Is a Non-Caloric Sweeteners-Free Diet Good To Treat Functional Gastrointestinal Disorder Symptoms? A Randomized Controlled Trial

Viridiana Montserrat Mendoza-Martínez

General Hospital of Mexico: Hospital General de Mexico Dr Eduardo Liceaga

Mónica Rocío Zavala-Solares

La Salle University

Aranza Jhosadara Espinosa-Flores

General Hospital of Mexico Dr Eduardo Liceaga: Hospital General de Mexico Dr Eduardo Liceaga

Karen Lorena León-Barrera

General Hospital of Mexico Dr Eduardo Liceaga: Hospital General de Mexico Dr Eduardo Liceaga

Raúl Alcántara-Suárez

General Hospital of Mexico Dr Eduardo Liceaga: Hospital General de Mexico Dr Eduardo Liceaga

José Damian Carrillo-Ruíz

General Hospital of Mexico Dr Eduardo Liceaga: Hospital General de Mexico Dr Eduardo Liceaga

Galileo Escobedo

General Hospital of Mexico Dr Eduardo Liceaga: Hospital General de Mexico Dr Eduardo Liceaga

Marcela Esquivel-Velázquez

General Hospital of Mexico Dr Eduardo Liceaga: Hospital General de Mexico Dr Eduardo Liceaga

Guillermo Melendez-Mier

General Hospital of Mexico Dr Eduardo Liceaga: Hospital General de Mexico Dr Eduardo Liceaga

Nallely Bueno-Hernández (✉ nallely_bh5@yahoo.com.mx)

General Hospital of Mexico Dr Eduardo Liceaga: Hospital General de Mexico Dr Eduardo Liceaga

<https://orcid.org/0000-0002-3961-0987>

Research

Keywords: Non-Caloric Sweeteners, Sucralose, Functional Gastrointestinal Disorders, Diet, Irritable Bowel Syndrome, Gastroesophageal Reflux Disease.

Posted Date: August 3rd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-741222/v1>

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Version of Record: A version of this preprint was published at Nutrients on March 5th, 2022. See the published version at <https://doi.org/10.3390/nu14051095>.

Abstract

Background

A diet containing Non-Caloric Sweeteners (NCS) is used to reduce calorie intake and blood sugar peaks in overweight and obese subjects. Nevertheless, some animal studies suggest that NCS consumption may increase Functional Gastrointestinal Disorder symptoms (FGDs); however, there are scant clinical trials in humans. The aim of the study was to compare the effect of consuming a diet containing NCS (c-NCS) versus a Non-Caloric Sweetener-free diet (NCS-f) on FGDs in adult volunteers.

Methods

This was a randomized, controlled, parallel-group study using two different diets for five weeks: diet c-NCS contained 50-100 mg/day NCS (80% sucralose and 20% aspartame, acesulfame K, and saccharin); NCS-f diet contained less than 10 mg/day NCS. FGDs were recorded according to the Rome III criteria, gastrointestinal symptom questionnaire, Bristol scale, food frequency questionnaire, and consumption questionnaire at the beginning (PreTx) and at the end (PostTx) of the study by a gastroenterologist and a nutritionist. This study conducted according to the CONSORT guidelines and it was registered at clinicaltrials.gov (identifier code: NCT04129762).

Results

Participants were more often women than men in both groups (59% and 62%), with a median age of 22 years. FGDs were similar in both groups at the beginning of the study (PreTx) but significantly increased in the diet c-NCS group after five weeks (PostTx). The percentage of participants with diarrhea (PreTx=19% versus PostTx=56%; $p=0.02$), post-prandial discomfort (PreTx=9% versus PostTx=39%; $p=0.02$), constipation (PreTx=30% versus PostTx=56%; $p<0.01$), and burning or retrosternal pain (PreTx=13% versus PostTx=33%; $p<0.01$) significantly increased in the diet c-NCS group. Conversely, abdominal pain (PreTx=15% versus PostTx=3%; $p=0.04$), post-prandial discomfort (PreTx=26% versus PostTx=6%; $p=0.02$), burning or retrosternal pain (PreTx=15% versus PostTx=0%; $p=0.02$), early satiety (PreTx=18% versus PostTx=3%; $p<0.01$), and epigastric pain (PreTx=38% versus PostTx=3%; $p<0.01$) significantly decreased in the NCS-f diet group.

Conclusion

This study shows that diet c-NCS associates with increased FGDs including diarrhea, post-prandial discomfort, constipation, and burning or retrosternal pain. Interestingly, NCS-f diet concurs with decreased FGDs such as abdominal pain, post-prandial discomfort, burning or retrosternal pain, early satiety, and epigastric pain. A NCS-f diet could be a complementary strategy to alleviate FGDs.

Trial registration: The ethics committee of the hospital approved this study with the registration number DI/19/301/03/020. This trial was registered at clinicaltrials.gov (identifier code: NCT04129762).

Background

A diet containing Non-Caloric Sweeteners (c-NCS) is widely used to reduce calorie intake and blood sugar peaks in overweight and obese individuals. For this reason, the amount of foods and beverages containing Non-Caloric Sweeteners (NCS) has increased in the last few years. Sucralose, aspartame, acesulfame potassium (K), and saccharin are the most widely used NCS that have been approved by the United States Food and Drug Administration (FDA) [1] [2] [3].

In Latin America, the number of subjects consuming NCS is as high as 70% [4]. Nevertheless, some studies have shown that NCS consumption concurs with Functional Gastrointestinal Disorder symptoms (FGDs), since the amount of unabsorbed sweetener can be metabolized by gut microbiota, triggering changes in intestinal habit. Moreover, NCS consumption has been associated with altered secretion of hormones able to regulate intestinal transit such as glucagon-like peptide-1 (GLP-1), gastric inhibitory polypeptide (GIP), peptide YY (PYY), and cholecystokinin (CCK); however, the role of NCS in gastrointestinal pathogenesis remains uncertain [5] [6] [7] [8].

FGDs, such as irritable bowel syndrome (IBS), functional dyspepsia, or functional constipation, diarrhea, and gastroesophageal reflux disease (GERD) are recurrent conditions that account for at least 30% of referrals to gastroenterologists [9] [10] [11].

A study assessing gastrointestinal symptoms in experimental animals showed that rabbits fed 750–1000 mg/kg/day sucralose develop gastrointestinal symptoms including perianal soiling, scouring, and cecal enlargement as compared to controls [12] [13].

This evidence suggests potential deleterious actions of NCS consumption in the development of FGDs; nevertheless, there are scarce clinical studies in human populations.

The aim of the study was to compare the effect of consuming a diet c-NCS versus a Non-Caloric Sweetener-free (NCS-f) diet on FGDs in adult volunteers.

Material And Methods

Trial design

This was a randomized, controlled, parallel-group study conducted according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines [14]. This trial was registered at clinicaltrials.gov (identifier code: NCT04129762).

Ethical considerations

The ethics committee of the hospital approved this study with the registration number DI/19/301/03/020. All participants signed the informed consent and received an explanation of the purpose and procedures used in the study.

Eligibility criteria for participants

Inclusion criteria were women or men aged 18 to 35 yrs old, who agreed not to consume alcohol or NCS during the study. The exclusion criteria included participants with previous diagnosis of diabetes, hypertension, and metabolic diseases. Pregnant or lactating women were also excluded from the study. Participants were enlisted at the Laboratory of Proteomics and Metabolomics, Research Division at the General Hospital of Mexico Dr. Eduardo Liceaga.

Interventions

Each volunteer was randomly assigned to two types of diet for five weeks: diet c-NCS containing 50–100 mg/day NCS (80% sucralose and 20% aspartame, acesulfame K, and saccharin), and NCS-f diet that contained < 10 mg/day NCS. Volunteers in the NCS-f diet group received a list of all foods and drinks available in the market that contained NCS and sucralose liquid (48 to 96 mg) for use in their drinks. The volunteers in NCS-f diet had the same list and were instructed to avoid their consumption for the entire time of the study. FGDs were registered at the beginning (PreTx) and at the end (PostTx) of the study.

Outcomes

NCS consumption was measured using a Food Frequency Questionnaire (FFQ) and a NCS Consumption Questionnaire (SCQ), previously validated by our group in order to estimate the adherence to treatment and consumption of sweeteners [15]. Also, FGDs were registered at PreTx and at PostTx according to the Rome III criteria, gastrointestinal questionnaire symptoms, and Bristol scale by a gastroenterologist and a nutritionist. The gastrointestinal questionnaire symptoms evaluated the development of FGDs as early satiety, constipation, diarrhea, burning or retrosternal pain, epigastric pain, abdominal pain, and post-prandial discomfort, at the beginning and at the end of the study. The participants with stool consistency type 1 or 2 according to the Bristol scale were diagnosed with constipation. Subjects with Bristol type 3 or 4 were considered to have normal evacuations, and volunteers with Bristol type 5 to 7 were considered to have diarrhea. Body composition was measured by electrical bioimpedance (RJL Quantum IV system, RJL Systems Inc. Clinton Township MI, USA). Anthropometric data such as weight (Weighing Machine, MS 50 SECA; Hamburg Germany), height (Scale, MD 213 SECA; Hamburg Germany), waist and hip circumferences (Metric Tape W606 Lufkin; CdMx Mexico) were measurement by a nutritionist.

Sample size and randomization

The sample size calculation was performed with the GPower v.3.1 9.2 program, expecting an effect size of 0.4, with an alpha error of 0.05 and a power of 80%, resulting in a sample size of 30 participants per group. Nevertheless, the number of participants in the diet c-NCS group was increased in order to decrease intervention bias.

The randomization scheme was generated by using the Website randomization.com (<http://www.randomization.com>) and the rationalization scheme was by blocks (6 blocks of 5 patients

each one). Consecutive numbers were randomized to different kinds of diets and then assigned to the patients.

Statistics

Normality of data distribution was assessed using the Kolmogorov Smirnov test. T-Test, Paired T-Test, and χ^2 test were used to compare intervention groups at the beginning and at the end of the study. A P value < 0.05 was considered as statistically significant. SPSS Statistics 21 was used for the statistical analysis.

Results

One hundred and thirty-seven participants were included in the study from October 2019 to June 2020 and randomly assigned to diet c-NCS or NCS-free diet. Ninety-five participants completed the study, specifically, 34 volunteers in the NCS-free diet group and 61 volunteers in the diet c-NCS group. Figure 1 shows a flow chart of the study according to the CONSORT guidelines.

Table 1 shows the baseline characteristics of the population. Participants were more often women than men in both groups (59% and 62%), with a median age of 22 ± 3.2 yrs in NCS-f diet group, and 22 ± 3.1 yrs in diet c-NCS group. There were no significant differences between groups for weight (64.9 ± 12.71 vs. 64.9 ± 12.77 ; $P = 0.98$), waist-to-hip ratio (0.81 ± 0.67 vs. 0.81 ± 0.65 ; $P = 0.52$), and body mass index (24.16 ± 3.8 vs. 23.9 ± 3.1 ; $P = 0.75$) at the beginning of the study. Consumption of carbohydrates, proteins, lipids, and calories was not different between groups at the beginning of the study. Moreover, the amount and type of NCS consumed were similar in both groups at the beginning of the study (Table 1).

Table 1
Baseline characteristics of the volunteers.

	NCS-f n = 34	c-NCS n = 61	<i>p</i> *
Age, years (m ± SD)	22 ± 3.2	22 ± 3.1	0.74
Men, n (%)	14 (41)	23 (38)	0.73
Women, n (%)	20 (59)	38 (62)	0.91
Weight, kg (m ± SD)	64.9 ± 12.7	64.9 ± 12.7	0.98
WHR, (m ± SD)	0.81 ± 0.67	0.81 ± 0.65	0.52
BMI, kg/m ² (m ± SD)	24.16 ± 3.8	23.9 ± 3.1	0.75
Fat; (%±SD)	35.5 ± 7.2	35.5 ± 5.7	0.85
Fat free mass; (%±SD)	64.5 ± 7.2	64.1 ± 5.7	0.85
Total body water; (%±SD)	46.2 ± 5.4	45.9 ± 4.5	0.79
Carbohydrates, g/day ($\bar{x}$ ±SD)	289.4 ± 118	246.6 ± 104	0.08
Protein, g/day (m ± SD)	103.9 ± 74	97.6 ± 52	0.66
Lipid, g/day (m ± SD)	71.5 ± 59	68.4 ± 43	0.78
Kilocalorie, kcal/day (m ± SD)	2264.7 ± 1247	2036.1 ± 837	0.34
Consumption of NCS, n (%)	23 (67)	41 (67)	0.96
Consumption amount of NCS, mg/day (m ± SE)	42.5 (20)	50.0 (16)	0.77
Adherence to treatment (%)	85	90	0.26
Presence of gastro intestinal symptoms, n (%)	20 (58)	33 (54)	0.65
NCS-f = Non-Caloric Sweeteners free diet, c-NCS = Containing Non-Caloric Sweeteners, PreTx = Pretreatment, PostTx = Posttreatment, m = mean, SD = standard deviation, NCS = Non-Caloric Sweeteners, WHR = waist-hip ratio, BMI = body mass index, SE = standard error. * T-Test and X ² test.			

At the end of the study, in the NCS-f diet group, NCS (mg/day) consumption decreased as compared to baseline (PreTx = 42.5 ± 20.9 vs. PostTx = 2.6 ± 1.7; *P* = 0.06) in NCS-free diet group, whereas it tended to increase in the diet c-NCS group (PreTx = 50.03 ± 16 vs. PostTx = 74.2 ± 3.3; *P* = 0.15) without reaching significant differences (Table 2).

Table 2

Differences between diet groups (NCS-f and c-NCS) at the beginning (PreTx) and at the end (PostTx) of dietary interventions.

	NCS-f (n = 34)		<i>P</i> *	c-NCS (n = 61)		<i>P</i> *
	PreTx	PostTx		PreTx	PostTx	
Weight, kg (m ± SD)	64.9 ± 12.71	64.6 ± 12.7	0.25	64.9 ± 12.77	64.9 ± 12.7	0.85
WHR, (m ± SD)	0.81 ± 0.06	0.81 ± 0.05	0.50	0.81 ± 0.65	0.8 ± 0.06	0.50
BMI, kg/m ² (m ± SD)	24.16 ± 3.8	24 ± 3.9	0.33	23.9 ± 3.1	23.9 ± 3.2	0.87
Fat; (%±SD)	35.5 ± 7.2	34.3 ± 6.9	< 0.01	35.5 ± 5.7	34.6 ± 6.3	< 0.01
Fat free mass; (%±SD)	64.5 ± 7.2	65.4 ± 6.9	< 0.01	64.1 ± 5.7	65.4 ± 6.3	< 0.01
Total body water; (%±SD)	46.2 ± 5.4	47.6 ± 5.4	< 0.01	45.9 ± 4.5	47.3 ± 4.9	< 0.01
Consumption amount of NCS, mg/day (m ± SD)	42.5 ± 20.9	2.6 ± 1.7	0.06	50.03 ± 16	74.2 ± 3.3	0.15
Carbohydrates, g/day (m ± SD)	289.4 ± 119	219.4 ± 77	< 0.01	246.5 ± 108	260.3 ± 108	0.33
Protein, g/day (m ± SD)	104.7 ± 77	83.8 ± 67	0.03	94.3 ± 51	87.8 ± 41	0.38
Lipid, g/day (m ± SD)	73.2 ± 61	63 ± 51	0.22	67.5 ± 42	69.1 ± 42	0.80
Kilocalorie, kcal/day (m ± SD)	2281 ± 1282	1828 ± 1025	< 0.01	2014 ± 832	2058 ± 832	0.71
Presence of gastro-intestinal symptoms, n (%)	20 (58)	8 (23)	0.02	31 (50)	39 (63)	0.07
NCS-f = Non-Caloric Sweeteners free diet, c-NCS = Diet containing Non-Caloric Sweeteners, PreTx = Pretreatment, PostTx = Posttreatment, SD = standard deviation, NCS = Non-Caloric Sweeteners, WHR = waist-hip ratio, BMI = body mass index, m = mean, SE = standard error.* Paired T-Test, and X ² test						

Gastrointestinal symptoms

In the diet c-NCS group, the vast majority of FGDs increased after five weeks of dietary intervention. Specifically, the percentage of participants with diarrhea (PreTx = 19% to PostTx = 56%; *P* = 0.02), post-prandial discomfort (PreTx = 9% to PostTx = 39%; *P* = 0.02), constipation (PreTx = 30% to PostTx = 56%; *P*

< 0.01), and burning or retrosternal pain (PreTx = 13% to PostTx = 33%; $P < 0.01$) significantly increased at the end of the study as compared to baseline (Fig. 2A).

Participants in the NCS-f diet group showed significant decreases in all FGDs at the end of the study, especially, abdominal pain (PreTx = 15% to PostTx = 3%; $P = 0.04$), post-prandial discomfort (PreTx = 26% to PostTx = 6%; $P = 0.02$), burning or retrosternal pain (PreTx = 15% to PostTx = 0%; $P = 0.02$), early satiety (PreTx = 18% to PostTx = 3%; $P < 0.01$), and epigastric pain (PreTx = 38% to PostTx = 3%; $P < 0.01$) (Fig. 2B).

Dietary effects

Weight, waist-to-hip ratio, and body mass index showed no significant changes after dietary interventions in both groups. In the NCS-f diet group, consumption of carbohydrates (PreTx = 289.4 ± 119 vs. PostTx = 219.4 ± 77 ; $P = 0.001$) and energy (PreTx = 2281.9 ± 1282 vs. PostTx = 1828.2 ± 1025 ; $P = 0.007$) significantly decreased after diet. Conversely, in the diet c-NCS group, consumption of carbohydrates (PreTx = 246.5 ± 108 vs. PostTx = 260.3 ± 108 ; $P = 0.33$), lipids (PreTx = 67.5 ± 42 vs. PostTx = 69.1 ± 42 ; $P = 0.80$), and energy (PreTx = 2014.3 ± 832 vs. PostTx = 2058.3 ± 832 ; $P = 0.71$) tended to increase without reaching significant differences (Table 2).

Finally, volunteers from both groups exhibited a significant decrease in fat percentage after dietary interventions (NCS-f: PreTx = 35.5 ± 7.2 vs. PostTx = 34.3 ± 6.9 ; $p < 0.01$, and c-NCS: PreTx = 35.5 ± 5.7 vs. PostTx = 34.6 ± 6.3 ; $p < 0.01$). Additionally, subjects from both groups showed significant increases in free fat mass (NCS-f: PreTx = 64.5 ± 7.2 vs. PostTx = 65.4 ± 6.9 ; $p < 0.01$ and c-NCS: PreTx = 64.1 ± 5.7 vs. PostTx = 65.4 ± 6.3 ; $p < 0.01$) and total body water (NCS-f: PreTx = 46.2 ± 5.4 vs. final = 47.6 ± 5.4 ; $p < 0.01$ and c-NCS: PreTx = 45.9 ± 4.5 vs. PostTx = 47.3 ± 4.9 ; $p < 0.01$) at the end of dietary interventions (Table 2).

Discussion

The effects of NCS on FGDs are scantily studied and available data are predominantly from animal studies. To the best of our knowledge, this is the first study in human beings that evaluates the development of FGDs in response to a diet containing NCS, particularly sucralose. Emerging evidence suggests that FGDs occur as a consequence of changes in gut microbiota and hormones that regulate gastrointestinal motility. It is worth mentioning that despite numerous studies have consistently shown the deleterious effects of NCS on health, their consumption as part of the diet is increasing worldwide [4]. This phenomenon may be partially explained since many developing countries are experiencing transitions from a Mediterranean diet to a Western diet that contains more additives in ultra-processed food and drinks (UPFDs) [3] [16] [17] [18]. For instance, our results show that basally more than 60% of participants frequently consumed any kind of NCS, an amount significantly higher than that informed in a cross-sectional study in the USA, wherein 41.4% of adults reported often NCS consumption [19]. It is worth mentioning that the vast majority of the study participants did not know they consumed NCS because UPFDs labels did not mention the word "light". When reviewed ingredients mentioned in the FFQ

and SCQ, several foods and drinks contained NCS. In fact, all participants consumed, on average, 42–50 mg/day NCS before the study enrollment.

This prospective study demonstrates that NCS-f diet group decreases the presence of FGDs in young people, especially, early satiety, burning or retrosternal pain, epigastric pain, abdominal pain, and postprandial discomfort. In fact, at the beginning of the study, more than 50% of participants had at least one gastrointestinal symptom, which in turn significantly decreases after five weeks of NCS-free diet. In this group, epigastric pain (35%) and postprandial discomfort (20%) were the leading symptoms showing clear decreases. This phenomenon may be explained since some NCS appears to cause increases in incretins such as GLP-1, GIP, PYY, and CCK. GLP-1 decreases motility in the antro-duodeno-jejunal region and inhibits the migrating motility complex in healthy controls and IBS patients. CCK delays gastric emptying and GIP can also slow gastric emptying [20] [21], PYY causes delayed intestinal transit [13]. Interestingly, acesulfame-K in combination with fructose might cause slow gastric emptying by increasing motilin secretion that in turn promotes satiety, just five minutes after NCS administration [22]. Thus, removal of NCS from the diet may decrease incretin secretion, promoting gastrointestinal motility and gastric emptying, which in turn could be able to improve epigastric pain and discomfort after food or drink consumption.

Another phenomenon captured in our study is the significant increase in bowel habit alterations in the diet c-NCS group, especially, diarrhea, constipation, and post-prandial discomfort. A possible hypothesis to explain these findings involves changes in the intestinal environment caused by NCS consumption, including decreased strictly anaerobic bacteria, potential inflammation, and increased gastrointestinal motility, which allow expansion of pathogenic bacteria such as *Enterobacteriaceae* and *Clostridium leptum* [23].

Several *in vitro* and *in vivo* studies reported an association of sucralose ingestion with a higher amount of commensal strain subpopulations in gut microbiota. Some of these bacteria associate with diarrhea, constipation, or both, as a consequence of changes in intestinal permeability [24] [25] [26].

Abou-Donia *et al.* showed that sucralose administration for 12 weeks had numerous adverse effects on the intestine of Sprague-Dawley male rats, including elevation in fecal pH that in turn may associate with changes in the absorption of nutrients and drugs from the gastrointestinal tract. In the same study, the authors found a decrease in beneficial anaerobic bacteria, such as bifidobacteria, lactobacilli, and *Bacteroides* [27]. It is worth mentioning that the use of *Bifidobacterium* and *Lactobacillus* have benefits in the treatment of diarrhea and amelioration of IBS symptoms such as flatulence, stool pressure, pain, and a sensation of incomplete bowel movements. The use of *Bacteroides* species also benefit patients by preventing digestive tract colonization from other potential pathogens [28] [29] [30].

Nowadays, modifications of gut microbiota by reducing NCS intake are crucial; nevertheless, there are few clinical studies, particularly in humans. One of the most important is the study by Suez *et al.* in 2014, wherein they found in 172 individuals a positive correlation between NCS consumption and the *Enterobacteriaceae* family, the Deltaproteobacteria class, and the Actinobacteria *phylum* [7] [31] [24].

Disruption of the intestinal microbiota balance by NCS may potentially interfere with numerous essential gut functions, including normal immune responses, pathogen control, gastrointestinal motility, and nutrient metabolism.

Our results show that NCS-free diet improves FGDs, even though patients from both groups displayed a similar proportion of gastrointestinal symptoms at the beginning of the study. Furthermore, these changes did not depend on body composition (fat, fat-free mass, and total body water percentage), since no relevant clinical changes were found.

More studies are needed using relevant doses of sweeteners in a biological context and exploring the possible molecular mechanisms through which NCS affects gut microbiota profile and neuropeptides such as GLP-1, GIP, PYY, CCK, and vasoactive intestinal peptide.

This study has some limitations. First of all, we enrolled a small number of patients with FGDs diagnoses. In the second place, the study population appears very young since the FGDs prevalence increases at the age of 30 yrs. In the third place, the unbalanced number of male and female participants should be noted since sex hormone profiles may differentially affect the presence of gastrointestinal symptoms. Finally, other dietary aspects such as fasting periods, sugar, and fiber consumption were not controlled in the study population.

Conclusions

This study shows that a NCS-free diet might be of benefit to alleviate numerous FGDs such as abdominal pain, post-prandial discomfort, burning or retrosternal pain, early satiety, and epigastric pain. On the contrary, a diet containing NCS appears to increase diarrhea, post-prandial discomfort, constipation, and burning or retrosternal pain, a notion that should be taken into account by gastroenterologists and nutritionists in the treatment of FGDs.

List Of Abbreviations

BMI, body mass index

CCK, cholecystokinin

CONSORT, Consolidated Standards of Reporting Trials

FGDs, gastrointestinal disorder symptoms

GERD, gastroesophageal reflux disease

GLP-1, glucagon-like peptide 1

GIP, gastric inhibitory polypeptide

IBS, irritable bowel syndrome

NCS, non-caloric sweeteners

NCS-f, non-caloric sweeteners free

c-NCS, containing non-caloric sweeteners

PYY, peptide YY

PreTx, pretreatment

PostTx, posttreatment

SD, standard deviation

SE, standard error

UPFDs, ultra-processed food and drinks

WHR, waist-hip ratio

Declarations

Ethics approval and consent to participate: The ethics committee of the hospital approved this study with the registration number DI/19/301/03/020. All participants signed the informed consent and received an explanation of the purpose and procedures used in the study.

Consent for publication: All authors approved the publication of the manuscript in the Nutrition Journal.

Availability of data and materials: We have made publicly and freely available without restriction the data described in the manuscript, at:

https://www.dropbox.com/s/3riwj6oz7lprvqy/Base%20de%20Datos%2019-06-18_2.sav?dl=0

Competing interests: The authors declare no potential conflicts of interest.

Funding: This research was supported by grant from National Council on Science and Technology (CONACYT) registered with the funding number 261575.

Authors' contributions: NBH, GMM and VMMM; performed writing original draft, conceptualization and formal analysis. MRZS, JDCR and GE; performed writing–review and editing. AJEF, KLDLB, RAS and MEV; development of methodology and investigation. GMM and GE; funding acquisition.

Acknowledgements: We the thanks to staff and patients at the General Hospital of Mexico “Dr. Eduardo Liceaga” for all contributions to the study. To Ernesto Roldan-Valadez for all the facilities provided for data analysis.

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Figures

Figure 1

Flow chart according to CONSORT showing the process of recruitment, randomization, follow-up, and data analysis in the study. Adherence with FGDs: Functional Gastrointestinal Disorders symptoms, Food Frequency Questionnaire (FFQ), NCS Consumption Questionnaire (SCQ), and Bristol scale. Nonsteroidal anti-inflammatory drugs (NSAIDs).

Figure 2

Functional Gastrointestinal Disorder symptoms at the beginning (PreTx) and at the end (PostTx) of dietary interventions with NCS restriction.

Supplementary Files

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