure **A1C every 3 months** for most adults • Consider testing at least every 6 months in adults during periods of treatment and lifestyle stability, and when glycemic targets are being consistently achieved	A1C **≤7.0% for most patients** See "Targets," p. S29
Blood glucose meter accuracy	• Compare meter results with laboratory measurements at least **annually**, and when indicators of glycemic control do not match meter	Simultaneous fasting glucose/meter lab comparison within **20%**
Hypertension	• Measure BP at **diagnosis of diabetes and at every diabetes clinic visit**	**<130/80 mm Hg**
Waist circumference	• Measure as an indicator of abdominal fat	Target WC: **M <102 cm, F <88 cm** (see ethnic-specific values in "Management of Obesity in Diabetes," p. S77)
Body mass index	• Calculate BMI: mass in kg/(height in m)^2	Target BMI: **18.5–24.9 kg/m^2**
Nutrition	• Encourage nutrition therapy (by a Registered Dietitian) as an integral part of treatment and self-management (can reduce A1C by 1–2%)	Meet nutritional needs by following *Eating Well with Canada's Food Guide*
Physical activity	• Discuss and encourage aerobic and resistance exercise • Consider exercise ECG stress test for previously sedentary individuals at high risk for CAD planning exercise more vigorous than brisk walking	Aerobic: **≥150 minutes/week** Resistance: **3 sessions/week**
Smoking	• Encourage patient to stop at each visit; provide support as needed	Smoking cessation
Retinopathy	• **Type 1 diabetes:** Screen 5 years after diagnosis, then rescreen annually • **Type 2 diabetes:** Screen at diagnosis, then every 1–2 years if no retinopathy present • Screening should be conducted by an experienced eye care professional	Early detection and treatment
Chronic kidney disease	• Identification of CKD requires screening for **proteinuria** using random **urine ACR and assessment of renal function** using a serum creatinine converted to **eGFR** • **Type 1 diabetes:** In adults, screen after 5 years duration of diabetes, then annually if no CKD • **Type 2 diabetes:** Screen at diagnosis, then annually if no CKD • If CKD present, perform ACR and eGFR at least every 6 months	ACR (mg/mmol) Normal: **M <2.0; F <2.8** Microalbuminuria: **M 2.0–20.0, F 2.8–28.0** Macroalbuminuria: **M >20.0, F >28.0** **CKD if eGFR ≤60 mL/min**
Neuropathy/ foot examination	• **Type 1 diabetes:** Screen 5 years after diagnosis, then rescreen annually • **Type 2 diabetes:** Screen at diagnosis, then annually • Screen for neuropathy with 10-g monofilament or 128-Hz tuning fork at dorsum of great toe. In foot exam, look for structural abnormalities, neuropathy, arterial disease, ulceration, infection	**Early detection and treatment** If neuropathy present: foot care education, specialized footwear, smoking cessation If ulcer present: manage by multidisciplinary team with expertise

CAD assessment	• **Conduct CAD risk assessment periodically:** CV history, lifestyle, duration of diabetes, sexual function, abdominal obesity, lipid profile, BP, reduced pulses, bruits, glycemic control, retinopathy, eGFR, ACR
	• **Measure baseline resting ECG, then every 2 years if:** age >40 years, duration of diabetes >15 years, symptoms, hypertension, proteinuria, bruits or reduced pulses
	• **High-risk categories include:**
	  • Men ≥45 years, women ≥50 years or
	  • Men <45 years, women <50 years with ≥1 of: macrovascular disease, microvascular disease (especially retinopathy, nephropathy), multiple additional risk factors (especially family history of premature coronary or cerebrovascular disease in 1st-degree relative), extreme single risk (e.g. LDL-C >5.0 mmol/L, systolic BP >180 mm Hg) or duration of diabetes >15 years and age >30 years
		Vascular protection: first priority in prevention of diabetes complications is **reduction of CV risk by vascular protection** through a comprehensive multifaceted approach:
		• All people with diabetes: optimize BP, glycemic control and lifestyle (weight, exercise, smoking)
		• People with diabetes and at high risk of CV event, additional interventions: ACE inhibitor/ARB antiplatelet therapy (as indicated) and lipid-lowering medication (primarily statins)

Dyslipidemia	• **Measure fasting lipid levels (TC, HDL-C, TG and calculated LDL-C)** at diagnosis of diabetes, then every 1–3 years as clinically indicated. Test more frequently if treatment initiated	Lipid targets for those at high risk for CAD: • Primary target: LDL-C **≤2.0 mmol/L** • Secondary target: TC/HDL-C **<4.0**

Care objectives: People with diabetes will have better outcomes if primary healthcare providers: 1) identify patients with diabetes in their practice; 2) assist them by incorporating the suggested care objectives; 3) schedule diabetes-focused visits; and 4) use diabetes patient care flow sheets and systematic recall for visits.

Appendix 3

Examples of Insulin Initiation and Titration Regimens in People With Type 2 Diabetes

All people starting insulin should be counselled about the recognition, prevention and treatment of hypoglycemia. Consider a change in type or timing of insulin administration if glycemic targets are not being reached.

Example A: Basal insulin (Humulin-N, Lantus, Levemir, Novolin ge NPH) added to oral antihyperglycemic agents

- Insulin should be titrated to achieve target fasting BG levels of 4.0 to 7.0 mmol/L.
- Individuals can be taught self-titration, or titration may be done in conjunction with a healthcare provider.
- Suggested starting dose is 10 units once daily at bedtime.
- Suggested titration is 1 unit per day until target is reached.
- A lower starting dose, slower titration and higher targets may be considered for elderly or normal-weight subjects.
- In order to safely titrate insulin, patients must perform SMBG at least once a day fasting.
- Insulin dose should not be increased if the individual experiences 2 episodes of hypoglycemia (BG <4.0 mmol/L) in 1 week or any episode of nocturnal hypoglycemia.
- For BG levels consistently <5.5 mmol/L, a reduction of 1 to 2 units of insulin may be considered to avoid nocturnal hypoglycemia.
- Oral antihyperglycemic agents (especially secretagogues) may need to be reduced if daytime hypoglycemia occurs.

Example B: Premixed insulin (Novolin 30/70, Humulin 30/70, NovoMix 30, Mix 25 or Mix 50) added to oral antihyperglycemic agents

- Suggested starting dose is 5 to 10 units once or twice daily (prebreakfast and/or presupper).
- Suggested titration is 1 to 2 units added to prebreakfast dose and/or presupper dose daily until target BG values are reached based on prebreakfast and presupper BG readings.
- Prebreakfast premixed insulin achieves presupper target BG value (4.0 to 7.0 mmol/L).
- Presupper premixed insulin achieves target fasting BG value (4.0 to 7.0 mmol/L).
- 30/70 premixed insulin should be given 30 to 45 minutes before meals.
- NovoMix 30 and Mix 25 premixed insulin should be given immediately before eating.
- Stop increasing insulin when both target BG levels are reached.
- If both BG targets are not reached, continue to increase the relevant dose until both targets achieved.
- The individual needs to self-monitor BG at least twice daily to safely titrate insulin.
- Insulin dose should not be increased if the individual experiences 2 or more episodes of hypoglycemia (BG <4.0 mmol/L) in 1 week or any episode of nocturnal hypoglycemia.
- Oral antihyperglycemic agents (especially secretagogues) may need to be reduced if daytime hypoglycemia occurs.

Example C: Intensive insulin therapy with basal/bolus insulin

- Calculate total daily dose of 0.3 to 0.5 units/kg then distribute as follows:
  a. 40% of total insulin dose as basal insulin (Humulin-N, Lantus, Levemir, Novolin ge NPH).
  b. 20% of total insulin as bolus (prandial) insulin (Apidra, Humalog, Humulin R, Novolin ge Toronto, NovoRapid) 3 times per day rapid-acting insulin analogue or short-acting insulin).

Sample Instructions for Patients With Type 2 Diabetes Who Are Starting and Adjusting Insulin

You will be taking insulin _____ at _____.

It is important that you continue to take your other diabetes medications as prescribed unless you have been told to change the dose or stop them.

How to adjust your insulin dose

- Your target fasting blood glucose level is _____ mmol/L.
- You will inject _____units of _____at_____.
- You will continue to increase your insulin dose by _____ unit(s) every _____ day(s) until your fasting blood glucose level is _____ mmol/L.
- Do not increase your insulin when your fasting blood glucose is _____ mmol/L.
- You should call for further instructions when your blood glucose reaches _____ mmol/L for 3 or more days: phone number_____.
- A side effect of insulin is low blood glucose (hypoglycemia); low blood glucose can occur with too much insulin, increased activity or not enough food.

Monitoring your blood glucose

- It is important to test your blood glucose while your insulin treatment is being modified.
- You should test your blood glucose and record the value every day before breakfast and _____.
- Test before each meal, unless you are instructed differently.
- It is important to record your blood glucose values and any changes in activity or food in your diary and bring this to your next appointment; this information helps us to understand your diabetes control.
- Unless otherwise instructed, you are trying to reach a target blood glucose of 4.0 to 7.0 mmol/L before meals, and 5.0 to 8.0 mmol/L after meals.
- If you think your blood glucose is low, a check it and record that information in your diary.

Instructions for taking your diabetes medications

| Current medications	Dose	Time of day	Special instructions

Appendix 4

Rapid Screening for Diabetic Neuropathy

Multiple screening methods are published. These methods (1) are designed to screen for the presence or absence of diabetic neuropathy, as opposed to screening for specific sites on the feet that are at risk of ulceration (multisite testing). If neuropathy is identified by either of these methods, other sites may be tested to identify high-risk areas for ulceration.

Rapid Screening for Diabetic Neuropathy Using the 10-g Semmes-Weinstein Monofilament

1. Show the 10-g Semmes-Weinstein monofilament to the patient.
2. Touch it first to the patient's forehead or sternum so that the sensation is understood.
3. Instruct the patient to say "yes" every time the monofilament stimulus is perceived.
4. With the patient's eyes closed, apply the monofilament to the dorsum of the great toe proximal to the nail bed as shown in the illustration below. Use a smooth motion – touch the skin, bend the filament for a full second, then lift from the skin.
5. Perform this stimulus 4 times per foot in an arrhythmic manner so the patient does not anticipate when the stimulus is to be applied.
6. Add up all correct stimuli for a score out of 8. A score of 7 or 8 correct responses likely rules out the presence of neuropathy.
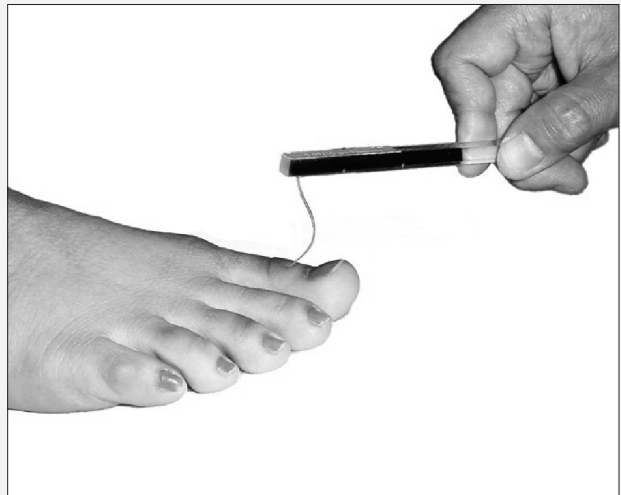
Rapid Screening for Diabetic Neuropathy Using the 128-Hz Vibration Tuning Fork (The "On-Off" Method)

1. Strike the tuning fork against the palm of your hand hard enough that it will vibrate for approximately 40 seconds.
2. Apply the base of the tuning fork to the patient's forehead or sternum and ensure that the vibration sensation (not just the touch sensation) is understood.
3. With the patient's eyes closed, apply the tuning fork to the bony prominence situated at the dorsum of the first toe just proximal to the nail bed. Ask if the vibration sensation is perceived.
4. Ask the patient to tell you when the vibration stimulus is stopped, and then dampen the tuning fork with your other hand.
5. One point is assigned for each vibration sensation perceived (vibration "on"). Another point is assigned if the correct timing of dampening of the vibration is perceived (vibration "off").
6. Repeat this procedure again on the same foot, then twice on the other foot in an arrhythmic manner so the patient does not anticipate when the stimulus is to be applied.
7. Add up all correct stimuli for a score out of 8. A score of 7 or 8 correct responses likely rules out the presence of neuropathy.
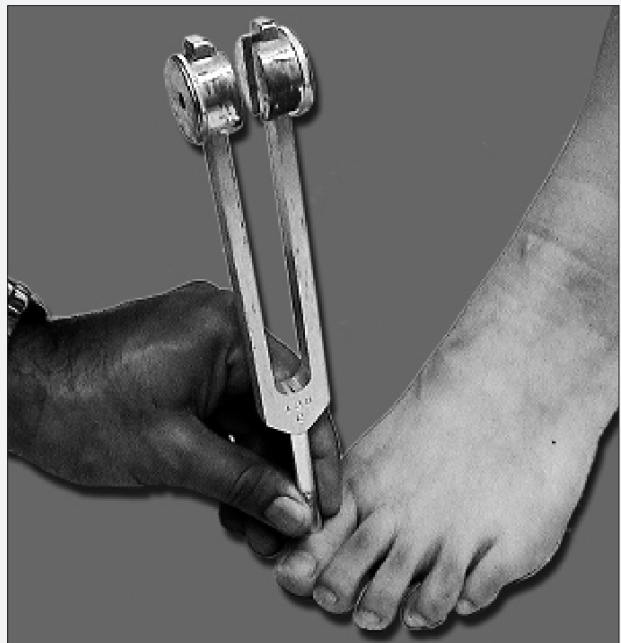
1. Perkins BA, Olaleye D, Zinman B, et al. Simple screening tests for peripheral neuropathy in the diabetes clinic. *Diabetes Care.* 2001;24:250-256.

Appendix 5

Diabetes and Foot Care: A Patient's Checklist

Many people with diabetes have problems with their feet. Ask your doctor to explain your risk factors for foot problems. You can prevent serious foot problems by following these basic guidelines.

DO...	DON'T...
…check your feet every day for cuts, cracks, bruises, blisters, sores, infections or unusual markings.	…cut your own corns or calluses.
…use a mirror to see the bottom of your feet if you can't lift them up.	…treat your own in-growing toenails or slivers with a razor or scissors. See your doctor or foot care specialist.
…check the colour of your legs and feet. If there is swelling, warmth or redness or if you have pain, see your doctor or foot specialist right away.	…use over-the-counter medications to treat corns and warts. They are dangerous for people with diabetes.
… clean a cut or scratch with a mild soap and water and cover with a dry dressing for sensitive skin.	…apply heat to your feet with a hot water bottle or electric blanket. You could burn your feet without realizing it.
…trim your nails straight across.	…soak your feet.
…wash and dry your feet every day, especially between the toes.	…take very hot baths.
…apply a good skin lotion every day on your heels and soles. Wipe off any excess lotion.	…use lotion between your toes.
…change your socks every day.	…walk barefoot inside or outside.
…always wear a good supportive shoe.	…wear tight socks, garters or elastics, or knee highs.
…always wear professionally fitted shoes from a reputable store. Professionally fitted orthotics may help.	….wear over-the-counter insoles – they can cause blisters if they are not right for your feet.
…choose shoes with low heels (under 5 cm high).	…sit for long periods of time.
…buy shoes in the late afternoon (since your feet swell slightly by then).	…smoke.
…avoid extreme cold and heat (including the sun).	
…exercise regularly.	
…see a foot care specialist if you need advice or treatment.	

Adapted with permission from: Casella A. Feeling well…diabetes and foot care, a patient's checklist. *Knowing Diabetes.*
© Diabetes Hamilton, 2002

Appendix 6

Diabetic Foot Ulcers: Essentials of Management

1. Assess underlying cause(s): neuropathy and/or ischemia.

2. Ulcers should be probed with a blunt-tipped instrument to detect sinus tracks or palpable bone suggestive of deep infections.

3. Plantar-surface ulcers require pressure relief. Individuals with plantar-surface foot ulcers should be non-weight-bearing as much as possible and utilize off-loading footwear or appliances (1).

4. Clinically noninfected ulcers do not routinely require cultures or antibiotics (2).

5. More serious infections in chronic foot ulcers tend to be polymicrobial and typically require empiric use of broad spectrum systemic antibiotics as soon as possible. Antibiotics can be subsequently tailored according to culture and sensitivity results. Cultures obtained by curettage or biopsy tend to be more reliable than surface swabs (3).

6. Wound bed preparation involves debridement of necrotic tissue (neuropathic wounds and noncritical ischemic wounds only) and maintenance of adequate moist wound environment with appropriate wound dressings. Hydrogels are used to increase wound bed moisture in dry or minimally draining neuropathic ulcers. Dressings that provide therapeutic levels of ionic silver or iodine may reduce critical degrees of wound bacterial colonization (4).

7. Comorbidities need to be managed (e.g. hyperglycemia).

8. Refer to a specialized wound clinic where available.

REFERENCES

1. Lavery LA, Baranoski S, Ayello EA. Options for off-loading the diabetic foot. *Adv Skin Wound Care.* 2004;17:181-186.

2. Lipsky BA, Berendt AR, Deery HG, et al; for the Infectious Diseases Society of America. Diagnosis and treatment of diabetic foot infections. *Clin Infect Dis.* 2004;39:885-910.

3. Frykberg RG, Zgonis T, Armstrong DG, et al; for the American College of Foot and Ankle Surgeons. Diabetic foot disorders. A clinical practice guideline (2006 revision). *J Foot Ankle Surg.* 2006;45(5 suppl):S1-S66.

4. Schultz GS, Barillo DJ, Mozingo DW, et al; for the Wound Bed Advisory Members. Wound bed preparation and a brief history of TIME. *Int Wound J.* 2004;1:19-32.

APPENDICES