nutrición clínica y Dietética Hospitalaria

Artículo Original

Nutr Clín Diet Hosp. 2024; 44(1):290-294
DOI: 10.12873/441beltran

Effect of caloric restriction and low fructose consumption on oxidative damage in adults with obesity

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Recibido: 16/noviembre/2023. Aceptado: 15/enero/2024.

ABSTRACT

Background: The consumption of macronutrients rich in sugars, mainly fructose, promote metabolic changes and induce insulin resistance, hepatic and extrahepatic fatty acid deposits, as well as an increase in the generation of free radicals and oxidative stress.

Methods: Randomized clinical study, 74 subjects participated, divided into 2 group: a calorie-restricted diet (n=37) and a low-fructose diet (n=37). They were evaluated at the beginning and 6 weeks after the implementation of the diet, using anthropometric and biochemical parameters. Descriptive statistics were used to analyze the data, Student's t test for two independent samples considering unequal variances and for means of two paired samples. Level $p<0.05$ was considered in each analysis test.

Results: The body mass index (BMI) shows statistically significant differences $p< 0.05$ in the group with calorie restriction after applying the diet. The waist and hip circumference were modified by the implementation of the diet in each independent group ($p<0.001$ for each statistical difference, respectively), only the waist-hip index (WHR) was modified when the results were compared between both groups, $p<0.05$. In the biochemical parameters after the implementation of the diets, in the low-fructose diet group an increase in blood glucose was observed from 175.97 to 187.40 mg/dl, cholesterol from 34.05 to 36.89 mg/dl and HDL from 104.77 to 115.47 mg/dl. However, no statistically significant differences were found when comparing both groups. No statistically significant differences were observed in lipid peroxidation parameters or oxidized carbonyls.

Conclusion: The modifications in hepatic metabolism could be related to the energy quantity and the source of macronutrients**.**

KEYWORDS

Nutrition, Diet, Hepatic Metabolism, Oxidative Stress.

INTRODUCTION

Currently, obesity as a pathological entity continues to be considered one of the main health problems, linked to various comorbidities such as hypertension, diabetes, angor pectoris, arthritis, among others. Furthermore, obesity has reached epidemic proportions and is a major contributor to the global burden of chronic disease and disability[1]. Despite all the advances in information about obesity, it is still limitedly defined as the excessive accumulation or abnormal distribution of body fat (BF), which affects health[2]. Growing evidence suggests that oxidative stress is one of the factors with the greatest intervention that links obesity with associated diseases[3], it could trigger the differentiation of preadipocytes into adipocytes and promote the growth of mature adipocytes[4,5]. It has been shown that reactive oxygen species (ROS) modulate the hypothalamic satiety and appetite centers and influence body weight gain[6]. A characteristic of adipocytes in patients with obesity is that they have a greater density of catecholamine receptors (beta-3 adrenergic receptors), which allows an increase in the rate of lipolysis, the release of fatty acids and the formation of free radicals and induces the activity of proinflammatory factors[7,8].

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However, it has been shown that obesity, through various metabolic factors such as mitochondrial oxidation and peroxisomal production of fatty acids, can induce oxidative stress. Various investigations have supported that diets rich in lipids are also capable of generating ROS because their catabolism increases the production of ROS and decreases the rate of production of adenosine tri phosphate (ATP) for each molecule of oxygen consumed at the mitochondrial level[9], and after the increase in adipose tissue, the activity of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) decrease significantly[10].

On the other hand, excessive intake of carbohydrates in the diet, mainly fructose, is considered a cause of obesity[11]. This simple carbohydrate is consumed by children and adults through so-called "sugar-sweetened beverages"[12]. Some studies have shown that interventions aimed at reducing the consumption of these beverages reduce weight gain, adiposity, liver fat and insulin resistance indices, depending on the population, the degree of restriction and the duration of the cited study[13-15].

Despite there being evidence on the metabolic changes induced by different types of diet, it remains to be investigated which of these would be the most appropriate selection in the nutritional management of patients with obesity, which allows influencing their possible complications; Therefore, the objective of this study was to determine the effect of the administration of two diets, one with calorie restriction and the other low in fructose, on oxidative damage in adults with obesity.

METHODS

It is considered to be a randomized clinical trial. The sample size (n) was determined by applying the formula for finite populations; 21,908 adults registered with obesity in the city of Celaya Guanajuato were taken as the universe.

For the study, 74 participants were included, following the inclusion criteria: [1] men and women over 18 years of age, [2] with a BMI greater than 30 kg/m^2, [3] having a fructose consumption >70 g/day, [4] and stating that they do not consume alcoholic beverages or drugs, [5] who are not undergoing nutritional treatment or consuming nutritional supplements; Likewise, participants who did not comply with 80% of the assigned diet or who became pregnant during the clinical trial were excluded. The participants were recruited in the city of Celaya, Guanajuato, who attended the Interdisciplinary Health Care Program (PAIS) of the Celaya – Salvatierra Campus of the University of Guanajuato and who agreed to participate in the study.

The 74 participants were randomly divided into two groups (n=37 each), the first group was assigned a calorie-restricted diet; to the second, a low-fructose diet (content of <20 g/day of fructose), for a continuous period of 6 weeks. Both groups were evaluated at the beginning and 6 weeks after the implementation of the diet. The low-fructose diet was developed with a list of allowed, restricted and prohibited foods indicating the allowed amount of <20 g of fructose per day. Diet adherence was assessed using a 24-hour food intake recall on three days of the week (two weekdays and one weekend day). The patient's energy requirement was estimated using the Harris and Benedict formula which considers age, sex, weight, and height. A minimum physical activity factor of 10% (sedentary lifestyle) and the thermic effect of food (TEF) of 10% were considered. The distribution of macronutrients was 60% carbohydrates, 25% lipids and 15% proteins. To verify the 80% adherence to both diets, it was quantified through The Food Processor program in which the amount of fructose and calories consumed per day were estimated.

To obtain body weight, the patient was placed in the central and symmetrical position of the scale, fasting, with minimal clothing and after having emptied the bladder[16]. For this measurement, a TANITA BC-601 brand scale with a precision of 100 g was used. The technique established by Lohman and collaborators was used to determine height, using a SECA 213® stadiometer[17]. To obtain the BMI, the formula proposed by Quetelet was used: BMI= weight (kg)/height(m)^2 [18]. Waist and hip circumferences were measured with the technique suggested in NOM 043-SSA2-2012[19], using a SECA 203® brand fiberglass measuring tape. Subsequently, the ICC was determined.

Oxidative damage was determined by quantifying the levels of oxidized lipids and proteins in the patients' serum, as described by Martínez-Morúa et al. in 2013[20]. Fundamentally, oxidized lipids were determined spectrophotometrically by the quantification of the adduct that is formed when aldehydes react, mainly malondialdehyde (MDA) with thiobarbituric acid (TBA), for which MDA-TBA is a marker of oxidative damage to lipids. Oxidized proteins were determined spectrophotometrically by quantifying the product of the reaction between the carbonyl group and 2,4-dinitrophenylhydrazine, this adductor is a marker of protein oxidation[20]. A blood sample was collected by venipuncture after a 12-hour fast from each participant. The serum was immediately separated and stored at -20°C until analysis. The determination of glucose, triglycerides, uric acid, high-density lipoproteins (HDL), and low-density lipoproteins (LDL) was carried out by enzymatic spectrophotometric techniques using commercial kits from the VITROS ® Chemistry Products brand.

The present study adhered to the provisions of the ethical principles for research on human beings established in the Declaration of Helsinki[21] and the regulations of the General Health Law regarding research for Health[22]. The study was approved by the Research and Bioethics Committees of the University of Guanajuato, with registration number CIDSC-2710923 and CBDCSI-110160930, respectively.

The data were analyzed in the SSPS version 23 statistical package, using descriptive statistics, the discrete variables were

reported as frequency or percentages and the continuous variables were reported as means and standard deviation. The difference between both diets was performed with a Student's t test for two independent samples considering unequal variances and the effect of the diets before and after implementation was analyzed with a Student's t test for means of two paired samples. Level $p<0.05$ was considered in each analysis test.

RESULTS

In the analysis of the BMI results, through the Student t test for paired groups (Table 1), it was found that there are statistically significant differences in BMI in the group with calorie restriction diet ($t=3.67$, $p<0.05$); while, both diets show statistically significant differences in waist circumference, $p<0.001$, hip circumference, $p<0.001$ and WHR, $p < 0.001$. However, when comparing both groups using Student's t for independent groups, only the WHR shows statistically significant differences after the implementation of the diet ($t=1.997$, $p< 0.05$).

Regarding the biochemical parameters (Table 2), it is observed that in the low-fructose diet group there is an increase in plasma glucose levels from 175.97 ± 33.42 mg/dl before the diet to 187.40 ± 33.09 mg/dl after the implementation of the diet with a statistical difference of $t= -2.453$ and $p< 0.019$, an increase in cholesterol levels from 34.05 ± 7.24 mg/dl to 36.89 ± 82 mg/dl with a statistical difference of $t= -2.52$, $p< 0.0162$ and an increase in HDL from 104.77 ± 25.86 mg/dl to 115.47 ± 28.47 mg/dl with a statistical difference of $t= -2.387$, $p< 0.0225$. No statistically significant differences are found when comparing both groups before and after diet implementation.

With respect to the oxidation markers expressed as TBARS and oxidized carbonyls (Table 3), it is shown that there are no statistically significant differences.

Table 1. Anthropometric variables show the mean ± SD for the low fructose and calorie restriction group before and after the application of the diets

	Low fructose diet (n=37)		**Calorie restricted diet (n=37)**	
Age (years)	31 ± 7 (X̄±SD)		30 ± 8 (X̄±SD)	
Sex (F/M)	22 /15		27/10	
	Before	**After**	**Before**	**After**
Weight (Kg)	96.430 ± 16.54	95.41 ± 17.14	91.36 ± 13.60	90.48 ± 13.89
BMI, (Kg/m^2)	35.86 ± 5.22	35.59 ± 5.46	34.55 ± 3.82	34.22 ± 3.95[a]
Waist circumference (cm)	107.42 ± 11.12	105.33 ± 11.32[b]	104.47 ± 10.18	101.28 ± 10.47[b]
Hip circunference(cm)	115.62 ± 11.91	114.53 ± 11.5[b]	116.51 ± 7.36	114.42 ± 6.95[b]
Waist-hip ratio (WHR)	0.932 ± 0.078	0.922 ± 0.076[b]	0.901 ± 0.077	0.885 ± 0.82[cb]

[a] $p<0.05$ before and after the same group.
[b] $p<0.0001$ before and after in the same group.
[c] $p<0.05$ between both groups after the diet.

Table 2. Comparison of biochemical parameters between low fructose and calorie restriction group

	Low fructose diet (n=37)		**Calorie restricted diet (n=37)**	
	Before	**After**	**Before**	**After**
Glucose (mg/dl)	175.97 ± 33.42	↑ 187.40 ± 33.09[a]	182.16 ± 31.35	184.24 ± 29.26
Cholesterol (mg/dl)	34.05 ± 7.24	↑ 36.89 ± 82[a]	35.21 ± 7.79	36.92 ± 7.97
Triglycerides (mg/dl)	5.87 ± 2.07	5.47 ± 1.5	5.6 ± 1.48	6.38 ± 1.32
HDL, (mg/dl)	104.77 ± 25.86	↑ 115.47 ± 28.47[a]	115.33 ± 31.28	115.5 ± 25.63
LDL, (mg/dl)	34.13 ± 14.84	32.27 ± 13.92	31.16 ± 14.76	31.27 ± 15.52
Uric acid (mg/dl)	35.77 ± 16.41	32.94 ± 8.86	33.16 ± 11.86	33.18 ± 9.42

[a] $p\leq0.05$.

Table 3. Oxidation markers in serum between low fructose and calorie restriction group

	Low fructose diet (n=37)		Calorie restricted diet (n=37)	
	Before	**After**	**Before**	**After**
TBARS (nmoles/mL serum)	33.29 ± 16.92	33.82 ± 20.01	32.20 ± 14.48	32.23 ± 13.18
Oxidized proteins (ng carbonyls/µl serum)	0.527 ± 0.37	0.642 ± 0.53	0.642 ± 0.44	0.704 ± 0.45

DISCUSSION

Contrary to glucose, at the liver level, fructose enters the hepatocyte without limitation and once inside, it could bypass the first enzymatic regulation reaction of glycolysis, which leads to an increase in the catabolism of fructose by glycolysis. The above increases the production of glycolytic intermediates that are derived to other metabolic pathways, including fatty acid synthesis and glucose production[22]. This should be reflected in an increase in fat percentage, and possibly an increase in weight and BMI. In our study, both groups had a BMI greater than 30 and did not show an increase in weight or BMI. On the contrary, in the members of the group that received the calorie-restricted diet, there was a decrease in BMI; The above is very consistent since caloric restriction induces the mobilization of energy reserves due to the decrease in energy consumption. While, since there were no changes in the group with restriction in fructose consumption, it suggests that restriction for 6 weeks is not enough to reduce body weight or BMI unlike calorie restriction. It is important to note that the restriction in fructose consumption had no effect on body weight and BMI, but there was a decrease in adiposity that was reflected in hip circumference and WHR. In fact, both diets decreased adiposity. The results show that 6 weeks of restriction of fructose consumption alone induced redistribution of body composition, which is supported by what has been described that the metabolic derivatives of fructose oxidation increase the synthesis of triglycerides that could be involved in adiposity. visceral and reduced leptin control[23]. In agreement with those described by Lofley and Root, the amount and source of obtaining macronutrients contained in the diet plays an important role in modifying the adiposity of people, reflected in the waist and hip circumference. These authors found an association of increased waist circumference with a higher intake of total carbohydrates, dietary fiber and fructose and a greater increase in hip circumference was associated with a higher intake of total carbohydrates, sucrose, fructose, animal proteins and vegetable fats, in addition to having a sex-dependent relationship[24].

The increase in blood levels of glucose, cholesterol, and HDL in the group with a low-fructose diet coincides with that reported by Geidl-Flueck et al., who show evidence that alterations are induced after ingesting beverages containing fructose in the metabolism of hepatic lipids and the mobilization of triglycerides from adipose tissue, manifesting a greater basal lipogenic capacity with fatty acids[25]. In the opposite case, it is known that constant consumption of beverages containing fructose is capable of increasing the profile of fatty acids and induce insulin resistance[26,27]. It seems to indicate that the production of new hepatic fatty acids after frequent consumption of sugary products could be associated with lipotoxicity and metabolic stress in adults with obesity and increases the possibility of generating fatty liver[28]. These modifications at the metabolic level could imply a deterioration in mitochondrial oxidative stress[29,30], implying an increase in the oxidation of lipids and proteins.

However, in the present study, calorie restriction and decreased fructose consumption did not modify the levels of oxidized proteins and lipids, suggesting that a longer follow-up time is required to observe a significant change. The above is supported by the fact that there was a decrease in adiposity, and possibly a decrease in inflammation, which is expected to later be reflected in a decrease in stress and oxidative damage.

CONCLUSIONS

The modifications in hepatic metabolism could be related to the energy quantity and the source of macronutrients. It remains to be defined the time necessary for a significant change to be reflected in the oxidation products and to establish whether these changes will be permanent; as well as determine what factors could contribute to its permanence. If so, establish prevention criteria for the consumption of these macronutrients that contribute to the search for targeted treatments and avoid enzymatic change at the liver level.

ACKNOWLEDGMENTS

The authors appreciate the support of the University of Guanajuato and PRODEP UGTO-PTC-546 for their support in the development of this project.

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