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CHRONIC USE OF SWEETENERS AND INSULIN RESISTANCE

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ABSTRACT

The aim of this paper is to critically analyze the available data on the chronic use of low-calorie sweeteners (LCS) and their potential impact on the development of insulin resistance (IR). Insulin resistance, a key element of metabolic syndrome and a risk factor for type 2 diabetes, is increasing in parallel with the rising consumption of sweeteners used as sugar substitutes. The review covers the classification of LCS (synthetic, natural, sugar alcohols), their metabolism, and biological mechanisms that may modulate carbohydrate metabolism. Potential pathways of action include activation of sweet taste receptors T1R2/T1R3 in the intestine and pancreas, effects on incretin secretion, modulation of gut microbiota, regulation of appetite in the central nervous system, and interactions with insulin signaling pathways in peripheral tissues.

Clinical studies indicate that short-term LCS intake usually does not affect glycemia and insulinemia in healthy individuals. However, in people with obesity or without prior exposure, an increased glycemic and insulin response has been observed, particularly after sucralose. Stevia has shown hypoglycemic benefits in some studies, while aspartame remains largely neutral. Data on saccharin and microbiota suggest possible individual sensitivity. Observational studies associate chronic LCS intake with a higher risk of type 2 diabetes, although this may result from reverse causality.

The conclusions emphasize that LCS may support sugar and body weight reduction when used as part of a healthy lifestyle. However, they do not provide universal protection against IR, and their effects depend on the type of sweetener, metabolic status, and gut microbiota. Long-term randomized studies including diverse populations are required.

KEYWORDS

Insulin Resistance, Hyperinsulinemia, Low-Calorie Sweeteners, Microbiota, Type 2 Diabetes, Metabolic Syndrome

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Introduction

Insulin resistance is a condition characterized by reduced sensitivity of tissues to insulin, despite its normal or elevated plasma levels. Skeletal muscle, liver, and adipose tissue—key regulators of carbohydrate metabolism—are the most susceptible to this disorder [1]. Under normal conditions, insulin, through membrane receptors and the IRS-1/PI3K/Akt signaling cascade, increases glucose uptake and inhibits hepatic glycogenolysis. In insulin resistance, this process is impaired, leading to compensatory hyperinsulinemia which, in the long term, may result in β-cell dysfunction, fasting hyperglycemia, impaired glucose tolerance, and ultimately type 2 diabetes [1,2].

This condition is part of the broader concept of metabolic syndrome, which includes insulin resistance, visceral obesity, hypertension, dyslipidemia, and increased risk of atherosclerosis and cardiovascular disease [2,3]. In recent decades, the prevalence of insulin resistance has risen dramatically in both developed and developing countries. NHANES data indicate that in the United States, over 35% of adults meet the criteria for insulin resistance or its early forms, with rates exceeding 70% in obese populations [3,4]. Similar trends are observed in Europe, e.g., in the German DEGS1 study and the UK Biobank, where insulin resistance was particularly prevalent among individuals with overweight, low physical activity, and diets rich in simple sugars [4].

The rising incidence of insulin resistance coincides with major changes in dietary patterns, including increased consumption of highly processed foods and sugar-sweetened beverages. Awareness of the adverse metabolic effects of excessive sugar intake has led to the search for alternative sweetening agents providing sweetness with minimal or zero caloric value [5–7]. Consequently, over the past three decades, the consumption of low-calorie sweeteners (LCS)—also referred to as high-intensity or non-caloric sweeteners—has markedly increased. In the U.S., the proportion of adults regularly consuming LCS-containing products rose from 15% in the 1990s to over 25% in the second decade of the 21st century, while among children and

adolescents the rate nearly tripled [5]. Comparable trends are observed in Europe and worldwide, with the steepest increases in countries where "light" beverages dominate the market [7].

LCS are widely used in beverages, dairy desserts, baked goods, fruit preserves, chewing gums, dietary supplements, pharmaceuticals, and other products [6,7]. Their main declared benefits include reducing caloric intake, supporting weight control, lowering simple sugar consumption, and preventing dental caries [6–8]. Regulatory authorities such as EFSA, FDA, and JECFA have deemed LCS safe within established acceptable daily intake (ADI) levels [8].

Nevertheless, recent reports have questioned their metabolic neutrality. Experimental and observational studies suggest that chronic intake of certain sweeteners may influence gut hormone secretion, gut microbiota composition and function, and even glycemic and insulin responses [9–11]. Behavioral effects, such as compensatory caloric intake due to a perceived "energy saving," have also been highlighted [9]. Findings remain inconsistent: some studies indicate no effect or even benefit, while others suggest increased risk of insulin resistance and impaired glucose tolerance with long-term LCS use [9,10].

Given the rising prevalence of insulin resistance and widespread LCS consumption, a critical review of available scientific evidence is warranted. The aim of this paper is to analyze current data on the impact of chronic sweetener use on the development and progression of insulin resistance, with particular emphasis on clinical studies, meta-analyses, and underlying biological mechanisms.

Classification of Sweeteners

Low-calorie sweeteners (LCS) comprise a diverse group of compounds with a common feature—an intense sweet taste with minimal or zero caloric value. Compared to sucrose, their sweetness is typically several dozen to several hundred times greater, which allows for the use of much smaller amounts to achieve the desired sensory effect [6–8]. Although they are commonly divided into "natural" and "synthetic," this distinction does not always reflect differences in safety, metabolism, or health effects. A more precise classification considers their chemical structure, source of origin, and technological properties.

Natural-origin sweeteners, such as stevia or monk fruit, contain plant-derived compounds—mainly glycosides—that are not fully digested in the human gastrointestinal tract. Stevia, after ingestion, is metabolized in the large intestine by microbiota to steviol, which is subsequently conjugated in the liver and excreted in urine [8,12]. Monk fruit contains mogrosides, which are also resistant to enzymatic hydrolysis in the small intestine [13]. Natural sweeteners usually exhibit good thermal and acid stability, which enables their use in carbonated beverages, baked goods, and dairy products. Interestingly, in vitro studies and animal models have also attributed them potential antioxidant, hypotensive, and anti-inflammatory properties [12,13].

High-intensity synthetic sweeteners, such as aspartame, acesulfame K, saccharin, and sucralose, were developed and introduced in the 20th century in response to growing health awareness and the need to reduce dietary caloric intake. Aspartame, a methyl ester of the dipeptide phenylalanine and aspartic acid, breaks down after ingestion into its constituent amino acids and methanol, which requires caution in individuals with phenylketonuria [8]. Sucralose, a chlorinated derivative of sucrose, is largely unabsorbed and excreted unchanged, but its chemical stability makes it widely used in products requiring heat processing [8,14]. Saccharin and acesulfame K exhibit high resistance to heat and acidic environments, which accounts for their application in a wide variety of beverages and processed foods [8].

A third major group consists of sugar alcohols (polyols), such as erythritol, xylitol, sorbitol, and maltitol. Although their sweetness is lower than that of sucrose, they provide considerably fewer calories and are characterized by a low glycemic index [15]. Polyols are partially absorbed in the small intestine, while the unabsorbed fraction undergoes fermentation in the large intestine, which in some individuals may cause a laxative effect. Erythritol is an exception, as it is almost completely absorbed and excreted unchanged in urine, making it better tolerated [15].

In terms of safety, each sweetener has an acceptable daily intake (ADI) established by relevant authorities (EFSA, FDA, JECFA), expressed in mg/kg body weight/day, determined on the basis of toxicological and metabolic studies [8]. Importantly, even natural sweeteners are not free from potential side effects—their impact on microbiota, gut hormones, and metabolism may vary depending on dose, frequency of consumption, and the consumer's health status [6–8,11]. For this reason, while the classification of sweeteners facilitates their understanding from chemical and technological perspectives, it should not automatically determine their health evaluation.

Mechanisms of Potential Impact on Carbohydrate Metabolism

The impact of low-calorie sweeteners (LCS) on carbohydrate metabolism has been the subject of intensive research; however, results are often inconsistent. This occurs because the final effect depends on the complex interaction of many physiological and behavioral mechanisms, some of which are well documented, while others remain hypothetical [6–11,17].

One of the best-studied mechanisms is the activation of sweet taste receptors T1R2/T1R3, located most abundantly on lingual papillae, but also throughout the gastrointestinal tract, in the pancreas, and in other metabolically active tissues. Their stimulation in the intestine may modulate the expression of glucose transporters such as SGLT1 and GLUT2, increasing the ability of enterocytes to absorb sugars [18,28]. In turn, activation of these receptors in pancreatic β-cells may influence insulin secretion independently of blood glucose concentration [19]. Animal studies have shown that long-term exposure to certain LCS, e.g., sucralose, leads to changes in T1R3 receptor expression, which may modify the hormonal response to dietary stimuli [29].

Another important area is the modulation of incretin secretion. GLP-1 and GIP are key gut hormones that enhance postprandial insulin response, delay gastric emptying, and increase satiety. Clinical studies provide conflicting results—some report no changes in incretin secretion after LCS intake [20], while others suggest that in individuals without prior exposure to sucralose, GLP-1 secretion may increase in response to a glucose load [21]. It is possible that the effect depends on prior adaptation to a given sweetener, dosage, and coexisting dietary components [9,10].

Considerable attention has also been paid to the influence of LCS on gut microbiota. Chronic use of certain sweeteners, such as saccharin, has been shown in animal models to induce dysbiosis, characterized by an increased proportion of pro-inflammatory bacteria and a decrease in microorganisms producing short-chain fatty acids [11,27]. Loss of microbial balance may be associated with impaired gut barrier integrity, translocation of bacterial endotoxins, and chronic low-grade inflammation—mechanisms linked to the development of insulin resistance [23]. However, human studies, such as that by Serrano et al. [22], indicate that this effect is not universal and may depend on the baseline composition of the gut microbiota prior to LCS supplementation.

Equally important, though more difficult to document conclusively, is the effect of LCS on central mechanisms regulating appetite and the brain's reward system. Neuroimaging studies show that LCS consumption activates brain structures associated with sweet taste perception, but to a lesser extent than glucose, which may lead to a sense of "incomplete reward" and drive increased consumption of other energy sources [25]. The "cephalic phase insulin release" hypothesis further suggests that sweet taste, even without caloric intake, can trigger reflexive insulin secretion [24]. If glucose is not supplied following such an insulin release, blood glucose levels may fall, intensifying hunger.

Preclinical studies also provide evidence that LCS may affect the expression of genes related to insulin signaling in peripheral tissues. Aspartame and sucralose, under certain experimental conditions, modulated GLUT4 expression in skeletal muscle and the IRS-1/PI3K/Akt pathways, potentially influencing the efficiency of glucose uptake in response to insulin [26,29]. Although these findings require confirmation in human studies, they suggest a possible molecular mechanism underlying some of the observed metabolic effects.

Finally, the dietary context and metabolic status are increasingly emphasized in shaping LCS effects. In individuals with normal body weight and good insulin sensitivity, LCS often do not alter glycemic parameters, whereas in individuals with obesity, type 2 diabetes, or metabolic syndrome, more pronounced hormonal and glycemic responses may sometimes be observed [10,21,27]. Moreover, LCS consumption in combination with a high-fat or refined carbohydrate-rich diet may exacerbate potential adverse metabolic effects [27,30].

In summary, the mechanisms of LCS action are multi-level and encompass both peripheral processes (intestine, pancreas, liver, peripheral tissues) and central processes (brain, appetite regulation). The final effect is determined by many variables—the type of sweetener, dosage, duration of exposure, overall diet, as well as individual microbiota composition and metabolic predispositions.

Clinical Data

The assessment of the impact of low-calorie sweeteners (LCS) on insulin resistance in humans is based primarily on interventional studies, including both randomized controlled trials and observational studies. The results of these works are diverse and depend on the type of sweetener used, the duration of the intervention, participant characteristics, and the methodology applied to measure metabolic outcomes.

In short-term studies, ranging from a single exposure to several days, no significant changes in fasting glucose or insulin resistance indices are usually observed in healthy individuals. For example, Ford et al. reported that a single intake of sucralose or saccharin in doses corresponding to typical population consumption did not cause significant changes in postprandial glucose or insulin levels in healthy volunteers [20]. However, Pepino et al. documented that in obese individuals who did not regularly consume sweeteners, sucralose ingestion prior to an oral glucose tolerance test (OGTT) increased postprandial glucose and insulin responses by about 20% [21]. These findings suggest that prior exposure to LCS and baseline metabolic status may significantly influence the body's response.

Stevia often demonstrates a different profile in clinical studies. Anton et al. found that in individuals with type 2 diabetes and overweight, replacing sucrose with stevia reduced postprandial glucose and insulin levels without increasing appetite or energy intake [29]. Aspartame, in doses close to the acceptable daily intake (ADI), generally does not cause significant changes in glycemia or insulinemia in the short term, as confirmed by studies such as those by Renwick and Molinary [30].

More complex observations emerge in medium-term studies (several weeks to months). Grotz et al. conducted a 12-week intervention in which individuals with type 2 diabetes received sucralose at 15 mg/kg body weight/day; no significant changes were found in HbA1c, fasting glucose, or HOMA-IR [31]. By contrast, Suez et al. reported that a 7-day supplementation with saccharin in healthy individuals impaired glucose tolerance in some participants, accompanied by changes in gut microbiota composition [11]. This effect was, however, individual—only a subset of participants developed metabolic changes, suggesting that baseline microbiome composition influences the response to LCS.

In an 8-week trial, Barriocanal et al. found that stevia improved fasting glucose and certain lipid parameters in overweight individuals with impaired glycemia [32]. Aspartame, studied in interventions lasting 6–12 weeks, showed no significant effects on insulin sensitivity or body weight [8,30].

Long-term clinical studies on LCS are scarce but provide valuable insights. Peters et al. compared the effects of replacing sugar-sweetened beverages with either water or diet beverages (containing a mixture of sucralose, aspartame, and acesulfame K) in overweight adults. Both groups showed significant weight loss, but only the LCS group experienced a greater reduction in waist circumference, without changes in HOMA-IR [33]. Observational studies, such as the Nurses' Health Study and the Health Professionals Follow-up Study, suggest that regular consumption of diet beverages may be associated with a higher risk of developing type 2 diabetes [34]. However, the authors emphasized the possibility of reverse causation—individuals with overweight or diabetes risk factors may be more likely to consume LCS, which could confound the observed associations.

When comparing different LCS, sucralose shows the most divergent findings—from no effect in long-term trials [31] to significant increases in insulinemia in short-term trials among previously unexposed individuals [21]. Saccharin may induce metabolic changes linked to gut microbiota [11], though data remain inconsistent. Aspartame is generally neutral regarding glycemia and insulin resistance [8,30]. Stevia, on the other hand, shows beneficial effects in some studies, particularly among individuals with impaired glycemia [29,32]. Data on polyols indicate that erythritol and xylitol may reduce postprandial glycemia, but studies evaluating their effects on insulin resistance in the long term are lacking [15].

The conclusions from clinical studies are clear in only one respect—the effects of LCS on carbohydrate metabolism depend on context: the type of sweetener, baseline metabolic status, gut microbiota, and prior exposure to the compound. There is no conclusive evidence that LCS at typical doses cause insulin resistance in healthy individuals; however, under certain conditions (e.g., lack of prior exposure, presence of insulin resistance, or gut dysbiosis), they may modulate the metabolic response. Long-term randomized controlled trials with large sample sizes are needed, incorporating both metabolic parameters and microbiome analyses.

Clinical Significance and Recommendations

The clinical significance of low-calorie sweetener (LCS) use in the context of insulin resistance goes beyond the simple substitution of sugar with non-caloric substances. This is an area where scientific evidence, positions of health organizations, and clinical practice continue to intersect, and recommendations evolve as new data emerge. From a public health perspective, LCS may serve as part of a strategy to reduce added sugar and energy intake, potentially contributing to weight reduction and improvement of metabolic parameters. However, the long-term effectiveness of this approach depends on several factors, including the type of sweetener used, dietary context, baseline metabolic status of the patient, and individual physiological responses [35–37].

The positions of regulatory agencies and scientific societies in this regard are varied, though consistent in many respects. The European Food Safety Authority (EFSA) considers the acceptable daily intake (ADI) for individual LCS to be safe, including in people with type 2 diabetes, provided that the established limits are respected [8,35]. According to EFSA, compounds such as stevia, aspartame, and sucralose do not pose toxicological risks within the ADI, and their use may contribute to reducing sugar and calorie intake [14,35]. A similar position has been taken by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), which has repeatedly confirmed the toxicological safety of LCS, while also highlighting the need to monitor their long-term metabolic effects [38].

The American Diabetes Association (ADA), in its 2023 Standards of Care, emphasizes that LCS may serve as a tool to support the reduction of simple sugar intake, but only when they replace high-sugar products rather than being added to an already energy-rich diet [36]. By contrast, the World Health Organization (WHO), in its latest 2023 guidelines, has taken a more skeptical stance, recommending avoidance of chronic LCS use for body weight control, citing meta-analyses of observational studies that suggest a possible link between regular LCS consumption and increased risk of type 2 diabetes, hypertension, and cardiovascular events [37]. It is important to note, however, that the WHO primarily relied on observational data, which do not allow for establishing causality, whereas randomized trials generally show neutral or modest effects of LCS on body weight and glycemia.

A critical element of clinical evaluation is consideration of specific patient groups in whom LCS use may be associated with different metabolic outcomes. In children and adolescents, where metabolism is more dynamic and body weight is lower, the relative intake of LCS per kilogram of body weight may be higher, requiring particular attention [37]. In pregnant women, the safety of most LCS has been confirmed in toxicological studies, yet cohort studies suggest that LCS consumption during pregnancy may correlate with higher BMI in offspring later in life, potentially due to metabolic programming during the prenatal period [39]. In patients with insulin resistance, metabolic syndrome, or early type 2 diabetes, glycemic and hormonal responses to LCS appear to be more pronounced, especially with sucralose and saccharin, likely due to interactions with gut microbiota and differences in sweet taste receptor expression [11,21,27]. Finally, individuals with phenylketonuria must avoid aspartame due to its phenylalanine content [8].

Analysis of available clinical studies indicates that not all LCS are equal in terms of their metabolic effects. Stevia has shown in some studies the ability to lower postprandial glucose and insulin levels, possibly through effects on GLP-1 and GIP secretion [29,32]. Aspartame, when consumed within the ADI, appears metabolically neutral with regard to glycemia and insulin sensitivity [8,30]. Sucralose, on the other hand, may elicit an increased insulin and glycemic response in individuals who have not previously consumed it, whereas in regular users this effect is smaller or absent [21,31]. Saccharin, in animal studies, has been linked to gut dysbiosis and impaired glucose tolerance, while findings in human studies are less conclusive [11,22].

From the perspective of practical clinical recommendations, LCS may be used as part of strategies for weight and glycemic control, provided their introduction is accompanied by patient education, dietary modifications, and monitoring of metabolic parameters. Replacing sugar with LCS without reducing overall energy intake will not bring the expected metabolic benefits. It is also advisable to consider rotation and individualized selection of LCS, based on tolerance and possible physiological responses, and to avoid situations in which their use leads to compensatory increases in calorie consumption.

In summary, according to current evidence, LCS may serve as a tool to support the prevention and treatment of metabolic disorders, but their effectiveness is greatest when they are part of a comprehensive approach that includes diet, physical activity, and lifestyle modification. Nevertheless, further well-designed long-term studies are necessary to clearly determine their impact on the risk of insulin resistance, type 2 diabetes, and cardiovascular diseases in different populations.

Conclusions

Available scientific evidence indicates that LCS represent a heterogeneous group of compounds with differing metabolism, sweetening potency, and potential effects on carbohydrate metabolism. Toxicologically, within EFSA, FDA, and JECFA ADI levels, they are considered safe [8,35,38]. However, their metabolic safety is more complex, and existing studies do not provide a definitive answer on their long-term impact on the risk of insulin resistance and type 2 diabetes.

Short-term interventions with LCS—both synthetic and natural—most often do not significantly affect glycemia, insulinemia, or insulin resistance indices in healthy populations [29,32]. In overweight or obese individuals, substituting sugar with LCS may support weight reduction and glycemic control [33,36]. Yet, observational studies frequently report a positive correlation between LCS consumption and higher metabolic risk, likely reflecting reverse causality—individuals with existing metabolic issues more often consume "light" products [41].

Differences between individual LCS are crucial: sucralose and saccharin have been linked to microbiota alterations and impaired glucose tolerance in animal models [26,27]; stevia has shown neutral or beneficial effects (mild hypoglycemic and lipid profile improvements) [29]; aspartame, despite past controversy, appears metabolically neutral when consumed within ADI [8,29].

Dietary and environmental context is increasingly recognized as decisive: LCS show the greatest preventive and therapeutic potential against insulin resistance and type 2 diabetes when replacing added sugars in high-calorie diets as part of a comprehensive lifestyle approach [33,36]. In low-fiber, high-fat, ultra-processed diets, their benefits may be negligible or even counterproductive [24,41].

From a public health perspective, LCS use is part of WHO, EFSA, and ADA strategies to reduce free sugar intake [35,38]. Still, recommendations remain cautious for sensitive groups such as children, pregnant women, and elderly individuals with multimorbidity [8,38,40].

In conclusion, LCS can be considered a tool to reduce sugar and caloric intake when thoughtfully integrated into a healthy dietary pattern. They may aid glycemic and weight control in overweight and metabolically compromised individuals, but they are not a universal solution to insulin resistance. Their long-term metabolic effects remain incompletely understood, underscoring the need for further well-designed randomized studies across diverse LCS, populations, and real-world dietary contexts.

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