Singh *et al.*
The Egyptian Journal of Internal Medicine (2023) 35:43
https://doi.org/10.1186/s43162-023-00232-1

The Egyptian Journal of Internal Medicine

REVIEW

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The contentious relationship between artificial sweeteners and cardiovascular health

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Abstract

Sweet has always been a fundamental human taste, and while glucose and other kinds of sugar are our primary energy sources, they can also have detrimental effects on health, including weight gain, obesity, cardiovascular diseases, diabetes, and other metabolic diseases. Artificial sweeteners (AS), introduced as sugar substitutes, are a group of chemical compounds that attribute sweetness with almost zero calories and are considered safe for consumption by the Food and Drug Administration (FDA). Although they may help restrict the daily caloric intake of sugar to less than 10% of the daily caloric intake, there are still questions about the long-term safety of AS. A higher risk of hypertension, insulin resistance, high blood sugar, abdominal obesity, and dyslipidemia has been linked to AS. The effect of AS on the cardiovascular system is still unclear, and further research is required. This review examines the potential mechanism of how artificial sweeteners cause cardiovascular diseases.

Keywords Artificial sweeteners, Cardiovascular health, Atrial fibrillation, Aspartame, Saccharin

Introduction

Artificial sweeteners, (AS) common substitutes for sugar, were first introduced to the food market in the 1800s, but their consumption did not increase dramatically until the 2000s [1]. High sugar intake is associated with weight gain, obesity, and hypertriglyceridemia, which can lead to Cardiovascular disease(CVD), diabetes, and other metabolic diseases [2]. As a result, people are opting for low-calorie and sugar-free products; any food marketed as " Sugar-free" or " Diet food" contains artificial sweeteners. Currently, in the U.S. Food and Drug Administration (FDA) has approved six synthetically derived artificial sweeteners, as listed in Table 1 [3–7], as food additives: aspartame, sucralose, neotame, acesulfame potassium, saccharin, and advantame. Advantame was most recently approved artificial sweetener by the FDA as a broad purpose sweetener and flavor enhancer. There are also two naturally occurring artificial sweeteners that are also approved by the FDA: stevia leaf extract and monk fruit extract [1]. Artificial sweeteners have become a key part of everyday life nowadays. They are used in a variety of food and drinks and are heavily marketed as better alternatives to table sugar by the food industry. They produce more pronounced sweetness and have zero to a few calories per gram. The aggressive marketing of these sugar substitutes by their makers has resulted in their overuse. Additionally, the increased prevalence of conditions such as obesity, metabolic syndrome, and

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Table 1 Artificial sweeteners and their sweetness (compared with sucrose) [3–7]

Chemical name	Chemical components	Sweetness (compared with sucrose)
Aspartame	Phenylalanine and aspartic acid	160–220x
Sucralose	1,6-dichloro-1, 6-dide-oxyfructose and 4-chloro-4deoxygalactose	600x
Neotame	Secondary amine of 3,3-dimethylbutanoal and aspartame	7000–13,000x
Acesulfame-potassium	Acetoacetic acid and potas-sium	200x
Saccharin	1,2-benzisothiazole	300x
Advantame	Aspartame (above) and vanillin	20,000x

diabetes, in addition to increased consumer knowledge, has resulted in a continuous radical shift in favor of using artificial sweeteners [8]. Increased sugar intake leads to well-established adverse health outcomes such as weight gain, dental caries, diabetes, and cardiometabolic disorders. Thus, the World Health Organization (WHO) has suggested keeping total sugar intake to less than 10% of the total daily calorie intake. But since people all over the world enjoy sweet flavors, the food industry began to employ the use of artificial sweeteners as substitutes to cut added sugar amount and the number of calories associated with them while preserving sweetness at the same time [9]. Although all artificial sweeteners have a sweet characteristic to them, they are all chemically different compounds. As a result, dependent on the artificial sweetener, it is this characteristic that decides the type of reaction of gut microorganisms and their impact on the digestive tract in regard to the way they are moved in the small and large bowl, digested, and expelled [10]. Artificial sweeteners are typically considered safe to consume since they are approved for consumption by the FDA. However, there are still concerns that exist about the long-term safety of consuming them. According to recently emerging epidemiological cohort studies, the usage of artificial sweeteners is linked to unfavorable cardiovascular conditions and mortality. Nonetheless, these population association studies have not been able to prove causation. There are presently no reports of randomized controlled trials examining if prolonged use of artificial sweeteners in humans results in negative cardiovascular consequences. However, Guru et al. in their study did show that artificial sweeteners did result in electrophysiological anomalies, including prolonged PR interval and increased atrial fibrillation inducibility in rats [11]. In this review article, we will be discussing the potential mechanism of how artificial sweeteners cause cardiovascular diseases.

Methods

This literature review was performed in March 2023 by searching the PubMed database for the most up-to-date literature regarding Artificial sweeteners and their side effects and effects on the cardiovascular system.

Mechanism

Artificial sweeteners are associated with an increased risk of metabolic syndrome, a cardiometabolic risk factor that includes hypertension, insulin resistance, excessive blood sugar, abdominal obesity, and dyslipidemia [12]. There are three plausible mechanisms (see Fig. 1): (1) alteration of gut microbiota, (2) acceleration of senescence and atherosclerosis, and (3) relation with arrhythmogenesis.

Effect on gut microbiota

One potential mechanism through which artificial sweeteners may contribute to cardiovascular disease is by disrupting the balance of gut bacteria by selectively promoting the growth of certain bacterial species while suppressing others. The gut microbiota plays a key role in regulating metabolism and immune function, and disturbances in the gut microbiota have been linked to various diseases, including obesity, type 2 diabetes, and cardiovascular disease (CVD). The consumption of artificial sweeteners may alter the expression of genes involved in carbohydrate metabolism, impacting the growth and activity of gut bacteria, which can potentially lead to metabolic and inflammatory changes that contribute to vascular dysfunction and cardiovascular disease [13].

Effects on atherosclerosis

Impaired endothelial function following the consumption of artificial sweeteners aids in the initiation and development of cardiovascular disease. Artificial sweeteners might accelerate atherosclerosis and senescence via impairment of the function and structure of apoA-I and HDL. High-density lipoprotein (HDL) and its major protein constituent, ApoA-I, play a role in processes related to senescence. However, the function and structure of ApoA-I and HDL can be altered by non-enzymatic glycation, which leads to the formation of advanced glycated end (AGE) products. Long-term consumption of artificial sweeteners (AS), even in lower concentrations, may lead to the modification of ApoA-I and protein cleavage, similar to non-enzymatic glycation leading to the production of advanced glycated end (AGE) products. This can have negative consequences on cardiovascular health and aging [14]. The modification of ApoA-I by artificial

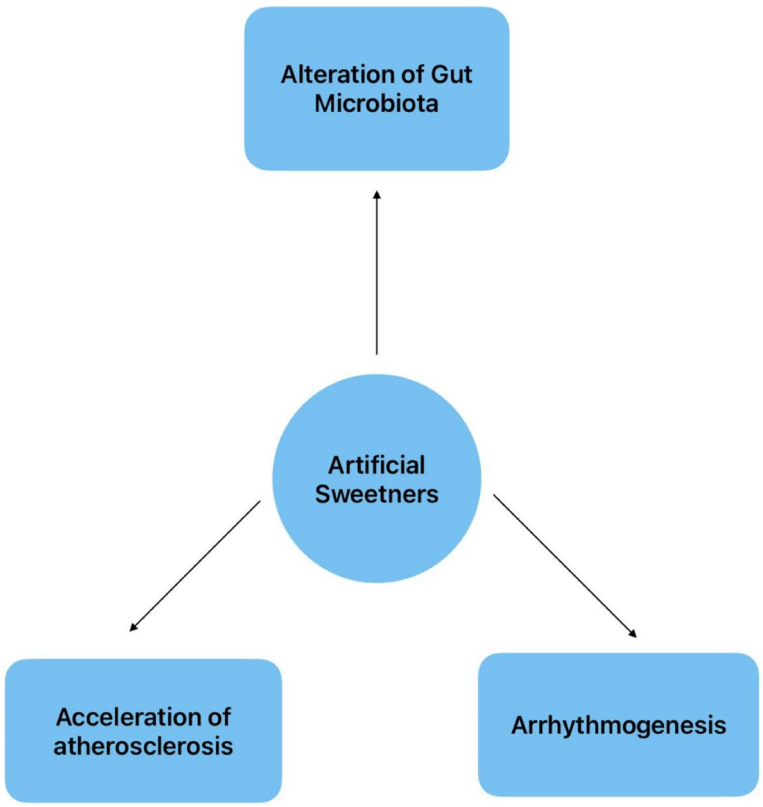

Fig. 1 Plausible mechanisms through which artificial sweeteners may contribute to cardiovascular disease

sweeteners is associated with the loss of antioxidant ability and impairment of phospholipid binding ability. The loss of antioxidant ability may contribute to increased oxidative stress, which accelerates the process of atherosclerosis. The impairment of phospholipid binding ability may affect the ability of ApoA-I to transport lipids, which is critical for maintaining cholesterol levels and preventing the development of atherosclerosis. Macrophage metalloproteinases degrade HDL-associated ApoA-I at both the N- and C-termini in coronary artery disease patients. This proteolytic cleavage of ApoA-I can result in the production of dysfunctional ApoA-I and HDL, which can contribute to the development and progression of atherosclerosis [15]. Aspartame may cause oxidative stress in cardiac tissue and has been demonstrated to affect cardiac function, leading to decreased heart rate variability (HRV), sympathetic dominance, and loss of vagal tone. The increased susceptibility to cardiovascular illness could be explained by the lack of protective vagal tone [16]. Aspartame's toxic effects can also cause structural alterations in the heart, which present as compensatory myocyte hypertrophy. Long-term consumption of artificial sweeteners (Splenda) caused a slight elevation in left ventricular end-diastolic pressure (LVEDP) which could lead to impaired LV relaxation.

Effects on arrhythmias

The regulation of cardiac electrophysiology and arrhythmogenesis is significantly influenced by the autonomic nervous system [17]. Monosodium glutamate (MSG) and aspartame are found to be excitotoxins of cardiac tissue leading to "lone" atrial fibrillation, which infers to tachycardia in the absence of hypertension, heart failure, and coronary artery disease. Aspartate and glutamate, respectively, are the derivatives of amino acids that cause the reaction to MSG and aspartame. Glutamate receptors have been found in various tissues throughout the body, including the heart's electrical conduction system and the heart itself. These receptors play essential roles in the maintenance of cardiac electrophysiology. When glutamate and aspartate are consumed in their free form as food additives, they can be absorbed rapidly into the bloodstream, leading to higher levels of these amino acids in the body than would normally occur through the gradual breakdown of protein in the digestive process. This rapid absorption can have different effects on the body, including the overstimulation of their receptors and potential excitotoxicity in the cardiovascular system [18]. Future studies could examine different types of artificial sweeteners, as well as their potential interactions with other dietary factors and lifestyle

factors. In addition, more research is needed to explore new possible mechanisms through which artificial sweeteners may impact cardiovascular health.

Discussion

Artificial sweeteners, or AS, are sugar substitutes that provide sweetness to foods and beverages without the added calories that come with regular sugar. As a result, they have become increasingly popular among people looking to reduce their calorie intake or manage their blood sugar levels, particularly among individuals with diabetes. It has also been linked to decreased body weight, body mass index, percentage of body fat, and intrahepatocellular fat [19], which could be beneficial for blood pressure and other cardiovascular changes [20]. Another beneficial aspect of AS is the prevention of postprandial hypotension (PPH) which is linked to an increased risk of falls, syncope, angina, and transient ischemic attacks, especially in elderly persons and patients with autonomic dysfunction. Among nutritive sweeteners, glucose promotes the most drop in postprandial blood pressure and should be avoided in PPH patients [21]. While artificial sweeteners are very popularly used these days, especially in patients with Diabetes, recently there have been concerns about their negative effects. Data in both animal models and humans suggest that their effects may contribute to metabolic syndrome and the obesity epidemic [22]. A study conducted by Mathur et al. showed that Artificial Sweeteners could cause a higher insulin resistance [23] and there is a direct association between hyperinsulinemia, Insulin resistance and cardiovascular disease [24]. Insulin resistance causes improper calcium homeostasis and atrial remodeling, increasing the risk of atrial fibrillation [25]. A study by Mossavar et al. in postmenopausal US women showed Increased risk of stroke, particularly the small artery occlusion subtype, CHD, and all-cause mortality that were linked to higher intake of Artificially sweetened beverages [26]. Frequent consumption of artificially sweetened beverages in mid- and late-life can lead to an increased risk of vascular events [27] and AS alters HDL, particularly apoA-1, and thus reduce the antiatherogenic action of HDLc [28]. AS can induce changes in the gut microbiota's composition also known as dysbiosis [29, 30] and the etiology of several diseases such as metabolic syndrome, type 2 diabetes, hyperlipidemia, and cardiovascular disorders, is influenced by gut microbiota dysbiosis [31]. A study by Zhang et al. demonstrated that the dysbiosis of the gut microbiota promotes age-related atrial fibrillation through the activation of atrial NLRP3-inflammasome and they found that a healthy microbial intervention over a lengthy period of time might stop age-related atrial fibrillation [32]. Long-term administration of sucralose in mice dramatically lowered serum levels of high-density lipoproteins (HDL) and increased serum levels of low-density lipoproteins (LDL) [33]. While, study by Basson et al. showed sucralose had the greatest impact on promoting peroxisome proliferator activated receptor alpha (PPARα) expression in rats [1]. Peroxisome proliferator-activated receptor (PPAR)-alpha is a ligand-activated transcriptional factor that belongs to the family of nuclear receptors. PPAR-alpha regulates the expression of genes involved in fatty acid beta-oxidation and is a major regulator of energy homeostasis [1]. A variety of sugar replacements have received FDA approval and are regarded as safe. However, the American Heart Association and the American Diabetes Association advise limiting the use of sweeteners because there isn't enough proof to support their long-term impact on body weight and cardiometabolic risk factors [29].

Conclusion

AS were first introduced to the food market in the 1800s as substitutes for sugar. The rationale of introducing AS was to provide sweetness with almost zero calories thereby trying to avoid the detrimental effects on health. They can lower sugar and calorie intake, resulting in beneficial effects such as weight loss, reduced body mass index, decreased body fat percentage, and intrahepatocellular fat reduction. These benefits contribute to blood pressure control and prevent postprandial hypotension. Long-term use of AS poses a substantial risk to cardiovascular health. AS use is noted to cause insulin resistance, stroke, cardiovascular diseases, and mortality, although more research is required to determine the effects. Various mechanisms have been suggested, associating the use of AS to increased risk of metabolic syndrome thereby increasing the risk of cardiovascular diseases. AS can cause acceleration of senescence and atherosclerosis via impairment of the function and structure of apoA-I and HDL. AS use alters gut microbiota, contributing to metabolic, inflammatory changes, vascular dysfunction, and cardiovascular disease. AS use is associated with heart structural changes, myocyte hypertrophy, elevated LVEDP, and impaired LV relaxation. Many claimed benefits of AS remain unverified in large clinical studies, and recent evidence challenges established benefits. Healthcare providers must carefully evaluate individual benefits and risks before recommending AS use. Different populations have varying goals when using AS products, which should be considered in holistic dietary recommendations. Healthcare providers should be aware of current evidence-based guidelines and inform consumers about potential risks of AS use.

Abbreviations

AS	Artificial sweeteners
CVD	Cardiovascular disease
FDA	Food and Drug Administration
HDL	High-density lipoprotein

Acknowledgements
None.

Code availability
Not applicable.

Authors' contributions
The information on Artificial sweeteners has been contributed by Sandeep Singh, Aditya Kohli, Stuti Trivedi, and Sai Gautham. All the authors have prepared the original draft. Conceptualization and design by Sandeep Singh, Aditya Kohli, Stuti Trivedi, Sai Gautham, and FNU Anamika. Draft editing, table, and figure contributed by Nikita Garg, Meet Patel, and Ripudaman Singh Munjal. Supervision by Rohit Jain and Ripudaman Singh Munjal. All authors read and approved the final manuscript.

Funding
No funding was obtained.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
No ethics approval needed. Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 18 May 2023 Accepted: 14 June 2023
Published online: 20 June 2023

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