

# Coeliac disease: the great imitator

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“Know syphilis in all its manifestations and all other things clinical will be added unto you.”<sup>1</sup>

WHEN THE SUPREME CLINICIAN William Osler wrote this, he was drawing attention to the ubiquity of syphilis and the remarkable range of its late-stage manifestations, today virtually unknown. However, I argue that its place has been taken by coeliac disease (CD), another great imitator. As a diagnostic challenge, CD is the “syphilis” of the 21st century.

Western civilisation owes much of its foundation to a strange molecular rearrangement of the chromosomes of wild grasses in the Middle East to produce a high-protein, high-yielding grain — wheat — with six sets of chromosomes. This enabled the nomads to settle down with some assurance of a regular food supply and time to think and develop skills such as writing.

This progress, however, came at a price. Gliadin, the principal wheat protein, presented to sensitised T cells in conjunction with HLA-DQ2 or HLA-DQ8 antigen, leads to the production of cytokines. The cytokines cause tissue damage within the mucosa and activate plasma cells to produce antibodies to gliadin, tissue transglutaminase and endomysium. Wheat, rye, barley and, to a minor extent, oats have progressively lesser amounts of the toxic amino acid sequence. Why only a small proportion of the population who are bearers of HLA-DQ2 and HLA-DQ8 produce these changes is unknown, as is why cigarette smoking reduces the risk of CD by 80%.<sup>2</sup> However, what we are progressively learning is that the ill effects of the molecular events extend far beyond the small-bowel mucosa. For every classical thin, pale, pot-bellied patient with steatorrhoea, there are many with few or no symptoms, amounting in most North American and European societies to 0.5% to 1.0% of the population, particularly those of northern European ancestry.<sup>3</sup>

It is becoming evident that a host of disorders in many systems are aetiologically related to the presence of CD, often manifesting themselves in the context of an inapparent coeliac state (Box 1). For some, such as fatty liver “transaminitis” or hepatitis, the link is clear. Our research (as yet unpublished) shows that about 40% of both children and adults with this disorder (who typically have laboratory and histological evidence of CD but few clinical signs) have liver abnormalities that resolve within a few months on an appropriate diet.

Dermatitis herpetiformis is another condition that is clearly linked to CD. Most, if not all, cases of this form of

## ABSTRACT

- Coeliac disease (CD) is caused by a complex immunological response provoked by grain protein in susceptible people.
- The majority of people with CD are symptom-free adults; the remainder are prone to a bewildering variety of signs and symptoms, ranging from infertility to type 1 diabetes.
- Many patients with undiagnosed CD spend years seeking help for complaints such as chronic tiredness or mild abdominal symptoms.
- In primary care, an appropriate target group to test for CD is people with anaemia (especially women), chronic tiredness, non-specific abdominal symptoms (including so-called “irritable bowel syndrome”), or a family history of CD.
- The response to an appropriate gluten-free diet is often life-transforming for symptomatic patients.
- Positive serological tests for CD require confirmation by duodenal biopsy and, if confirmed, referral to a dietitian and a coeliac society, followed by a life-long gluten-free diet.

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dermatitis are related to gluten intolerance, although the duodenal changes may only manifest themselves after prolonged high intake of gluten.<sup>34</sup> With a gluten-free diet, the condition resolves and the intense itchiness subsides.

Another association is with type 1 diabetes. The prevalence of CD in people with type 1 diabetes is about 3 to 8%,<sup>4</sup> while the prevalence of type 1 diabetes in people with CD is about 5%.<sup>32</sup> However, there are no data on whether patients with diabetes and CD experience improvement in their diabetes symptoms in response to a gluten-free diet.

Another group of associations is exemplified by the anaemias — essentially a complication of malabsorption, particularly of iron and folate. These conditions respond fully to nutrient replacement.

However, the largest, possibly most important and least understood group of diseases that appear to have links with CD are those with a statistical association, such as epilepsy,<sup>32</sup> the neuropathies<sup>32</sup> and myelopathies,<sup>10</sup> the ataxias,<sup>12</sup> and male and female infertility.<sup>16,17</sup> With these conditions, the story is only beginning to unfold, and responses to diet are less evident.

Such associations are only likely to be detected, and their nature and course unravelled, if physicians have a much lower threshold for suspecting CD behind many different clinical syndromes (Box 2). By performing simple and relatively inexpensive laboratory tests — such as tests for transglutaminase antibody (sensitivity, 93%; specificity, 99%) and the endomysial antibody (sensitivity, 85%–98%; specificity, 97%–100%) — followed by endo-

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**1: Clinical disorders associated with coeliac disease****Gastrointestinal**

Liver disease "transaminitis", hepatitis, fatty liver, primary biliary cirrhosis, cirrhosis\*  
 Recurrent aphthous mouth ulcers<sup>4</sup>  
 Irritable bowel syndrome<sup>5</sup>  
 Lymphocytic gastritis<sup>6</sup>  
 Ulcerative jejunitis<sup>7</sup>  
 Reflux oesophagitis<sup>8</sup>  
 Adenocarcinoma of small bowel<sup>9</sup>

**Neurological**

Peripheral neuropathy<sup>10</sup>  
 Epilepsy<sup>11</sup>  
 Ataxia<sup>12</sup>  
 Myelopathy<sup>10</sup>

**Psychiatric**

Depression<sup>13</sup>  
 Schizophrenia<sup>14</sup>

**Endocrine**

Type 1 diabetes<sup>15</sup>  
 Infertility in men and women<sup>16,17</sup>  
 Recurrent abortion<sup>18</sup>  
 Thyroid disorders<sup>19</sup>  
 Addison's disease<sup>19</sup>

**Renal**

IgA nephropathy<sup>20</sup>

**Haemopoietic**

Anaemia (iron, folate and vitamin B<sub>12</sub> deficiency)<sup>21</sup>  
 Coagulation disorders from vitamin K deficiency<sup>21</sup>  
 IgA deficiency<sup>4</sup>  
 Hyposplenism<sup>20</sup>  
 T-cell lymphoma<sup>20</sup>

**Locomotor**

Osteopenia<sup>22</sup>  
 Arthralgia/arthritis<sup>23,24</sup>

**Dermatological**

Dermatitis herpetiformis<sup>25</sup>  
 Psoriasis<sup>26</sup>  
 Brown pigmentation of face and buccal mucosa<sup>27</sup>

**Dental**

Defects in tooth enamel<sup>28</sup>

**Genetic**

Down syndrome<sup>29</sup>

**Cardiovascular**

Cardiomyopathy<sup>30</sup>

**Other**

Alopecia areata<sup>31</sup>  
 Sjögren's syndrome<sup>32</sup>  
 Finger clubbing<sup>27</sup>  
 Pharyngeal and oesophageal carcinoma<sup>33</sup>

\* Duggan JM and Duggan AE (unpublished observations).

**2: Coeliac disease: mode of presentation, and prevalence of the various symptoms/findings among presenting patients<sup>35,36</sup>**

Mode of presentation	Proportion of patients with this primary presentation	Prevalence of symptom/finding
Anaemia	10%–18%	12%–22%
Feeling "tired all the time"	20%	58%
Malabsorption/bowel symptoms	43%	60%
Coeliac disease in first-degree relative(s)	13%	5%–10%
Symptoms in childhood	na	50%
Incidental finding at endoscopy	8%	na

na = not applicable.

and duodenal biopsy and referral to a coeliac society if CD is indicated. Given that GF diets are complex, lifelong, expensive and socially disruptive, they must always be preceded by histological proof from a biopsy. Nevertheless, the potential benefits for some patients may be enormous.

In the Australian context, an appropriate strategy is to request testing for endomysial and transglutaminase antibodies, ensuring that the laboratory tests for IgG antibodies in patients who have IgA deficiency, which is common in patients with CD.<sup>37</sup> An appropriate group of patients to target would be those who have the type of symptoms described above in the UK study.<sup>36</sup>

In summary, there can be little doubt that the transglutaminase/endomysial antibody assay should be part and parcel of the diagnostic armamentarium of every physician, given that CD can manifest as a disturbance of function of virtually any body system. A priori, there must be many other associations yet to be discovered.

**Competing interests**

None identified.

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scopic duodenal biopsy in antibody-positive patients, the disease is readily diagnosed.

Possibly the clearest data on a feasible approach to the disease are given in a study in nine general practices in the United Kingdom.<sup>36</sup> The study found 30 patients with CD in a target group of 1000 adults with major complaints of feeling "tired all the time", having abdominal symptoms or having a positive family history of CD. While universal screening for CD may not be feasible, or indeed appropriate, the study shows that screening patients with one or more of these symptoms may be a practicable alternative for discovering more cases of undiagnosed CD. However, there are a number of caveats. While the patient with long-term lethargy and folate or iron deficiency in the presence of a reasonable diet is likely to undergo life-transforming change on a gluten-free (GF) diet with appropriate supplementation, the imposition of a GF diet for the chance finding of CD in an effectively symptom-free patient may be a disservice. This is especially so for many of the associated disorders such as type 1 diabetes, for which we at present lack evidence of benefit of instituting a GF diet. Moreover, having found elevated transaminase and glutaminase antibody levels, the practitioner is obliged to seek an endoscopy

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