International Sweeteners Association

Low/no calorie sweeteners and the human gut microbiota

HIGHLIGHTS

Human randomised controlled trials show no consistent impact of low/no calorie sweeteners on the gut microbiota, when consumed at approved levels.

Key considerations when evaluating research include differences in the metabolic fate of each sweetener, study design, dietary control, tested doses, and analytical methodologies.

The human gut microbiota is a complex ecosystem of trillions of microorganisms residing in the intestinal tract, including bacteria, viruses, and certain eukaryotes. Two dominant phyla, *Bacteroidetes* and *Firmicutes*, account for more than 90% of the total microbial population.[1]

These microorganisms contribute to essential physiological functions including the digestion of otherwise indigestible substrates, synthesis of essential metabolites (e.g., short-chain fatty acids [SCFAs]), regulation of the immune system, and protection against pathogens. They also play important roles in metabolic, endocrine, and neurobehavioral processes.[1]

Although disruptions in microbial composition and diversity – commonly referred to as *dysbiosis* – have been associated with conditions such as obesity, insulin resistance, and other metabolic diseases, there is no consensus of what constitutes a "healthy" gut microbiome, reflecting its high interindividual variability and responsiveness to environmental factors.[1]

The terms "microbiome" and "microbiota" are commonly used interchangeably due to the lack of consensus definitions. Gut **microbiota** refers to the microorganisms living in our digestive system, while gut **microbiome** is a more complex entity including those microbes plus their genes, functions, and the overall environment they create.[1]

Diet and the human gut microbiome

Diet is one of the most important and modifiable factors influencing the composition and function of the gut microbiome. Dietary patterns can rapidly and significantly alter microbial diversity and abundance, thereby influencing the production of metabolites that impact host physiology. Diet–microbiome interactions are highly individualised and influenced by multiple factors, including host genetics, age, baseline microbiota composition, habitual diet, medication use, and exposures from the external environmental (external exposome).[2]

Do low/no calorie sweeteners affect the gut microbiome?

Evidence from human randomized controlled trials (RCTs) is growing and generally indicates no clear effect of different types and doses of low/no calorie sweeteners (LNCS) on the gut microbiota when consumed within Acceptable Daily Intake (ADI) levels.[3-6]

In contrast, much of the evidence suggesting microbiota-mediated metabolic effects derives from *in vitro* and animal studies. However, these studies often employ unrealistically high doses of LNCS or rely on models with limited translational relevance to humans. For example, differences between the rodent and human gut microbiome limit the biological relevance of animal findings.[1,3-6]

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Evidence from human studies

Early observational findings and a pilot human study have suggested a potential link between LNCS consumption, dysbiosis, and glucose intolerance.[7] This was a small interventional study reporting that saccharin administration for one-week induced glucose intolerance in four out of seven participants by altering the gut microbiota. However, the study was uncontrolled, underpowered (pilot study with only seven participants), used saccharin at 100% of the ADI (equivalent to 45 packets of sweeteners per day for a 60 kg individual), and achieved statistical significance only through post hoc analyses that arbitrarily classified the seven participants into two groups (four responders, in whom the effect was seen and three non-responders, in whom no effect was reported). Subsequent studies were designed specifically to address these limitations using double-blind, placebo-controlled, adequately powered randomised controlled designs, rejecting these findings.[8]

Generally, most RCTs to date show no significant or clinically meaningful changes in gut microbiome composition or faecal SCFAs levels following consumption of individual sweeteners such as aspartame, saccharin, sucralose, and stevia within the ADI.[8-12] In contrast, two RCTs have suggested that some LNCS, mainly saccharin and sucralose, may impair glucose tolerance by inducing dysbiosis.[13,14] However, adverse effects on glycaemic regulation are not supported by broader evidence: systematic reviews of numerous RCTs consistently show no effect of LNCS on glycaemic or insulinaemic responses.[15,16]

Notably, the largest, longest, and real-world RCT to date (n=341 adults with overweight or obesity) found that participants consuming a variety of LNCS-containing foods and beverages as part of a weight-loss maintenance diet for one year exhibited a more favourable microbial composition compared with non-consumers.[17] This multicenter European study also reported a beneficial higher abundance of bacterial taxa associated with SCFA and methane production, alongside improved weight-loss maintenance in the LNCS group. Similarly, a recent pragmatic trial in 80 participants with obesity found that replacing sugar-sweetened beverages with low/no calorie sweetened drinks or water for four weeks did not alter gut microbiota composition.[18]

The heterogeneity in findings across studies may be partly explained by differences in study design. Baseline microbiota composition and interindividual variability in dietary response may also contribute to inconsistent results. There is a critical need to improve the rigour of research design in this field. Further well-designed, long-term clinical trials with careful dietary control are needed to better understand the potential effects of different sweeteners on the gut microbiome.[1-6]

Important considerations in interpreting research

When evaluating research on LNCS and gut microbiota, several factors must be considered. These include differences in absorption, distribution, metabolism, and excretion (ADME) among individual sweeteners, as well as the biological plausibility of their interaction with gut microbes.[19]

Importantly, findings from one LNCS cannot be generalised to others due to well-established differences in their chemical structure and metabolic fate.[20]

For example:

- **Aspartame** is rapidly hydrolysed and absorbed in the small intestine. Neither the intact compound nor its metabolites reach the colon; therefore, a direct effect of aspartame on gut microbiota is not biologically plausible.
- **Acesulfame-K** is almost completely absorbed and excreted unchanged in urine, with less than 1% eliminated in the faeces. Thus, its interaction with gut microbiota is likely negligible as the concentration that reaches the gut microbiota is extremely low.
- **Saccharin** is largely absorbed (>85%) without gastrointestinal metabolism, meaning only small amounts reach the colon. Therefore, only very high doses of this sweetener could lead to changes in the composition of the gut microbial population.
- **Sucralose** is poorly absorbed and largely excreted unchanged in faeces. Although it reaches the colon, it is not metabolised by gut bacteria and is unlikely to act as a microbial substrate.
- **Steviol glycosides** reach the colon and are metabolised into steviol by gut bacteria. However, steviol itself is not further degraded and is fully absorbed, indicating no evidence of adverse effects on the gut microbiota.

Current evidence does not support the hypothesis that low/no calorie sweeteners may adversely affect human health via effects on the gut microbiome when consumed at approved levels.

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