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Association of Natural and Artificial Nonnutritive Sweeteners on Gastrointestinal Disorders: A Narrative Review

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Abstract

Introduction: Non-caloric sweeteners (NCS) are natural or chemical additives, found in food products and beverages as a measure to reduce their energy content. Several studies report possible effects on the gastrointestinal tract, especially in patients with predisposition such as Irritable Bowel Syndrome (IBS) and Inflammatory Bowel Disease (IBD). The aim of this review is to describe the association between NCS consumption and changes in bowel habits.

Methods: The PubMed, Scopus and Embase literature from 1980 to 2017 was reviewed and we included those that relate aspects of change in bowel habit, microbiota and NCS consumption.

Results: Studies have shown possible effects on intestinal motility and microbiota, through increased secretion of hormones and microbiota regulation however, available studies have been heterogeneous in the population studied. Consumption of NCS especially sucralose and polyols were associated with symptoms in patients with IBS and IBD by intervention in the microbiota and immune system.

Conclusion: We conclude that increased use of NCS worldwide may increase the symptoms of patients with IBS and IBD, however, it is important to conduct further human studies to assess this association.

Keywords: Non-caloric sweeteners; Crohn's disease; Ulcerative colitis; Irritable bowel syndrome

Background

The nonnutritive sweeteners (NNS), artificial (AS) and natural (NS) are commonly used worldwide dietary supplements. The high consume of these is the result of changes in lifestyle, specifically in countries with occidental diet. The NNS are used in the industrial formulation of food and beverages, especially for the low caloric intake, the low costs and the greater sweetness sensation compared with sucrose (regular sugar) and other caloric sweeteners [1]; On the other hand, due to the incomplete absorption of the NNS, the gastrointestinal tract suffers a series of alterations, especially in colonic microbiota. These variations in bacterial population could cause changes in the intestinal habit and motility, generating symptoms in patients with predisposition such as Irritable Bowel Syndrome (IBS) or Inflammatory Bowel Disease (IBD) [2]. Since 1980, studies assessing bacterial cultures have reported associations between the use of sweeteners and the presence of intestinal symptoms. However, more recent literature shows contradictory results, causing discussion on the matter [3].

The objective of this review is to describe the association between NNS and the respective gastrointestinal alterations related to intestinal habit.

The PubMed, Scopus, and Embase databases were searched for studies published in English and Spanish between January 1980 and December 2017. The key search words used were gastrointestinal disease AND non-caloric sweeteners, microbiota OR microbiome AND non-caloric sweeteners. Once both authors of the study agreed with the research statement, articles with two associations of the principal related variables in the tittle or summary were included in the analysis. Observational, experimental and review studies were included, this approach was because it was provided more information and the expert's opinion in the analysis.

In this narrative review NNS were defined as sweeteners that provide sweetness without energy or with negligible values, we used the terms high-intensity sweeteners, low-calorie sweeteners and non-caloric sweeteners as synonyms (Table 1 and Figure 1).

Results and Discussion

More than a century ago, NNS were introduced in the food industry trying to give food the sweet taste without the usual high caloric and sugar intake. NNS consume got popular because of the low costs, the low caloric intake and the good perception of health benefits in weight loss and normalization of blood glucose [4]. Today with all these advantages, their use in food and beverages is more common. A study from the United States of America (USA) from 2005 to 2009 showed that 15% of the volume of food and beverages contains NNS and that this percentage has been gradually increasing [5].

There have been identified several NNS in the Food Industry, however, the Food and Drug Administration (FDA) has approved only six high intensity sweeteners such as saccharine, aspartame, neotame, acesulfame K, sucralose and advantame; and two Generally Recognized

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Author and year	Target or aim	Key Findings
Abou-Donia MB et al.	They explored the effect of Splenda (100, 300, 500, or 1000 mg/kg) on Sprague-Dawley rats for 12 weeks.	• Splenda reduced beneficial fecal microflora, increased fecal pH, and enhanced expression levels of P-glycoprotein, cytochrome P450, and enzyme CYP2D1 [9].
Bian X et al.	They explored the effects of acesulfame K on the gut microbiome and the changes in fecal metabolic profiles.	• Acesulfame K produces shifts in the gut bacterial community composition, enrichment of functional bacterial genes related to energy metabolism, and fecal metabolomics changes were highly gender-specific [8].
Boonkaewwan C et al.	Elucidate the anti-inflammatory and immunomodulatory activities of stevioside and its metabolite, steviol.	• Stevioside attenuates synthesis of inflammatory mediators in Lipopolysaccharide-stimulated THP cells line by interfering with the IKK and NF-kappa B signaling pathway, and induced TNF secretion is partially mediated through TLR4 [58].
Brown RJ and Rother K I	To identify articles examining the effects of NNS on gastrointestinal physiology and hormone secretion using PubMed (1960-2012).	• In humans, few studies have examined the hormonal effects of NNS, and inconsistent results have been reported, with the majority not recapitulating *in vitro* data [31].
Brown RJ et al.	Determine the effect of NNS on glucose, insulin, and glucagon-like peptide -1 in humans.	• NNS synergize with glucose to enhance GLP-1 release in humans, and secretion may be mediated via stimulation of sweet-taste receptors on L-cells by NNS [28].
Chattopadhyay S et al.	A review about of NNS.	• NNS: Increasing amounts of sweets and soft drinks could cause health effects [6].
Daly K et al.	To investigate the changes in the intestinal microbiota of piglets weaned to a diet supplemented with either a natural sugar, lactose or an NNS, consisting of saccharin and neohesperidin dihydrochalcone.	• The addition of either lactose or saccharin/neohesperidin dihydrochalcone to the piglets' feed dramatically increased the caecal population abundance of *Lactobacillus*, with concomitant increases in intraluminal lactic acid concentrations [46].
Daly K et al.	To research the effect of NNS and gut microbiota.	• The results of a few recent studies carried out in this area have produced controversies. • There is evidence that human fecal samples, used in most human microbiome studies, may provide a poor representation of microbial contents of the proximal intestine [3].
Ford HE et al.	Randomized, single-blinded, crossover study in eight healthy subjects to investigate whether oral ingestion of sucralose could stimulate L-cell-derived GLP-1 and peptide YY release *in vivo*.	• Sucralose ingestion did not increase plasma piglets or PYY. Modified sham feed of sucralose did not elicit a cephalic phase response for insulin or GLP-1. Appetite ratings and energy intake were similar for all groups [26].
Frankenfeld, CL et al.	To evaluate gut microbiome in relation to recent high-intensity NNS consumption in healthy adults.	• No differences in median bacterial abundance (class or order) across consumers and nonconsumers of NNS. Overall bacterial diversity was different across nonconsumers and consumers of aspartame and acesulfame-K [45].
Fujita Y et al.	To research whether secretion of incretins in response to carbohydrates is mediated via taste receptors by feeding rats the NNS (saccharin, acesulfame-K, d-tryptophan, sucralose, or stevia).	• Oral glucose increased plasma glucagon-like peptide levels approximately 4-fold and GLP-1 levels approximately 2.5-fold postadministration, none of the sweeteners tested significantly increased levels of these incretins [24].
Geraedts MC et al.	Measure how different tastants NNS induce differential effects on the release of satiety hormones.	• All commercial sweeteners elevated cholecystokinin and GLP-1 levels, with Tagatesse exerting the strongest effects. Tastants, and in particular sweet, play a role in the regulation of satiety hormone release, both in a concentration- and time-dependent manner [22].
Geraedts M C et al.	Exposing the intestine to proteins or tastants, particularly sweet, affects satiety hormone release.	• Combining pea with sucrose and sucralose induced even higher levels of CCK and GLP-1. Synchronous addition of pea and sucralose to enteroendocrine cells induced higher levels of CCK and GLP-1 than addition of each compound alone [23].
Jang HJ et al.	Evaluate Gut-expressed gustducin and taste receptors, and how they regulate secretion of GLP-1.	• The human L cell line NCI-H716 expresses alpha-gustducin, taste receptors, and several other taste signaling elements. GLP-1 release from NCI-H716 cells was promoted by sugars and the NNS sucralose, and blocked by the sweet receptor antagonist lactisole or siRNA for alpha-gustducin [20].
Labrecque MT et al.	Evaluate the impact of ethanol in either water or saccharin on the fecal microbiome in pregnant and non-pregnant mice using a qPCR approach.	• Levels of *Clostridium* were reduced in ethanol-saccharin but not ethanol-water drinking mice, even though the total levels of ethanol consumed were the same for the two groups. • Eubacteria were increased in the pregnant, but decreased in the non-pregnant, ethanol-saccharin drinking group [60].
Ma J et al.	Evaluate the effect of the NNS, sucralose, on gastric emptying and incretin hormone release in healthy subjects.	• Evaluate the effect of the NNS, sucralose, on gastric emptying and incretin hormone release in healthy subjects [25].
Qin X	A comment about of the increase in the incidence of IBD.	• Saccharin, play a causative role in IBD as a result of the accelerated degradation of the mucous layer and underlying endothelium; and the sucralose may have a similar but stronger impact on gut bacteria, digestive protease inactivation and gut barrier function [55].
Qin XF	A comment about of impaired inactivation of digestive proteases by deconjugated bilirubin: the possible mechanism for IBD.	• The author suggest the impaired inactivation of digestive proteases by deconjugated bilirubin, as the result of the inhibition of bilirubin deconjugation enzyme, beta-glucuronidase, originated from the luminal bacteria and mucosa of the gut, to be a possible mechanism for IBD. • Saccharin could be the causative or one of the most important risk factors for IBD as for its inhibition on GUSB in the intestine [52].
Sehar I et al.	Stevioside was tested for its immunomodulatory activity on different parameters of the immune system at three different doses (6.25, 12.5 and 25 mg/kg p.o.) on normal as well as cyclophosphamide treated mice.	• Stevioside was found effective in increasing phagocytic activity, haemagglutination antibody titre and delayed type hypersensitivity; and stevioside substantially increase proliferation in the LPS and ConA stimulated B and T cells, respectively [53].
Shankar P et al.	A systematic review of several databases and reliable websites on the internet to identify literature related to NNS.	• Studies endorse the safety of NNS. While moderate use of NNS may be useful as a dietary aid for someone with diabetes or on a weight loss regimen, for optimal health it is recommended that only minimal amounts of NNS be consumed [57].

Spencer M et al.	Utilizing the PubMed and Embase databases, the authors conducted a search for articles on individual NNS and each of these terms: fermentation, absorption, and GI tract.	• Data suggest that NNS affect the GI tract include motility and the gut microbiome. • Human data is lacking, and most of the currently available data is derived from *in vivo* studies. • The effect on motility is mainly indirect via increased incretin secretion, though the clinical relevance of this finding is unknown as the downstream effect on motility was not studied [7].
Steinert RE et al.	Research if whether the human gut responds in the same way to NNS and carbohydrate sugars, which are perceived by lingual taste as equisweet; focused on the secretion of GI satiety peptides in relation to appetite perception.	• Glucose stimulated GLP-1 and PYY secretion, and reduced fasting plasma ghrelin, whereas fructose was less effective. • NNS did not affect gastrointestinal peptide secretion with minimal effects on appetite. 2DG increased hunger ratings, however, with no effects on GLP-1, PYY or ghrelin [27].
Suez J et al.	To demonstrate that consumption of commonly used NNS formulations drives the development of glucose intolerance through induction of compositional and functional alterations to the intestinal microbiota.	• NNS-mediated deleterious metabolic effects are abrogated by antibiotic treatment, and are fully transferrable to germ-free mice upon faecal transplantation of microbiota configurations from NNS-consuming mice, or of microbiota anaerobically incubated in the presence of NNS. • The results link NNS consumption, dysbiosis and metabolic abnormalities [4].
Suez J et al.	A commentary about of NNS and the microbiome, the findings and challenges.	• Several of the bacterial taxa that changed following saccharin consumption were previously associated with type 2 diabetes in humans. • NNS consumption could induce glucose intolerance in mice and distinct human subsets, by functionally altering the gut microbiome [35].
Sylvetsky A et al.	Summarize the literature pertaining to the epidemiology and current recommendations for pediatric NNS use and presents the results of studies investigating metabolic responses to NNS among children.	• No benefits of NNS use in young children, though it is possible that consumption of NNS may be beneficial in limiting weight gain in overweight adolescents [61].
Uebanso T et al.	To examine the effects of sucralose or acesulfame-K ingestion (at most the maximum ADI) levels, 15 mg/kg body weight) on the gut microbiome in mice.	• Daily intake of maximum ADI levels of sucralose, but not acesulfame-K, affected the relative amount of the *Clostridium cluster XIVa* in fecal microbiome and cholesterol bile acid metabolism in mice [34].
Yingkun N et al.	To evaluate the effect and the possible mechanism of stevioside in LPS induced acute lung injury, male BALB/c mice were pretreated with stevioside or Dex 1 hour before intranasal instillation of LPS.	• Stevioside inhibited the production of pro-inflammatory cytokines and the expression of COX-2 and iNOS induced by LPS; and inhibited the phosphorylation of IkappaB-alpha and NF-kappaB caused by LPS [59].

THP: Tamm-Horsfall Protein 1; NF-kappaB: Factor nuclear factor kappa B; IKK: I kappa B kinase; TNF: Tumor necrosis factor-alpha; Toll-like receptor; NNS: Nonnutritive sweeteners; GLP-1: Glucagon-like peptide-1; CCK: Cholecystokinin; qPCR: Quantitative polymerase chain reaction; IBD: Inflammatory bowel disease; GUSB: Beta-glucuronidase; LPS: Lipopolisacárido; ConA: Concanavalin A; GI: Gastrointestinal; PYY: Peptide tyrosine tyrosine; 2DG: 2-Deoxy-d-glucose; UK: United Kingdom; Dex: Dexamethasone; COX-2: Ciclooxigenasa 2; iNOS: nitric oxide synthase; ADI: Acceptable daily intake.

Table 1: All articles PubMed, Scopus, and Embase databases searched with key words used (gastrointestinal disease AND non-caloric sweeteners, microbiota OR microbiome AND non-caloric sweeteners).

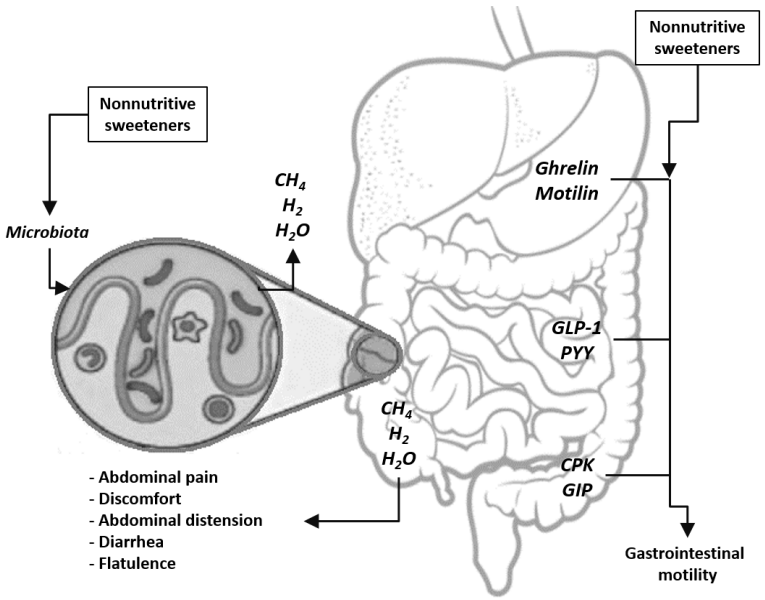

Figure 1: Effect of sweeteners on microbiota and production of abdominal pain, discomfort, abdominal distension, diarrhea and flatulence, through of an increase of hydrogen (H_2), methane (CH_4) and water (H_2O) levels; Furthermore, the relationship between gastrointestinal motility and enteroendocrine secretion with sweeteners. The cyclic secretion of motilin, and perhaps of ghrelin, regulates interdigestive gastrointestinal motility. Cholecystokinin, (CCK), gastric inhibitory polypeptide (GIP), glucagon-like peptide-1 (GLP-1) and pancreatic polypeptide Y (PPY) are released after meals; where motilin and ghrelin are suppressed. This represents the change of an interdigestive gastrointestinal motor pattern to a postprandial one.

as Safe (GRAS), stevia and luo han guo [1]. Each one of them has different intensities of sweetness, origin and characteristics related to gastrointestinal processes, as shown on Table 2 [6,7].

Due to the lack of absorption of NNS by the intestinal microvilli, especially of sucralose, it has been suggested that a possible consequence of this could be intestinal dysbiosis. Recent studies have described that intestinal microbiota is importantly involved in the guest's metabolism and that has a key role in the food digestion, energetic homeostasis, the immune system's development, the enteric nerves regulation and the prevention of pathogenic invasion [8]. Abou-Donia et al. showed in animal models that the absorption of sucralose is only of 11 to 27%, the rest remaining in the gastrointestinal tract until its excretion in the feces; and suggest that this significantly modifies the growth of intestinal bacteria (Table 3) [6,9]. Also, recent studies have reported that the NNS such as saccharine affect glucose tolerance by means of the modulation of intestinal bacterial concentrations and that the latter could produce several proinflammatory intermediaries, causing an inflammatory process in the guest [4,8].

In patients with gastrointestinal predisposition, such as IBD or IBS, these changes in the microbiota and in intestinal motility could be of great importance during the disease follow-up, as shown in Table 3.

Changes in gastrointestinal motility secondary to NNS consume

Gastrointestinal tract motility is a process modulated by a neural and hormonal complex. The latter includes intestinal peptides secreted by neuroendocrine cells during interdigestive and postprandial periods. This process is an important determinant of the hormonal secretion of the bowel and the luminal transit, which affects the amount of absorption of the nutrients by the enteroendocrine cells in different parts of the bowel [10].

Also, enteroendocrine cells release more than 30 peptides, such as motilin and ghrelin, during the inter-digestive period; and cholecystokinin (CCK) and gastric inhibitory polypeptide (GIP), during the postprandial period. These hormones are the main mediators during the change of the gastrointestinal motor pattern from the inter-digestive period to the postprandial, and during the emptying of the lumen; detected by the enteroendocrine cells dependent of the gastrointestinal motor activity [11,12]. On the other hand, some studies suggest that the effects of the glucagon-like peptide-1 (GLP-1) in the gastrointestinal motility are upon the interaction of certain brain centers or afferent nerve pathways [13,14]. An increase of GLP-1 reduces the motility in the antrum-jejunal segment and inhibits the migratory motor complex in healthy subjects and in patients with IBS. Particularly the CCK has strong effects over the bowel's smooth muscle contractility; and several other studies suggest that the CCK, GIP and the pancreatic polypeptide Y (PPY) could slow the gastric emptying and the intestinal transit too [15-19].

Nevertheless, there is evidence that NNS consume modifies the expression of hormones such as GLP-1, GIP, PYY and CCK; which consequently could affect gastrointestinal motility. It has been demonstrated in studies of animal and human models that NNS (especially assessed in sucralose) can affect the secretion of peptides and serotonin and that this could indirectly affect the gastrointestinal motility [7,20-22].

Sweeteners	Main characteristics
Saccharine	Has a metallic-bitter flavor. It is used as sodium salt or calcium. It is 200 to 700-fold sweeter than sucrose.
Aspartame	It is a methyl ester of a dipeptide (L-aspartic acid and L-phenyl alanine), that under very acid or alkaline conditions can generate methanol by hydrolysis. It is 200 times sweeter than sucrose.
Neotame	It is a byproduct of the dipeptide aspartic acid and phenylalanine. It is 7000 to 13 000 times sweeter than sucrose.
Acesulfame K	It is a potassium crystalline salt, 200 times sweeter than sucrose.
Sucralose	It is absorbed from 11 to 27%, the remainder stays in the gastrointestinal tract until its excretion in feces, 600 times sweeter than sucrose.
Advantame	It is 20000 times sweeter than sucrose.
Stevia	It is a natural sweetener, stable in heat, 200 to 400 times sweeter than sucrose.
Luo han guo	It is 100 to 250 times sweeter than sucrose.
Polyols (xylitol, mannitol sorbitol, maltitol)	They are alcohols of 4 sugar carbons, product of the fermentation of sugar and sucrose. It has poor digestibility and elevated osmotic potential in the intestinal lumen. 60 to 80% sweeter than sucrose.

Table 2: Principal NNS in the market, sweetness intensities, sources and characteristics of interest in the gastrointestinal processes [6,7].

Gastrointestinal motility	
Sucralose	In combination of vegetal protein, it increases the GLP-1 secretion, which reduces the motility in the antrum-duodenal-jejunal segment and inhibits the migratory motor complex.
Irritable Bowel Syndrome	
Sucralose	Reduces the number of *Bacteroidetes*, *Lactobacillus* and *Bifidobacterial*.
Aspartame	Reduces the number of *Lactobacillus*, *Enterobacteria*, *Clostridia* and *Roseburia*.
Saccharin	Reduction of eubacterias.
Sucralose and erythritol	Induce greater intestinal permeability.
Inflammatory Bowel Disease	
Polyols	Increase hydrogen and methane (abdominal pain, discomfort, abdominal distension, diarrhea, flatulence).
	Production of SCFAs (inflammation and permeability).
Saccharine	It inhibits the activity of beta-glucuronidase (UC and CD).
Stevia	Increases phagocytosis and the activity of the lymphocytes T and B response.

GLP-1: Glucagon-like peptide-1; SCFAs: Short-chain fatty acids; UC: Ulcerative Colitis; CD: Crohn Disease.

Table 3: Changes in the gastrointestinal tract associated to NNS consume.

However, another study in animal models did not show differences in CCK and GLP-1 concentrations in duodenal samples between the group receiving placebo and the one with sucralose. Despite, there was a significant increase in both hormones in the latter when sucralose was mixed with vegetal protein; which suggests that together this macronutrient and sucralose could have a synergic action in the secretion of CCK and GLP-1 [23].

Contrary to these findings, in animal models with sucralose, saccharine and acesulfame showed that there was no increase of GLP-1 or GIP, despite the concentrations of NNS were 1.000-fold greater than the concentrations used in diet sodas [24].

On the other hand, in clinical trial seven healthy patients were given intragastric infusions of 50 g of sucrose diluted in water, 80 mg of sucralose in 500 mL of normal saline solution (NSS), 800 mg of sucralose in 500 mL of NSS and 500 mL of NSS, found that sucralose did not stimulate the secretion of GLP-1 or GIP, and that gastric emptying had not stopped, according to exhaled carbon dioxide tests assessment [25]. In another randomized controlled clinical trial, healthy patients received 50 mL of water with sucralose 0,083% or maltodextrin and sucralose, showed that the administration of sucralose did not raise the concentrations of GLP-1 or PYY in blood [26]. Steinert et al. assessed twelve healthy volunteers in a randomized double blind clinical trial; the patients were given intragastric infusions of aspartame, acesulfame, sucralose, fructose, glucose and water. It was found that the equivalent sweetness of NNS did not affect the GLP-1, ghrelin and PYY secretion [27].

Nevertheless, in a crossover clinical trial with twenty-two healthy patients who received 240 mL of diet cola or mineral water ten minutes after an oral glucose load of 75 g, the concentrations of GLP-1 were significantly higher in the individuals receiving diet cola than in the ones receiving mineral water. This suggests that sucralose combined with glucose could increase the secretion of GLP-1, but not the sucralose alone [28].

Current literature available based on *in vivo* studies show that the GLP-1, GIP, PYY and CCK secretion could result indirectly in gastrointestinal motility changes; however, in humans these effects have only been demonstrated when sucralose is combined with glucose.

Therefore, NNS affect gastrointestinal motility secondary to an increase of GLP in the presence of glucose or any other macronutrient (Table 3).

Effects over intestinal microbiota

The microbiota and their interactions with the host or surrounding environment has been extensively investigated for the last 50 years and results show that 90% of intestinal microbiota is represented by phylum such as Firmicutes, Bacteroidetes and Actinobacteria, and in lower concentration Verrucomicrobia and Proteobacteria [7,29]. Intestinal microbiota has several functions like the synthesis of certain vitamins (K and B12), sensitivity modulation, digestive motility, permeability, regulation of the intestinal barrier, and it has recently been described that it is also involved with some metabolic pathways, food allergies and food intolerance [30]. Changes in the microbiota could contribute to a chronic low inflammatory process, facilitating the progression of chronic diseases or the exacerbation of their symptoms. In several studies it has been demonstrated that certain macronutrients consume could modulate and affect composition of the microbiota such as NNS [31,32]. Aderson et al. have shown that saccharine significantly affects the balance of aerobic and anaerobic bacteria [33], and Uebanso et al. monstrated results that suggest that daily intake of maximum acceptable daily intake (ADI) levels of sucralose, but not acesulfame-K, affected the relative amount of the *Clostridium cluster XIVa* in fecal microbiome and cholesterol bile acid metabolism in mice [34]. On the other hand, *in vitro* and *in vivo* studies it has been noted that sucralose consume is associated with greater presence of subpopulations of commensal strains in the microbiota such as *Bacteroides*, *Lactobacillus* and *Bifidobacterium*. Nonetheless, aspartame consume has been associated with a lower number of *Lactobacillus* and greater of *Enterobacteriaceae*, *Clostridials* y *Roseburia* [33]. Other studies of animal models show that the combination of ethanol and saccharine significantly decreases the number of intestinal Eubacteria [35].

Studies assessing the association between the changes in the intestinal microbiota and gastrointestinal diseases such as IBS and IBD, are becoming increasingly numerous and NNS could cause significant changes in the microbiota that affect the symptoms of these diseases.

NNS and irritable bowel syndrome

The IBS is characterized by recurrent episodes of abdominal pain, distension and changes in the intestinal habit, which could be diarrhea predominant (IBS-D), constipation predominant subtype (IBS-C), or IBS with mixed bowel habits (IBS-M). It is a prevalent disease accounting for 10 to 20% of the general population [2], and 4.4 to 35% of the Mexican population, depending on the specific region [36,37].

IBS is considered a multifactorial disease in which different environmental, genetic, physiologic and psychosocial factors contribute to its development through direct or indirect influence over the brain-bowel axis. However, a bacterial infection, changes in the intestinal microbiota homeostasis, an inadequate immune response and low-grade inflammation are additional contributing factors, which role is calling the attention for the comprehension of the pathophysiology of IBS [29,38].

More than 50% of the patients with IBS worsen their symptoms with the consume of food rich in fermentable carbohydrates (fermentable, oligo-, di-, mono-saccharides and polyols or FODMAPs) such as, sugar alcohols also called polyols xylitol, sorbitol and mannitol commonly used as sweeteners and they have a negative effect on the gut microbiota. Other NNS like aspartame, neotame, sucralose, saccharine, cyclamate, stevia and acesulfame K, through different pathways, could cause imbalance in the intestinal microbiota; which in turn contributes to alterations in the immune system, greater intestinal permeability and sensitivity, microinflammation, as well as changes in motility, especially in patients with IBS-C [4,31,39,40].

In a meta-analysis Mayer et al. reported that lower number of *Bifidobacterium* and *Lactobacillus*, and changes in the balance of *Firmicutes-Bacteroides* in fecal samples are a consequence of stress and diet changes; which all together triggers symptoms in patients with IBS [41]. On and other hand, some studies suggest that commercial saccharine greatly affects the microbiota function due to its composition of 95% of glucose. In animal models, there have been reported changes of the microbiota secondary to saccharine metabolism, since it increases the glycan degradation pathways to produce short-chain fatty acids (SCFAs); which rises the amount of energy in the bowel and consequently promotes obesity. Therefore, saccharine could indirectly unleash a mechanism of dysbiosis in the host and exacerbate the symptoms in predisposed patients [4,41,42].

Polyols are a group of versatile, reduced-calorie carbohydrates that provide sweet taste with about half the calories, such as sorbitol, mannitol,

maltitol and xylitol. These have poor digestibility and absorption in colon, generating osmotic effects in the intestinal lumen, increasing the water volume, which together with the rapid fermentation by bacteria, easily produces gas. This is the basis of gastrointestinal symptoms after the ingestion of NNS in patients with visceral hypersensitivity. Free-fructose diets have based on the latter; however, there are only observational studies in patients with functional motility disorders that support this hypothesis, unfortunately indirectly assessed through the effect in gastric emptying and the gastric and intestinal hormonal profile [25,42,43].

Mugajic et al. showed that the lack of absorption of different sugars and NNS could be an indicator of greater intestinal permeability. This study concluded that the sucralose and erythritol absorption, was significantly associated with greater intestinal permeability during IBS-C and IBS-D episodes [44].

Furthermore, a study where it was evaluated the sucralose effect in animal models in doses of 100, 300, 500 mg/kg of weight for 12 weeks; reported lower concentrations of fecal aerobic bacteria, which persisted during the whole follow-up. Other studies showed that the combination of saccharine and neohesperidin dihydrochalcone in volunteers was associated with the growth of Lactobacillus relative population. In general, both in animal models and in interventional studies with patients conclude that the refined sugar and NNS consume changes the composition of intestinal microbiota and its functions [45,46]. Therefore, there is a great research field on the matter of the changes in the microbiota as an attempt to have a better understanding of digestive disorders [47].

The etiology of IBS remains unknown, however change of the intestinal microbiota secondary to dietary factors like the consumption of sweeteners could have a significant effect on the symptoms.

NNS and inflammatory bowel disease

IBD is a group of inflammatory conditions, represented by Crohn's disease (CD) and Ulcerative Colitis (UC), both of unknown etiology. At present, it is understood that a combination of environmental risk factors such as stress, appendectomy, smoking, socioeconomic conditions, nonsteroidal anti-inflammatory drugs, oral contraceptives, infections, hygiene conditions and diet modulate the immune response in front of intestinal bacteria that produce chronic inflammation in genetically predisposed patients [48,49].

Epidemiologic studies have demonstrated that different types of diets can affect the microbiota composition and in consequence, could increase the risk of IBD. The disease has been associated with a diminution in the number of Firmicutes and growth of Proteobacteria [50].

Prebiotics have the function of maintaining the balance in the microbiota composition in colon, some of which could be directly related to the progress of IBD [10]. A series of observational studies and clinical trials have shown that a diet restricted in FODMAPs (sorbitol, xylitol and mannitol), could diminish the symptoms in more than 50% of the patients with IBD. As carbohydrates are slowly absorbed and fermented by the microbiota, hydrogen and methane concentrations in colon increase, leading to worsening of intestinal gas and other typical IBD symptoms such as abdominal pain, distension, diarrhea and flatulence. This can easily explain why these restrictive diets cause an important improvement of the symptoms [51,52].

On the other hand, colonic microbiota has a key role in the immune response of patients with IBD. There is an association between the polymorphisms of the nucleotide-binding oligomerization domain 2 (NOD2)/caspase recruitment domain 15 (CARD15) gene and CD, and this is thought to be regulated by microbiota. In patients with IBD the changes in NOD2 reduce the enteric tolerance to bacteria, and consequently produce inflammation. The latter together with a diet rich in polyols has shown an increase of intestinal dysbiosis as well as mucosa inflammation and deterioration of intestinal permeability [50-53]. Sorbitol, mannitol and xylitol are susceptible to fermentation with secondary production of hydrogen, methane, carbon dioxide and SCFAs; recognized as potential regulators of the inflammatory process and of intestinal permeability in patients with IBD [54].

Qin XF in a paper suggest that a decade ago, several discoveries made hypothesized that saccharin (the first and more ancient AS since the late 1880s), could have importance in the IBD through the inhibition of intestinal bacteria and affection to the digestive proteases, as well as excessive damage to the mucin layer and the underlying intestinal tissue [52]. In other paper suggested that in Canada the incidence of IBD is directly associated with the use of NNS in cereals, beverages, desserts, chewing gum, candy and other products; also, these products are used indiscriminately by the food industry in pediatric population from 1983 to 2005 [55,56].

Recently, studies in animal models have demonstrated that saccharine and sucralose could contribute to the onset of CD and UC because of the inhibition of the beta-glucuronidase activity and bacteria overgrowth during the homeostatic inactivation of digestive proteases. NNS like stevia are a source of sweet glucosides of sativoside that substantially increase the lymphocytes B and T proliferation and that induce the tumor necrosis factor α (TNF-α) secretion partially regulated by the Toll-like receptor 4 (TLR4), which are involved factors in the IBD activity (Table 3) [53,57-61].

The etiology of IBD is unknown, but consumption of sweeteners could influence the incidence and symptoms of the patients.

Conclusion

The specific effects of NNS on the microbiome have been conflicting and the available studies have been heterogeneous in terms of the population studied and both the NNS and doses evaluated. Nevertheless, scientific evidence suggests that the increase of the NNS consume, could be one of the dietetic factors causing a rise in the symptoms of IBS and IBD, secondary to changes caused in intestinal microbiota composition and gastrointestinal motility. Therefore, it is of great importance that further studies continue to evaluate the role of NNS over the gastrointestinal tract alterations.

Transparency Declaration

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported. The reporting of this work is compliant with PRISMA guidelines. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned (please add in the details of any organisation that the trial or protocol has been registered with and the registration identifiers) have been explained.

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References

1. Meyer-Gerspach AC, Wolnerhanssen B, Beglinger C (2016) Functional roles of low calorie sweeteners on gut function. Physiol Behav 164: 479-481.
2. Feehley T, Nagler CR (2014) Health: the weighty costs of non-caloric sweeteners. Nature 514: 176-177.
3. Daly K, Darby AC, Shirazi-Beechey SP (2016) Low calorie sweeteners and gut microbiota. Physiol Behav 164: 494-500.
4. Suez J, Korem T, Zeevi D, Zilberman-Schapira G, Thaiss CA, et al. (2014) Artificial sweeteners induce glucose intolerance by altering the gut microbiota. Nature 514: 181-186.
5. Sylvetsky AC, Rother KI (2016) Trends in the consumption of low-calorie sweeteners. Physiol Behav 164: 446-450.
6. Chattopadhyay S, Raychaudhuri U, Chakraborty R (2014) Artificial sweeteners - a review. J Food Sci Technol 51: 611-621.
7. Spencer M, Gupta A, Dam LV, Shannon C, Menees S, et al. (2016) Artificial sweeteners: a systematic review and primer for gastroenterologists. J Neurogastroenterol Motil 22: 168-180.
8. Bian X, Chi L, Gao B, Tu P, Ru H, et al. (2017) The artificial sweetener acesulfame potassium affects the gut microbiome and body weight gain in CD-1 mice. PLoS One 12: e0178426.
9. Abou-Donia MB, El-Masry EM, Abdel-Rahman AA, McLendon RE, Schiffman SS (2008) Splenda alters gut microflora and increases intestinal p-glycoprotein and cytochrome p-450 in male rats. J Toxicol Environ Health A 71: 1415-1429.
10. Wu T, Rayner CK, Young RL, Horowitz M (2013) Gut motility and enteroendocrine secretion. Curr Opin Pharmacol 13: 928-934.
11. Rehfeld JF (2012) Beginnings: a reflection on the history of gastrointestinal endocrinology. Regul Pept 177: S1-S5.
12. Schirra J, Kuwert P, Wank U, Leicht P, Arnold R, et al. (1997) Differential effects of subcutaneous GLP-1 on gastric emptying, antroduodenal motility, and pancreatic function in men. Proc Assoc Am Physicians 109: 84-97.
13. Nakade Y, Tsukamoto K, Iwa M, Pappas TN, Takahashi T (2007) Glucagon like peptide-1 accelerates colonic transit via central CRF and peripheral vagal pathways in conscious rats. Auton Neurosci 131: 50-56.
14. Wettergren A, Wojdemann M, Holst JJ (1998) Glucagon-like peptide-1 inhibits gastropancreatic function by inhibiting central parasympathetic outflow. Am J Physiol 275: G984-G992.
15. Hellstrom PM, Naslund E, Edholm T, Schmidt PT, Kristensen J, et al. (2008) GLP-1 suppresses gastrointestinal motility and inhibits the migrating motor complex in healthy subjects and patients with irritable bowel syndrome. Neurogastroenterol Motil 20: 649-659.
16. Grider JR (1994) Role of cholecystokinin in the regulation of gastrointestinal motility. J Nutr 124: 1334S-1339S.
17. Ogawa E, Hosokawa M, Harada N, Yamane S, Hamasaki A, et al. (2011) The effect of gastric inhibitory polypeptide on intestinal glucose absorption and intestinal motility in mice. Biochem Biophys Res Commun 404: 115-120.
18. Edholm T, Degerblad M, Gryback P, Hilsted L, Holst JJ, et al. (2010) Differential incretin effects of GIP and GLP-1 on gastric emptying, appetite, and insulin-glucose homeostasis. Neurogastroenterol Motil 22: 1191-1200.
19. Savage AP, Adrian TE, Carolan G, Chatterjee VK, Bloom SR (1987) Effects of peptide YY (PYY) on mouth to caecum intestinal transit time and on the rate of gastric emptying in healthy volunteers. Gut 28: 166-170.
20. Jang HJ, Kokrashvili Z, Theodorakis MJ, Carlson OD, Kim BJ, et al. (2007) Gut-expressed gustducin and taste receptors regulate secretion of glucagon-like peptide-1. Proc Natl Acad Sci USA 104: 15069-15074.
21. Mace OJ, Schindler M, Patel S (2012) The regulation of K- and L-cell activity by GLUT2 and the calcium-sensing receptor CasR in rat small intestine. J Physiol 590: 2917-2936.
22. Geraedts MC, Troost FJ, Saris WH (2011) Different tastants and low-caloric sweeteners induce differential effects on the release of satiety hormones. Food Chem 129: 731-738.
23. Geraedts MC, Troost FJ, Saris WH (2012) Addition of sucralose enhances the release of satiety hormones in combination with pea protein. Mol Nutr Food Res 56: 417-424.
24. Fujita Y, Wideman RD, Speck M, Asadi A, King DS, et al. (2009) Incretin release from gut is acutely enhanced by sugar but not by sweeteners in vivo. Am J Physiol Endocrinol Metab 296: E473-E479.
25. Ma J, Bellon M, Wishart JM, Young R, Blackshaw LA, et al. (2009) Effect of the artificial sweetener, sucralose, on gastric emptying and incretin hormone release in healthy subjects. Am J Physiol Gastrointest Liver Physiol 296: G735-G739.
26. Ford HE, Peters V, Martin NM, Sleeth ML, Ghatei MA, et al. (2011) Effects of oral ingestion of sucralose on gut hormone response and appetite in healthy normal-weight subjects. Eur J Clin Nutr 65: 508-513.
27. Steinert RE, Frey F, Topfer A, Drewe J, Beglinger C (2011) Effects of carbohydrate sugars and artificial sweeteners on appetite and the secretion of gastrointestinal satiety peptides. Br J Nutr 105: 1320-1328.
28. Brown RJ, Walter M, Rother KI (2009) Ingestion of diet soda before a glucose load augments glucagon-like peptide-1 secretion. Diabetes Care 32: 2184-2186.
29. Ringel Y, Maharshak N (2013) Intestinal microbiota and immune function in the pathogenesis of irritable bowel syndrome. Am J Physiol Gastrointest Liver Physiol 305: G529-G541.
30. Morcos A, Dinan T, Quigley EM (2009) Irritable bowel syndrome: role of food in pathogenesis and management. J Dig Dis 10: 237-246.
31. Brown RJ, Rother KI (2012) Non-nutritive sweeteners and their role in the gastrointestinal tract. J Clin Endocrinol Metab 97: 2597-2605.
32. Muegge BD, Kuczynski J, Knights D, Clemente JC, Gonzalez A, et al. (2011) Diet drives convergence in gut microbiome functions across mammalian phylogeny and within humans. Science 332: 970-974.
33. Anderson RL, Kirkland JJ (1980) The effect of sodium saccharin in the diet on caecal microflora. Food Cosmet Toxicol 18: 353-355.
34. Uebanso T, Ohnishi A, Kitayama R, Yoshimoto A, Nakahashi M, et al. (2017) Effects of low-dose non-caloric sweetener consumption on gut microbiota in mice. Nutrients 9: 560.
35. Suez J, Korem T, Zilberman-Schapira G, Segal E, Elinav E (2015) Non-caloric artificial sweeteners and the microbiome: findings and challenges. Gut Microbes 6: 149-155.
36. Lopez-Colombo A, Morgan D, Bravo-Gonzalez D, Montiel-Jarquin A, Mendez-Martinez S, et al. (2012) The epidemiology of functional gastrointestinal disorders in Mexico: a population-based study. Gastroenterol Res Pract 2012: 606174.
37. Valerio-Urena J, Vasquez-Fernandez F, Jimenez-Pineda A, Cortazar-Benitez LF, Azamar-Jacome AA, et al. (2010) Prevalence of irritable bowel syndrome in Veracruz City, Mexico: a community-based survey. Rev Gastroenterol Mex 75: 36-41.
38. Giamarellos-Bourboulis EJ, Pyleris E, Barbatzas C, Pistiki A, Pimentel M (2016) Small intestinal bacterial overgrowth is associated with irritable bowel syndrome and is independent of proton pump inhibitor usage. BMC Gastroenterol 16: 67.
39. Bokulich NA, Blaser MJ (2014) A bitter aftertaste: unintended effects of artificial sweeteners on the gut microbiome. Cell Metab 20: 701-703.
40. Ghoshal UC, Srivastava D, Ghoshal U, Misra A (2014) Breath tests in the diagnosis of small intestinal bacterial overgrowth in patients with irritable bowel syndrome in comparison with quantitative upper gut aspirate culture. Eur J Gastroenterol Hepatol 26: 753-760.
41. Mayer EA, Savidge T, Shulman RJ (2014) Brain-gut microbiome interactions and functional bowel disorders. Gastroenterology 146: 1500-1512.
42. Yoon SR, Lee JH, Lee JH, Na GY, Lee KH, et al. (2015) Low-FODMAP formula improves diarrhea and nutritional status in hospitalized patients receiving enteral nutrition: a randomized, multicenter, double-blind clinical trial. Nutr J 14: 116.
43. Tennant DR (2014) Potential intakes of total polyols based on UK usage survey data. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 31: 574-586.
44. Mujagic Z, Ludidi S, Keszthelyi D, Hesselink MA, Kruimel JW, et al. (2014) Small intestinal permeability is increased in diarrhoea predominant IBS, while alterations in gastroduodenal permeability in all IBS subtypes are largely attributable to confounders. Aliment Pharmacol Ther 40: 288-297.

45. Frankenfeld CL, Sikaroodi M, Lamb E, Shoemaker S, Gillevet PM (2015) High-intensity sweetener consumption and gut microbiome content and predicted gene function in a cross-sectional study of adults in the United States. Ann Epidemiol 25: 736-742.

46. Daly K, Darby AC, Hall N, Nau A, Bravo D, et al. (2014) Dietary supplementation with lactose or artificial sweetener enhances swine gut Lactobacillus population abundance. Br J Nutr 111: S30-S35.

47. Collins SM (2014) A role for the gut microbiota in IBS. Nat Rev Gastroenterol Hepatol 11: 497-505.

48. Bueno-Hernandez N, Nunez-Aldana M, Ascano-Gutierrez I, Yamamoto-Furusho JK (2015) Evaluation of diet pattern related to the symptoms of Mexican patients with Ulcerative Colitis (UC): through the validity of a questionnaire. Nutr J 14: 25.

49. Frolkis A, Dieleman LA, Barkema HW, Panaccione R, Ghosh S, et al. (2013) Environment and the inflammatory bowel diseases. Can J Gastroenterol 27: e18-24.

50. Durchschein F, Petritsch W, Hammer HF (2016) Diet therapy for inflammatory bowel diseases: the established and the new. World J Gastroenterol 22: 2179-2194.

51. Prince AC, Myers CE, Joyce T, Irving P, Lomer M, et al. (2016) Fermentable carbohydrate restriction (low fodmap diet) in clinical practice improves functional gastrointestinal symptoms in patients with inflammatory bowel disease. Inflamm Bowel Dis 22: 1129-1136.

52. Qin XF (2002) Impaired inactivation of digestive proteases by deconjugated bilirubin: the possible mechanism for inflammatory bowel disease. Med Hypotheses 59: 159-163.

53. Sehar I, Kaul A, Bani S, Pal HC, Saxena AK (2008) Immune up regulatory response of a non-caloric natural sweetener, stevioside. Chem Biol Interact 173: 115-121.

54. Hou JK, Lee D, Lewis J (2014) Diet and inflammatory bowel disease: review of patient-targeted recommendations. Clin Gastroenterol Hepatol 12: 1592-1600.

55. Qin X (2011) What made Canada become a country with the highest incidence of inflammatory bowel disease: could sucralose be the culprit? Can J Gastroenterol 25: 511.

56. Goldsmith JR, Sartor RB (2014) The role of diet on intestinal microbiota metabolism: downstream impacts on host immune function and health, and therapeutic implications. J Gastroenterol 49: 785-798.

57. Shankar P, Ahuja S, Sriram K (2013) Non-nutritive sweeteners: review and update. Nutrition 29: 1293-1299.

58. Boonkaewwan C, Toskulkao C, Vongsakul M (2006) Anti-Inflammatory and Immunomodulatory Activities of Stevioside and Its Metabolite Steviol on THP-1 Cells. J Agric Food Chem 54: 785-789.

59. Yingkun N, Zhenyu W, Jing L, Xiuyun L, Huimin Y (2013) Stevioside protects LPS-induced acute lung injury in mice. Inflammation 36: 242-250.

60. Labrecque MT, Malone D, Caldwell KE, Allan AM (2015) Impact of ethanol and saccharin on fecal microbiome in pregnant and non-pregnant mice. J Pregnancy Child Health 2: 193.

61. Sylvetsky A, Rother KI, Brown R (2011) Artificial sweetener use among children: epidemiology, recommendations, metabolic outcomes, and future directions. Pediatr Clin North Am 58: 1467-1480.