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ARTIFICIAL SWEETENERS - AS SAFE AS THEY SEEM? IMPACTS ON GUT MICROBIOTA, METABOLISM, INFLAMMATION, CARDIOVASCULAR HEALTH AND SPORTS PERFORMANCE - A LITERATURE REVIEW

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ABSTRACT

For a considerable length of time, artificial sweeteners have been seen as safe dietary ingredients, promoting weight control and regulating blood sugar levels. However, a growing number of scientific studies are questioning their supposed biological neutrality. Current analyses suggest that some of these substances may affect the composition and function of the gut microbiota, which in turn may affect the immune system and play a role in the development of chronic inflammatory bowel diseases such as ulcerative colitis and Crohn's disease. There is growing evidence of a potential link between long-term intake of artificial sweeteners and the onset of insulin resistance and type 2 diabetes. In addition, it has been noted that frequent consumption of artificially sweetened beverages may be associated with an increased risk of stroke, cardiovascular disease and higher overall mortality, especially among overweight or obese postmenopausal women. These substances are commonly used in protein supplements, energy drinks and sports supplements, which may also affect important post-exercise recovery processes - including inflammation, insulin regulation, gut function and hydration status. These observations highlight the need for further interdisciplinary research into the long-term effects of artificial sweeteners on metabolic health and overall body function, especially in groups with high levels of consumption, such as people with metabolic syndrome and patients with type 2 diabetes.

KEYWORDS

Artificial Sweeteners, Gut Microbiota, Glucose Metabolism, Inflammatory Bowel Disease, Type 2 Diabetes, Insulin Resistance, Metabolic Health

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Introduction.

Artificial Sweeteners (AS), commonly used as low-calorie sugar substitutes, play a crucial role in the dietary management of people struggling with obesity and type 2 diabetes. For many years, they have been recognised as a safe component to aid weight loss and blood glucose regulation. However, in the light of a growing number of scientific reports, doubts have been raised about their supposed biological inertness.There are assumptions that the use of artificial sweeteners may support weight loss, reducing the risk of type 2 diabetes. Additionally, it has been assumed that sweeteners do not cause rapid and large changes in blood sugar levels, which may help to maintain glycaemic stability in people with metabolic problems [1,2]. However, in recent years, more and more research has focused on the potential effects of these substances on the gut microbiot. It has been argued that artificial sweeteners can affect both the composition and behaviour of the gut microbiota, with potential implications for the whole body. AS increasingly used as alternatives to sugar, they have the ability to affect the expression of genes related to the metabolism of microorganisms in the gut. These changes can lead not only to modifications in the composition of the microbiome, but also affect its metabolic functions, which can have a variety of consequences for a person's health [2].

A more in-depth analysis of this issue is encouraged by studies that make us reflect on whether, surely, the benefits of AS use do not outweigh the loss. A French cohort study involving 102,865 adult participants (follow-up: 7.8 years) noted a positive relationship between the use of artificial sweeteners and overall cancer risk. Particularly strong associations were found for aspartame and acesulfame K. Aspartame consumption was associated with a higher risk of breast cancer and obesity-related cancers [3]. Studies in rats have revealed that initial exposure to acesulfame K (ACK) affects sugar preference, glucose metabolism, sweet taste receptor expression and collagen genes in the hippocampus. This, in turn, results in memory problems that depress the hippocampus in adulthood [4]. In a study on the Women's Health Initiative group (n = 81,714; follow-up period: 11.9 years), it was noted that frequent consumption of artificial sweeteners is significantly associated with a higher risk of death overall, especially from stroke, small cerebrovascular disease and coronary heart disease [5].

Methodology

A narrative review was conducted based on a comprehensive literature search in the PubMed and Google Scholar databases. Articles were selected using keyword queries such as artificial sweeteners, gut microbiota, glucose metabolism, inflammatory bowel disease, type 2 diabetes, insulin resistance and metabolic health. The search strategy focused on studies published between 2012 and 2024. The selected contributions include different types of articles, such as research papers, systematic reviews, meta-analyses and narrative reviews, which provide a comprehensive overview of the current state of knowledge. Particular attention was paid to studies investigating the relationship between artificial sweeteners and intestinal dysbiosis, glucose regulation, immune system modulation, and chronic inflammatory conditions such as inflammatory bowel disease (IBD).

Artificial sweeteners and the gut microbiota

Artificial sweeteners, although commonly used as an alternative to sugar, can significantly affect the delicate balance of the intestinal microbiota. Their regular consumption is associated with the risk of dysbiosis, a condition in which the natural harmony between the different species of bacteria residing in the gut is disrupted. In particular, there is a decrease in the number of beneficial micro-organisms such as Lactobacillus and Bifidobacterium which play a key role in maintaining the health of the digestive system [6]. At the same time, there is an increase in Proteobacteria as well as Clostridium difficile and E. coli, which can cause infections and inflammation in the gut [7]. A change in the composition of the microbiota is not without consequences. It leads to a weakening of the integrity of the intestinal barrier, resulting in a phenomenon known as “increased intestinal permeability”. In this condition, the intestinal walls become more permeable, allowing toxins, undigested food particles and other harmful substances to enter the bloodstream. The presence of these agents outside the gastrointestinal tract can, in turn, initiate chronic systemic inflammation, which is associated with many chronic diseases, including metabolic and autoimmune diseases [8].

Intestinal dysbiosis, described earlier, can be seen as a key element in the process leading to various general health problems. It is from here that a number of adverse biological effects begin. Initially, a chronic low-grade inflammation in the intestinal mucosa is triggered. This condition can exacerbate already existing inflammatory bowel diseases, such as Crohn's disease or ulcerative colitis, leading to a worse course of these conditions and making their therapy more difficult [9]. When the intestinal microflora loses its ability to function properly, there is a significant decrease in the production of short-chain fatty acids, which are crucial for energy regulation and glucose and lipid balance. Deficiency of these acids promotes fat deposition, which is important in the context of overweight and obesity. [10, 11]. In addition, abnormal gut microflora negatively affects tissue insulin sensitivity, leading to insulin resistance, which then increases the risk of type 2 diabetes. In subsequent phases, chronic inflammation caused by a disturbed gut environment contributes to problems with glucose metabolism, which exacerbates metabolic difficulties, affecting the functioning of the whole body [12, 13].

Neotame, an intense low-calorie sweetener approved by the FDA in 2002, is still poorly recognised for its effects on the gut microbiota. Scientists applied next-generation sequencing and metabolomic analysis using gas chromatography-mass spectrometry (GC-MS) to investigate the effect of neotame on the gut microbiome and the profile of metabolites in the faeces of CD-1 strain mice. Four-week administration of neotame led to a decrease in alpha diversity and a change in beta diversity of the microbiota. A significant decrease in Firmicutes and a concomitant increase in Bacteroidetes was observed. Functional analysis revealed differences in metabolic pathways between the experimental and control groups, including lower expression of genes involved in butyrate biosynthesis. Neotam also affected the composition of metabolites in cals- a significant increase in levels of many fatty acids, lipids and cholesterol was found, while concentrations of substances such as malic acid and glyceric acid were reduced. These results provide the first evidence for specific interactions of neotame with the gut microbiota and the potential consequences of these interactions for host metabolism [14]. Increased intestinal barrier permeability has been noted not only in inflammatory bowel disease, but also in systemic diseases such as diabetes, chronic kidney disease, cancer and cardiovascular disease. A growing body of evidence suggests that the gut microbiota has an important role in regulating intestinal barrier function through the production of metabolites, such as short-chain fatty acids (SCFAs) and lipopolysaccharides (LPS), which may contribute to increased intestinal permeability. Despite a growing body of research, the mechanisms behind this phenomenon are still not fully elucidated [8]. In addition, AS have been shown to affect the enteroendocrine system by regulating the secretion of intestinal hormones such as GLP-1 and PYY, and may also affect the production and release of neurotransmitters. Such perturbations in neuroendocrine signalling can affect intestinal peristalsis, the rate and efficiency of nutrient absorption and the intestinal microenvironment, generally leading to significant changes in the regulation of glucose metabolism.

A growing body of research also indicates that certain types of AS may promote the development of intestinal dysbiosis and inflammation, in part by affecting bile acid metabolism. Increased concentrations of these substances in the gut can compromise the integrity of the intestinal barrier and activate pro-inflammatory signalling pathways, potentially contributing to the emergence of insulin resistance and other metabolic disorders [15, 16].

The study reveals that long-term administration of acesulfame potassium (ACK) to mice induces significant changes in intestinal balance. The artificial sweetener stimulates the production of pro-inflammatory cytokines, reduces GLP-1R and GLP-2R receptor concentrations and contributes to structural and functional damage to the small intestine, including increased permeability. ACK also affects the composition of the intestinal microbiota and enhances the migration of lymphocytes to microvessels in the gut, which may have a role in the onset of inflammation. Although transfer of the microbiota from mice treated with ACK did not cause damage to the recipients, the results indicate a direct effect of this sweetener on the intestinal mucosa. These data challenge previous beliefs about the safety of long-term use of acesulfame K and highlight its possible role in the onset of inflammatory bowel disease [17].

Artificial sweeteners and the cardiovascular system

The results of one study suggest a possible correlation between high consumption of beverages with artificial sweeteners and an increased risk of certain serious health problems, such as stroke, heart disease and higher overall mortality. Such a trend was particularly evident among postmenopausal women [18]. Women who are overweight, and those who are obese, may be at particular risk, as may those who have not previously been diagnosed with cardiovascular disease or diabetes. This suggests that the negative effects of consuming artificially sweetened beverages may also occur in people who appear healthy, as long as they have other risk factors [10, 19]. Women who consumed two or more beverages with artificial sweeteners daily had a 23% higher risk of stroke and a 31% higher risk of ischaemic stroke. Consumption of beverages with artificial sweeteners is associated with a 29% higher risk of developing coronary heart disease. In addition, there is also a noticeable 16% increase in total mortality in the group of people who frequently use such products [5].

The researchers conducting the study emphasise the need for further, more thorough research to help not only confirm the initial epidemiological observations, but also to understand the biological mechanisms involved in the perceived relationships. Knowledge of these processes could be crucial in the development of dietary recommendations, especially in the context of preventing cardiovascular disease in postmenopausal women.

Artificial sweeteners and glucose metabolism disorders

New theories suggest that changes in the microbiota may affect tissue insulin sensitivity, which may lead to insulin resistance. Nonetheless, the results of studies in this area are still inconclusive and do not allow firm conclusions to be drawn, indicating the need for further, more detailed research [20].

A cohort study of 105,588 French adults showed that the use of artificial sweeteners is associated with an increasing risk of developing type 2 diabetes. Positive associations were recorded for both overall sweetener consumption and for specific substances: aspartame, acesulfame K and sucralose [21]. Furthermore, it has been shown that problems caused by artificial sweeteners may include changes in the gut microbiome, both in mice and in healthy humans, which in turn may be related to the causes of type 2 diabetes [13].

The authors noted specific changes in the microbiome associated with eating artificial sweeteners. In particular, increased levels of kynurenine - a substance associated with the development of type 2 diabetes- have been highlighted. In addition, overactive metabolic pathways associated with the production of substances that may contribute to diabetes have been discovered [22]. A multivariate analysis revealed that people who regularly used artificial sweeteners (“always or almost always”) had a higher risk of type 2 diabetes compared to those who avoided them. Even after accounting for body mass index, this risk remained significantly elevated. Similar trends were seen in women who had used sweeteners in sachet or tablet form for more than ten years - in this group, the risk of type 2 diabetes was higher than in those who had no such exposure. Also, when BMI was taken into account, the risk remained elevated [23].

Artificial sweeteners and inflammatory bowel diseases

Diets high in fat and regular consumption of sweetened beverages may increase the risk of inflammatory bowel diseases [24].

Therefore, the analysis of artificial sweeteners in terms of their impact on the development of inflammatory bowel diseases also deserves attention. In the context of inflammatory bowel diseases such as Crohn's disease and ulcerative colitis, there are increasing theories that suggest that artificial sweeteners may not only influence the course of these conditions, but also, perhaps, participate in the mechanisms that may cause them. This requires further research, but this direction opens up new possibilities in understanding the role of diet and its components in the development of chronic inflammatory diseases [25].

In a 12-week study involving 24 participants who regularly used aspartame, significant changes in the composition of the gut microbiota were noted. The hallmark of the dysbiosis observed was a reduction in the diversity of microbial species in the gut and an increase in the number of bacteria with pro-inflammatory properties. These changes were accompanied by elevations in inflammatory biomarkers such as C-reactive protein (CRP), as well as mild metabolic abnormalities, including higher fasting blood glucose levels.

The authors of the study suggested that the action of aspartame is to selectively promote the growth of microorganisms that can produce inflammatory mediators, which in turn could lead to the development of chronic inflammation and metabolism [26]. Dysbiosis, combined with disruption of the intestinal mucus structure, can lead to increased permeability of the intestinal barrier and the development of leaky gut syndrome. This, in turn, results in the passage of toxins and pathogens into the bloodstream, which initiates inflammatory cascades, favouring the development of generalised inflammation and exacerbations of inflammatory bowel disease (IBD). The juxtaposition of these modifications of the intestinal microflora and the higher permeability of the intestinal walls may favour the occurrence of intestinal inflammation [8].

Artificial sweeteners and the sports aspect

Artificial sweeteners, frequently found in protein shakes, energy drinks, and other fitness supplements, offer a sugar-free, low-calorie option. However, emerging research indicates they may influence several key aspects of post-exercise recovery- such as inflammation, insulin regulation, gut function, and hydration. These elements play essential roles in how effectively the body heals and rebuilds muscle tissue after training. Efficient muscle recovery relies on proper nutrient absorption, regulated inflammatory responses, and the stimulation of protein synthesis. Because artificial sweeteners can alter both metabolic pathways and the gut microbiome, it is important to examine whether their presence supports or impairs the muscle repair process. The study of how these sweeteners affect muscle regeneration- including their impact on inflammation, insulin sensitivity, gut health, and hydration status- is gaining growing scientific attention. Inflammation plays a crucial role in the muscle recovery process by aiding in the repair of tissue damage caused by exercise. Yet, when inflammation becomes chronic, it can delay recovery, increase muscle soreness, and interfere with long-term muscle development. Some research points to the possibility that certain artificial sweeteners may contribute to inflammation, raising questions about their impact on muscle healing [27].

According to physiological data from studies, traditional sweeteners (glucose, sucrose and fructose) stimulate the secretion of satiety hormones in the digestive tract. In addition, sucrose and glucose inhibit the secretion of ghrelin (the hunger hormone) and slow gastric emptying. Of these, it is glucose that shows the strongest effect on gastrointestinal hormones. In contrast, short-term consumption of artificial sweeteners such as sucralose has no effect on either the secretion of satiety hormones or the rate of gastric emptying. Since gastrointestinal hormones play a key role in the sensation of satiety, their stimulation may limit further energy intake. Therefore, the use of sweeteners that stimulate the secretion of these hormones as a so-called “preload” (initial dose) could help reduce caloric intake during later meals [28].

The study titled "Effects of pre-exercise sucralose ingestion on carbohydrate oxidation during exercise" found that calorie-free sweeteners can influence crucial hypothalamic pathways involved in appetite regulation. Given these findings, it would be valuable to investigate whether the use of sweeteners ultimately aids in long-term weight reduction by decreasing the intake of high-calorie sweets, or if, conversely, it stimulates appetite and makes weight management more difficult-an issue of particular importance for athletes [29].

The pink hue of a beverage can heighten its perceived sweetness, leading individuals to expect that it contains sugar or carbohydrates. This suggests that offering a pink-colored drink during exercise might provide ergogenic advantages, potentially due to a placebo effect. In the study "The placebo effect of a pink non-caloric, artificially sweetened solution on strength endurance performance and psychological responses in trained individuals," similar levels of motivation, emotional arousal, affect, and perceived exertion were reported

across trials involving a pink, non-caloric, artificially sweetened drink; a clear, non-caloric, artificially sweetened drink; and no drink at all. However, participants completed a greater amount of total physical work when given the pink solution. Thus, ingesting a pink, calorie-free, artificially sweetened beverage enhanced strength endurance without altering psychological responses. These findings are significant for future research on nutrition and for assessing athletic performance in practical sports settings [30].

Discussion

A growing number of studies based on animal models, clinical observations and epidemiological analyses show that the effects of artificial sweeteners (AS) on metabolic health are more complicated than previously thought and often controversial. Although these substances are promoted as a safe alternative to sugar, especially in the context of diabetes management and weight loss, a growing body of evidence calls into question their long-term benefits and may suggest negative metabolic effects [1].

Possible mechanisms explaining these effects include gut microflora imbalance, changes in hormonal regulation, increased insulin resistance and persistent, chronic low-grade inflammation. In addition, the effects of AS on the body vary and can be determined by a number of factors, such as the specific type of sweetener used, its dose, the duration of exposure, and the personal characteristics of the user, such as body weight, the presence of comorbidities or the initial state of the gut microbiota [2].

A legitimate question arises as to what extent changes in the microbial environment of the gastrointestinal tract are directly influenced by AS consumption, and to what extent they are the result of interactions with other aspects of lifestyle [31]. It should be noted that many health-promoting behaviours - or lack thereof - can have a significant impact on the microbial balance in the body. Factors such as tobacco addiction, excessive alcohol consumption, a poor quality diet low in fibre and predominantly in processed foods, as well as limited access to comprehensive health and dental care, may act synergistically to increase intestinal dysbiosis. Such environmental and social variables should be taken into account analysing microbiota and diet research, including the potency of the impact of AS [31, 32].

Conclusions

For many years, AS were considered to be a safe adjunct for weight reduction and blood glucose regulation. However, in the light of a growing number of scientific reports, doubts are being raised about their supposed biological inertness. Current research indicates that some of these substances may affect the homeostasis of the gut microbiota. Disturbances in its functioning may, in turn, affect the activity of the immune system, the proper functioning of which is closely linked to gut health. In the context of inflammatory bowel diseases (IBD), such as Crohn's disease or ulcerative colitis, there are increasing hypotheses suggesting that artificial sweeteners may not only influence the clinical course of these conditions, but also potentially participate in mechanisms that favour their initiation. This requires further research, but this direction opens up new perspectives in understanding the role of diet and its components in the pathogenesis of chronic inflammatory diseases. Studies suggest that the use of artificial sweeteners may have a role in the development of insulin resistance and increase the risk of the onset of type 2 diabetes. It is therefore important to continue detailed research into the long-term effects of their use. Future research on AS should use a multidimensional approach to understand their complex effects on human health, focusing especially on groups with high levels of consumption, such as patients with type 2 diabetes and those with metabolic syndrome. The study indicates that frequent consumption of beverages with artificial sweeteners may be associated with an increased risk of serious health problems, such as stroke, coronary heart disease and higher overall mortality. This effect was particularly evident in postmenopausal women, especially those who were overweight or obese, even if they had not previously suffered from diabetes or heart disease.

Although artificial sweeteners are valued for being low in calories and not directly affecting blood sugar levels, their use requires great caution and an understanding of the potential consequences.

Artificial sweeteners-often found in protein supplements, energy drinks and exercise supplements-may affect muscle recovery after exercise. Although they are low in calories and sugar-free, there is a growing body of research suggesting that they may affect key recovery processes such as insulin regulation, inflammation levels, gut function and hydration. Some studies show that consuming these sweeteners before physical activity can affect hypothalamic mechanisms that control appetite, which is important for weight control, particularly in athletes. Although artificial sweeteners may have some beneficial applications in terms of performance and metabolism, further research is needed to determine their long-term effects on metabolic health and physical fitness.

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