REVIEW ARTICLE

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Artificial sweeteners and their impact on human health

Sztuczne środki słodzące i ich wpływ na zdrowie człowieka

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Abstract

Introduction and Objective. Artificial sweeteners are non-caloric substances which are added to multiple products. There used by many people as substitutes for sugar in the belief this will be beneficial to their health. However, there is much controversy about artificial sweeteners and the safety of their consumption. The purpose of this review was to assess the newest articles on this topic, and define impact of artificial sweeteners on different aspects of health.

Review methods. 1) The research question was defined on the basis of recent literature; 2) inclusion criteria: indexed in Pubmed database, published in last 20 years, at least 75% of included articles published after 2015; 3) exclusion criteria: Case Reports, studies in languages other than Polish or English; 4) studies that seemed to be significantly biased.

Brief description of the state of knowledge. Each sweetener may have a unique impact on the human body and can be taken from a variety of sources. Only a few authors have taken these two facts into account in their studies, the results of which may be inconclusive or misinterpreted. Artificial sweeteners may increase the risk of cancer, cardiovascular diseases, diabetes mellitus and obesity; however, these thesis are uncertain due to lack of data and possible reverse causation in observational cohort studies. There is also the presumption that artificial sweeteners can alter gut microbiota and cause a change in the glycaemic response of the organism. In opposition to this, artificial sweeteners could be useful tool in reducing weight.

Summary. According to the current literature, it is difficult to state unequivocally that artificial sweeteners have a positive, neutral, or negative impact on human health. In future studies, researchers should differentiate the types of sweeteners and focus on including all possible sources.

Key words

sugar, artificial sweeteners, healthy lifestyle

Streszczenie

Wprowadzenie i cel pracy. Sztuczne substancje słodzące są dodawane do wielu różnych produktów żywnościowych. Zasadność ich stosowania budzi jednak liczne kontrowersje, przy czym wątpliwości związane są przede wszystkim z ich bezpieczeństwem dla zdrowia. Celem tej pracy było przedstawienie wyników publikacji na ten temat, które ukazały się w ostatnich latach, oraz określenie wpływu sztucznych substancji słodzących zdrowie człowieka.

Metody przeglądu.

1. Określiliśmy problem badawczy, opierając się na o najnowszej literaturze.
2. Do bazy publikacji włączyliśmy:
   – artykuły znajdujące się w bazie Pubmed,
   – teksty opublikowane w ciągu ostatnich 20 lat, przy czym co najmniej 75% artykułów, z których korzystaliśmy, to takie, które ukazały się drukiem po 2015 roku.
3. Wykluczyliśmy opisy przypadków i badania opublikowane w językach innych niż polski lub angielski oraz badania, które wydawały się zawierać znaczące błędy metodologiczne.

Opis stanu wiedzy. Każda sztuczna substancja słodząca może mieć unikalny wpływ na ludzki organizm. Co więcej, substancje te mogą pochodzić z różnych źródeł. Niewielu autorów wzięło pod uwagę te dwa fakty przy planowaniu swoich badań. Podejrzewa się, że sztuczne substancje słodzące mogą zwiększać ryzyko raka, chorób sercowo-naczyniowych, cukrzycy czy otyłości, ale brakuje wystarczających danych, by ostatecznie potwierdzić te przypuszczenia. Co więcej, sztuczne substancje słodzące wpływają na mikrobiotę jelitową, powodując zmiany w procesach metabolicznych zachodzących w organizmie. Skutki tych zmian również nie są dobrze zbadane.

Podsumowanie. W dostępnej obecnie literaturze brakuje danych pozwalających jednoznacznie określić wpływ sztucznych substancji słodzących na zdrowie człowieka. Do ostatecznego ustalenia tego wpływu konieczne zdaje się przeprowadzenie badań, w których uwzględnione zostaną różne rodzaje sztucznych substancji słodzących oraz różne źródła ich pochodzenia.

Słowa kluczowe

cukier, zdrowy tryb życia, sztuczne słodziki

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INTRODUCTION

Artificial sweeteners are consumed by billions of people around the world. There are several types that can be found in drinks, dairy products, chewing gums, desserts etc. (Tab. 1). As public awareness of civilization diseases rises, many people aspiring to achieve a healthy lifestyle decide to replace sugar in their diet with artificial sweeteners. The most common justification is that they preserve the taste of food products while, at the same time, allowing a significant reduction in the amount of calories in the diet because they are presented and perceived as 'non-caloric'. In fact, artificial sweeteners are divided into low-caloric and non-caloric. Aspartame contains the same amount of calories per gram as sugar; however, it is 400 times sweeter, which means that the energy intake from aspartame sweetened products is negligible. Acesulfame-K, saccharin, sucralose, neotame are not metabolized by the human organism, consequently too they have no energy value [1].

Table 1. Types of sugar substitutes

Sugar substitutes		
Plant-derived		Artificial
brazzein	Sugar alcohols:	acesulfame potassium
curculin	erythritol	advantame
fructooligosaccharide	glicerol	alitame
inulin	hydrogenated starch	aspartame
isomaltulose	hydrolysates	salt of aspartame-acesulfame
maltodextrin	isomalt	sodium cyclamate
miraculin	lactitol	neohesperidin
pentadin	maltitol	dihydrochalcone
polydextrose	mannitol	neotame
stevia	sorbitol	saccharin
thaumatin	xylitol	sucralose
and other		

In the European Union, the following artificial sweeteners are allowed to be used: acesulfame-K, aspartame, cyclamates, saccharins, sucralose, neohesperidine DC, neotame and salt of aspartame-acesulfame [2]. This is a heterogenic group of substances, with different chemical structures and way of metabolism, but they are all processed by chemical synthesis and stimulate the sweet taste receptors. A limit to the permitted daily consumption was established [3, 4] because consumption above the limit may lead to negative health effects. However, a lot of controversy has arisen around the topic of the safety of artificial sweeteners. Studies conducted *in vitro* on animal models did not align with the results of studies conducted on humans. The question arose as to whether a lack of the energy value of artificial sweeteners indeed facilitates body weight reduction. This review aims to summarize recent articles on the subject.

REVIEW METHODS

A review of the literature was carried out by searching the Pubmed and Google scholar databasse. The combination of following key words was used in search: artificial sweeteners, sugar substitutes, and non-nutritive sweeteners. Over 30 articles published between 2006–2023 were taken into account. More than 50% of the papers were published in last 5 years. Only papers that referred to the impact of artificial sweeteners on human health overall and on specific aspects, such as carcinogenicity, cardiovascular risk, gut microbiome, body weight and diabetes, included. No distinction was made between different artificial sweeteners. The majority of the articles described the most common sweeteners: aspartame, sucralose and acesulfame-K, and occur the most often in the review.

BRIEF REVIEW OF STATE OF KNOWLEDGE

Cancers. One of the attention-catching aspects for scientists regarding the use of artificial sweeteners is their potential carcinogenicity. The newest reports classify aspartame – one of the most common artificial sweeteners – as "possibly cancerogenic for humans". That statement is based on a "limited" evidence that aspartame causes hepatocellular carcinoma in humans, assuming that consumption of artificially sweetened beverages is a reliable approximation for aspartame intake. The studies that link aspartame with hepatocellular carcinoma were potentially biased or confounded, therefore the evidence is "limited" [5]. Some scientists postulate that the observed increased cancer incidence in populations of developed countries might also be caused to some extent by the usage of such substances as a part of a healthy diet. A study that particularly highlights this issue is the NutriNet-Santé cohort study conducted in France between 2008 and 2021 on a group of over 100,000 individuals [6]. This is the only prospective cohort study conducted on humans on such a large scale so far, which examined the carcinogenicity of the total amount of artificial sweeteners in the diet (from all sources). Researchers demonstrated that the consumption of artificial sweetening substances, mainly aspartame and acesulfame-K, is associated with an increased risk of developing tumors, particularly breast tumors and tumors related to obesity.

Other studies published so far focused on artificial sweeteners found in one product type (e.g. beverages), not taking into account all artificial sweeteners included in the diet of participants. That is why their results may be questioned. For instance, two independent cohort studies investigating the relationship between an increased risk of non-Hodgkin lymphoma and the consumption of artificial sweeteners yielded contradictory results – in one of them, no association was found [7], while in the other, an increased risk of non-Hodgkin lymphoma and multiple myeloma was observed in men [8]. On the other hand prospective cohort study conducted in Australia did not show any association between consumption of drinks containing artificial sweeteners and cancers related to obesity [9]. However, studies on animal models suggest the carcinogenic properties of artificial sweetener; the Ramazzini Institute published studies in 2006 and 2007 that reported a dose-dependent increase in the occurrence of malignant tumors in various organs in mice and rats under the influence of aspartame [10, 11]. Because of some controversies, the histopathological examination was repeated to confirm the presence of neoplastic cells in studied samples. The conclusions were confirmed – aspartame increases the risk of tumours in rodents, as well as in their offspring when they were exposed to this factor prenatally. In should be also noted that sugar consumption may be associated with carcinogenicity. In study by McCullough et al. patients consuming sugar-sweetened beverages were

proven to be at higher risk of obesity-related cancers, while patients consuming artificial sweeteners did not showed similarly strong positive association [12].

The discrepancies mentioned above and the fact that no evidence of carcinogenicity relevant to humans has been found so far in animal studies suggest that more precise data has to be gathered and analyzed, preferably in well-designed prospective clinical studies aimed at ultimately confirming or ruleing-out the connection between artificial sweeteners and carcinogenesis[13].

Cardiovascular risk. To date, long-term association between the consumption of artificial sweeteners and cardiovascular risk has not been well investigated. A recent study shows that while sugar consumption increases the cardiovascular risk and the increase is dose-dependent, consumption of artificial sweeteners in low doses does not increase the risk at all [14]. On the other hand, a study on the afore-mentioned NutriNet-Santé cohort revealed that individuals consuming a larger amount of artificial sweeteners from all sources of food had a higher risk of experiencing adverse cardiovascular events. An interesting discovery from this study was the fact that different sweeteners were associated with varying risks of these events. For instance, acesulfame-K and sucralose were linked to a greater risk of coronary heart disease, while the consumption of aspartame was associated with an increased risk of ischemic stroke. The authors claim that there is no point replacing sugar with artificial sweeteners. However, they do not exclude the possibility of some bias occurring in their study that would involve greater consumption of artificial sweeteners by obese participants due to their motivation to reduce body weight [15].

In another study conducted on a population of more than 80,000 women at postmenopausal age, researchers investigated the link between artificial sweeteners and cardiovascular events, including coronary artery disease, stroke and all-cause mortality [16]. In women who reported a higher consumption of artificially sweetened beverages, i.e., at least two cans per day, compared to those who did not consume them at all or consumed less than one can per week, a higher frequency of cardiovascular events was observed. The conclusions were similar after the exclusion of diabetic patients and patients with a history of cardiovascular diseases. Unfortunately, it was not possible to exclude women who, due to pre-diabetic conditions, increasing body weight, or elevated blood pressure values, chose to increase their consumption of artificially sweetened beverages.

Taking into account all conclusions of these studies, as well as their observational character, it is fair to say that high doses of artificial sweeteners may have some detrimental effect on the human cardiovascular system; however, further research is needed to confirm this finding.

Gut microbiome. Increasing attention is being drawn to the role of gut microbiome in the pathophysiology of different diseases. Gut microbiome is a set of populations of bacteria, viruses, fungi end other microorganisms that consists of more than 1,500 species [17]. It is unique for every individual, sensitive to any changes in diet, and crucial in maintaining the function of the immune, endocrine and digestive systems [18]. In recent years, the impact of artificial sweeteners on this fragile community of microorganisms has been studied.

It is difficult to determine the general impact of these substances because the absorption, distribution, metabolism, and excretion of each of them differs. For example, aspartame and its breakdown products do not have direct contact with the gut microbiota as they are rapidly absorbed in the small intestine and the stomach, and are then excreted through urine, as in the case of acesulfame-K. In contrast, a certain amount of consumed saccharine passes through the entire gastrointestinal tract without having direct contact with gut microbiota [19]. Research on laboratory animals indicates that artificial sweeteners can influence the gut microbiota. Surprisingly, these changes can be induced even by substances that do not directly pass through the large intestine, where the largest number of microorganisms reside. In one study, pregnant mice were administered acesulfame-K and sucralose at concentrations equivalent to the acceptable daily intake (ADI) for humans. This led to metabolic and quantitative changes in the microbiome of their offspring: the number of Firmicutes bacteria increased, while the number of A. muciniphila bacteria decreased [20]. Several other studies on animals confirmed changes in microbiome under the influence of artificial sweeteners [21, 22]. However, the causality between the two is questioned as the gut microbiota depends on the diet as a whole – consumption of carbohydrates, lipids, proteins and other nutrients. Consequently, it may have reflected the changes in the diet of animals during the study[19].

While studies on animals reflect changes in the sizes of populations of different intestinal bacteria, studies on humans do not confirm those findings. In Canada researchers conducted a double-blind, randomized clinical study on 17 healthy individuals aged 18–45 years [23]. Participants consumed aspartame and sucralose in doses of up to 20% of daily limit. Stool of participants was examined before and after two weeks of artificial sweeteners consumption. The results of these examinations did not reveal clinically significant changes in the quantitative and qualitative structure of the gut microbiota, nor did they show alternations in the levels of short-chain fatty acids, which are products of fermentation processes occurring in the intestines and serve functions including anti-inflammatory and nutritive roles for intestinal villi. A limitation of this study was the relatively short exposure period. It cannot be definitively stated that the same results would have been obtained if the study had lasted longer. Similarly, short-term consumption of saccharin, even at high doses, did not induce changes in the gut microbiome of healthy individuals [24].

On the other hand, another study demonstrated that in stool samples collected from healthy adults who consumed aspartame or acesulfame-K for four days, the quantity and relative proportion of major gut microbiota species remained unchanged, but slight alterations were observed in the overall species diversity [25]. Such alterations may sometimes lead to pathogenic cultures development. Shil et al. demonstrated that the consumption of artificial sweeteners increased the ability of certain bacteria to form biofilms and invade host epithelium. However, the precise detrimental effects of this process are yet to be investigated [26].

As described above, results of studies on the impact of artificial sweeteners on gut microbiota are often contradictory, but there is evidence that changes in the microbiome of the intestines can increase the risk of certain diseases. Suez et al. showed that such changes may result in impaired glucose tolerance, and eventually lead to diabetes [27]. Dramatically

different responses of gut microbiota to artificial sweeteners in the diet may originate from differences in its compositions between individuals, or between studied populations.

Body weight. Higgins and Mattes conducted a study in which they compared the impact of various sweeteners on body weight in overweight or obese individuals. Ror 12 weeks, participants consumed every day 1.25–1.75 liters of beverages sweetened with different substances. It was found that after this period, there was a significant increase in body weight among individuals who consumed sucrose (commonly known as sugar), as well as those who consumed Conversely, no significant changes in body weight were observed in individuals who consumed aspartame and sucralose [28].

Some studies indicate a positive correlation between the consumption of artificial sweeteners (or at least some types of artificial sweeteners) and long-term weight gain [28–30]. However, this is most likely caused by the fact that overweight or obese individuals, for various reasons, are more likely to consume artificially sweetened products, and they might find it harder to reduce their body weight. Another possible explanation of this phenomenon is that the consumption of artificial sweeteners might increase the subjective feeling of hunger, thus potentially lead to an increase in overall calorie consumption, and eventually to weight gain. [1]

Meta-analyses of studies on this subject suggest that despite all the afore-mentioned aspects, artificially sweetened beverages can be an effective tool to assist individuals aiming to adhere to recommendations for weight reduction [30].

The presence of low-calorie sweeteners in the diet does not automatically lead to weight reduction; it has to be combined with a caloric deficit. Simply replacing sugar with artificial sweeteners is not sufficient to decrease body weight or minimize its increase [31]. The new guideline released by World Health Organization recommend not using non-sugar sweeteners in order to control body weight in the long-term. It is also stated that the usage of artificial sweeteners does not diminish the risk of noncommunicable diseases. The authors suggest that both adults and children should try other methods of body weight reduce than replacing sugar with artificial sweeteners. The recommendation is conditional due to possible confounding of conducted studies, and does not apply to people with pre-existing diabetes [32].

Type 2 diabetes. A review of articles published so far indicates that artificial sweeteners may affect certain mechanisms regulating glucose metabolism. The authors mention a possible indirect impact that takes place through changes in gut microbiota [27]. Pepino et al. investigated how consuming sucralose affects the glycaemic and insulin responses of the body in obese individuals who had never previously consumed artificial sweeteners. Participants consumed either sucralose (experimental group) or water (control group); the oral glucose tolerance test was conducted after 10 minutes. It was found that in the experimental group, peak levels of glucose, insulin, and C-peptide in the blood were higher compared to the control group. A slower decline in insulin levels in the blood was also noted. Therefore, consuming sucralose could alter the body's response in oral glucose tolerance test in obese individuals who had not previously consumed artificial sweeteners [33]. A study by Ritu et al. also showed that the consumption of artificial sweeteners may reduce glucose levels (both fasting and post-prandial), as well as total cholesterol, triglyceride, and very-low-density lipoprotein in patients with type 2 diabetes [34].

A cohort study conducted in Europe on a group of over 60,000 women observed for 18 years, demonstrated that the consumption of artificial sweeteners, both in larger amounts and over a longer period, was associated with a higher risk of type 2 diabetes. This association diminished, but remained statistically significant, after excluding individuals with increased BMI (BMI-adjusted models) [35]. Another large cohort study conducted in the USA also showed that the consumption of sugar-sweetened beverages, fruit juices, and artificially sweetened beverages, was linked to a 16–18% higher risk of type 2 diabetes. Only substituting these beverages with water, unsweetened coffee, or tea reduced this risk by 2–10% [36]. However, the authors emphasize that the association between artificially sweetened beverages and type 2 diabetes might be due to reverse causation. Increased consumption of artificially sweetened beverages was inversely correlated with weight gain, which could stem from the fact that individuals at a higher risk of diabetes were more inclined to switch from sugary drinks to non-caloric sweetened beverages. The authors of a meta-analysis published in 2015 argued that the consumption of artificially sweetened beverages might be directly linked to an increased risk of type 2 diabetes [37]. However, due to insufficient data and the potential for reverse causation, the results of this analysis are uncertain. Researchers do agree, however, that replacing sugar with artificial sweeteners is not beneficial for the prevention of type 2 diabetes, and do not recommend such an approach.

Children and pregnant women. Comparatively fewer studies have been conducted on specific groups of the population, such as children and pregnant woman. The World Health Organization's meta-analysis emphasizes that the certainty of evidence in that topic is moderate to low due to lack of data, and the fact that the conclusions of conducted studies are often contradictory [38]. One of the randomized controlled trial suggests that replacing sugar sweetened beverages with artificially sweetened beverages contributes to reducing weight gain in normal-weight children [39]. However, the afore-mentioned WHO guideline claims that there is no benefit in consuming artificial sweeteners in order to control body mass. This recommendation also applies to children. Studies conducted on pregnant women suggest that there might be a link between usage of artificial sweeteners and preterm birth [40, 41]. Nevertheless, the authors claim that further investigation is needed to confirm their findings.

CONCLUSIONS

Artificial sweeteners are widely used in food products. Many people use them to reduce calorie intake without concern of possible negative side-effects. Even though nutritional agencies attest to their safety, there is an increasing number of reports about the potential impact of these substances on elevated risks of cancer, cardiovascular diseases, obesity, and type 2 diabetes. There are also suspicions that by affecting gut microbiota, artificial sweeteners might contribute to various metabolic disorders. Given the current state of knowledge, it is challenging to determine whether the impact of artificial sweeteners on health is beneficial, neutral, or negative.

A significant drawback of the research published so far is that the majority did not consider all possible sources of artificial sweeteners, focusing instead on consumption from one source – typically beverages. This means that the actual impact of these substances might be underestimated. Another difficulty in conducting long-term observations is the diversity of artificial sweeteners available on the market. There are indications that each of the currently used artificial sweeteners might affect the human body in different ways. Sometimes, a single product contains a combination of different substances, making it very challenging to study the effects of each one individually, and differentiate the variations in their actions.

Moreover, the actual causal relationships between consuming artificial sweeteners and the risk of diseases are still unknown and future studies in this field should address these issues. Because of the lack of conclusive findings, the consumption of artificial sweeteners should be approached with caution.

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