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The effect of two energy-restricted diets, a low-fructose diet versus a moderate natural fructose diet, on weight loss and metabolic syndrome parameters: a randomized controlled trial

Magdalena Madero[a,*], *Julio C. Arriaga*[a], *Diana Jalal*[b], *Christopher Rivard*[b], *Kim McFann*[b], *Oscar Pérez-Méndez*[a], *Armando Vázquez*[a], *Arturo Ruiz*[a], *Miguel A. Lanaspa*[b], *Carlos Roncal Jimenez*[b], *Richard J. Johnson*[b], *Laura-Gabriela Sánchez Lozada*[a,b]

[a] *Division of Nephrology, Department of Medicine, Instituto Nacional de Cardiología Ignacio Chávez, Juan Badiano no 1 Col Seccion XVI Tlalpan, México City, 14080, México*

[b] *Division of Renal Diseases and Hypertension, University of Colorado, Denver, CO, USA*

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ABSTRACT

One of the proposed causes of obesity and metabolic syndrome is the excessive intake of products containing added sugars, in particular, fructose. Although the ability of excessive intake of fructose to induce metabolic syndrome is mounting, to date, no study has addressed whether a diet specifically lowering fructose but not total carbohydrates can reduce features of metabolic syndrome. A total of 131 patients were randomized to compare the short-term effects of 2 energy-restricted diets—a low-fructose diet vs a moderate natural fructose diet—on weight loss and metabolic syndrome parameters. Patients were randomized to receive 1500, 1800, or 2000 cal diets according to sex, age, and height. Because natural fructose might be differently absorbed compared with fructose from added sugars, we randomized obese subjects to either a low-fructose diet (<20 g/d) or a moderate-fructose diet with natural fruit supplements (50-70 g/d) and compared the effects of both diets on the primary outcome of weight loss in a 6-week follow-up period. Blood pressure, lipid profile, serum glucose, insulin resistance, uric acid, soluble intercellular adhesion molecule–1, and quality of life scores were included as secondary outcomes. One hundred two (78%) of the 131 participants were women, mean age was 38.8 ± 8.8 years, and the mean body mass index was 32.4 ± 4.5 kg/m^2. Each intervention diet was associated with significant weight loss compared with baseline. Weight loss was higher in the moderate natural fructose group (4.19 ± 0.30 kg) than the low-fructose group (2.83 ± 0.29 kg) ($P = .0016$). Compared with baseline, each intervention diet was associated with significant improvement in secondary outcomes. Reduction of energy and added fructose intake may represent an important therapeutic target to reduce the frequency of obesity and diabetes. For weight loss achievement, an energy-restricted moderate natural fructose diet was superior to a low-fructose diet.

Author contributions: Magdalena Madero, Richard Johnson, Diana Jalal, Miguel Lanaspa, Carlos Roncal Jimenez, Armando Vazquez, and Laura-Gabriela Sanchez Lozada were involved in the study design. Julio Arriaga was responsible for recruiting patients and patient follow-up. Kim McFann was the statistician. Christopher Rivard and Arturo Ruiz were involved with the laboratory determinations. Oscar Perez Mendez supported the study with the lipid profile determinations.

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* *Corresponding author*. Tel.: +52 55 73 69 02; fax: +52 55 73 77 16.
E-mail address: madero.magdalena@gmail.com (M. Madero).

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1. Introduction

One of the proposed causes of obesity and metabolic syndrome is the excessive intake of products containing added sugars, in particular, fructose [1-9]. Fructose is a simple sugar that is present in honey and fruits; but the greatest source is from added sugars, such as table sugar (sucrose, a disaccharide of glucose and fructose) and high-fructose corn syrup (a mixture of free fructose and glucose usually in a 55:45 ratio). Experimental studies have shown that excessive concentrations of fructose (but not glucose) can induce all features of metabolic syndrome in rats [1], an effect that occurs independently of energy intake [1-3]. Clinical [4-7] and epidemiologic [8-9] studies also suggest that excessive fructose intake can cause metabolic syndrome. In particular, Stanhope et al [4] administered fructose to 34 healthy adults who subsequently developed postprandial hypertriglyceridemia, insulin resistance, and intraabdominal fat accumulation; these effects were not observed with glucose or starch-based diets. Similarly, in healthy subjects, fructose overconsumption has been associated with dyslipidemia and ectopic lipid deposition in liver and muscle [5]. In addition, Perez-Pozo et al [7] administered 200 g of fructose daily to healthy adult men and noted significant increases in ambulatory blood pressure, fasting serum triglycerides, weight, and insulin resistance (assessed by the homeostasis model assessment [HOMA]), with a significant decrease in high- density lipoprotein (HDL) cholesterol by 2 weeks [7]. Although the ability of excessive intake of fructose to induce metabolic syndrome in experimental animals and humans is mounting, to date, there is limited data regarding whether a diet specifically lowering fructose can reduce features of metabolic syndrome.

There is evidence to suggest that it is primarily the fructose content in added sugars that is important in promoting hypertension [10], possibly because natural fruits contain numerous beneficial substances, including antioxidants and flavonols. Because most diets that restrict fructose, such as low-carbohydrate–based diets, also reduce starches and high glycemic foods, we tested the hypothesis that a diet that specifically restricts fructose might reduce weight and features of metabolic syndrome in overweight and obese subjects. We further hypothesized that a diet in which the only source of fructose comes from natural fruits might be superior to one in which fruits consumption is limited. Therefore, we randomized participants to 2 energy-restricted diets, both of which excluded added sugars, a low-fructose diet allowing a limited consumption of fruits and a moderate-fructose diet in which natural fruits were allowed as the only source of fructose. We also included a modest caloric restriction in both diets, as this is the cornerstone of obesity management in clinical practice.

2. Methods

This was a randomized clinical trial to compare the short-term effects on features of the metabolic syndrome of 2 energy reduced diets that differed in their targets for fructose intake. The trial was conducted between March and October 2009 at the Instituto Nacional de Cardiología Ignacio Chávez, México. The study was approved by the human subjects committee at the institution (protocol approval no. 09-630, ClinicalTrials.gov NCT0086873). All participants gave written informed consent.

2.1. Participants

To participate in the trial, patients had to be 18 years or older and be overweight (body mass index [BMI] >25 kg/m^2) or obese (BMI >30 kg/m^2). Subjects were excluded if they had a history of diabetes, hypertension, chronic kidney disease, liver disease, anemia, or malignancy, were taking any medications, or were pregnant.

A total of 217 patients were screened, and 131 patients were recruited for the study. Participants were recruited from the community and within the Instituto Nacional de Cardiología Ignacio Chavez. Sixty-five and 66 patients were randomized to the low-fructose diet and the natural moderate fructose diet, respectively. A total of 107 (82%) of the participants completed the trial (Fig. 1). One hundred two (78%) of the 131 participants were women, mean age was 38.8 ± 8.8 years, and the mean BMI was 32.4 ± 4.5 kg/m^2. There were no differences in the baseline characteristics between the 2 groups (Table 1).

2.2. Weight loss intervention

The nutrient goals for both arms were 55% carbohydrates, 15% proteins, and 30% fat. Patients were given a total kilocalorie dietary plan according to the Harris Benedict formula that takes into account age, sex, and height [11]. In addition, the thermal effect of foods and rest energy were assessed and incorporated in the prescribed diets. The total calories that each patient required were rounded to the closest dietary plan of 1500, 1800, or 2000 kcal. After this kilocalorie evaluation was prearranged, patients were further randomized by using random number tables into each diet intervention arm. The low-fructose arm was assigned to a 2-week period of less than 10 g of fructose per day followed by a 4-week period of less than 20 g of fructose per day (Table 2). The moderate natural fructose diet consisted of 50 to 70 g of fructose consisting of mostly natural fructose from fruits. Patients were followed for 6 weeks. Added sugars from processed fruit juices and punch; sugar-sweetened soft drinks and beverages; and bakery products such as pies, cakes, strudels, doughnuts, and cookies, in addition to dairy dessert, chocolate, candy, and dried fruits, were excluded in both arms. Before randomization, patients completed a self-administered food frequency semiquantitative dietary questionnaire of 109 items to address their baseline energy consumption and their intake of nutrients from the major pyramid food groups. Food items were categorized into 10 food groups, and each food proportion was presented in units. The frequency of consumption of any food item was categorized as 1 to 7 days per week, 1 to 2 days per month, or never. This questionnaire was adapted from food questionnaire used for the US National Health and Nutrition

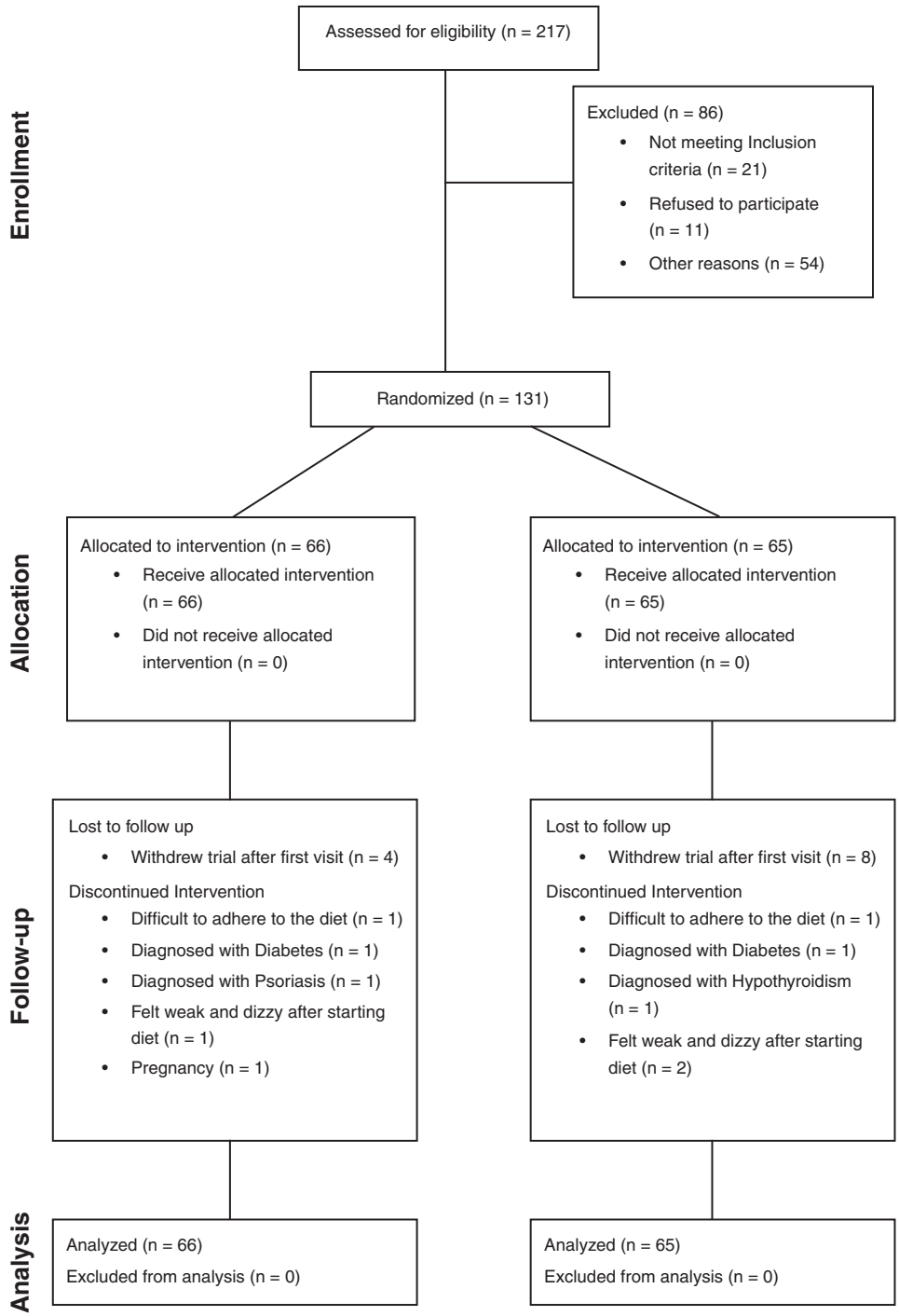

Fig. 1 – Participant flow through the trial.

Examination Survey but was modified to include the types of foods that are specific to the Mexican diet [12] (Table 2). After randomization, patients were followed on a weekly basis. Participants were provided weekly with a daily meal plan and were instructed to record their food and beverage intake at least once a week in a food diary. Adherence was defined as attending at least 80% of the scheduled clinic visits, being present at the last visit, and having blood work during this last visit. Physical activity was assessed by asking the patients if they performed any specific aerobic or anaerobic exercise besides their daily routine. No physical activity was prescribed for any group.

2.3. *Measurements*

Body weight and waist and hip circumference were measured weekly. Patients were weighted with their clothes on and without shoes. Weight was recorded with 2 different scales: a

Table 1 – Baseline characteristics of the cohort

Variable (units)	Low fructose diet (n = 66)	Moderate natural fructose diet (n = 65)	P > |t|
Age (y)	37.56 ± 1.14	40.15 ± 1.01	.09
Sex (female)	52 (78.79%)	50 (76.92%)	.80
Weight (kg)	82.74 ± 1.64	79.07 ± 1.66	.12
Glucose (mg/dL)	91.30 ± 2.75	89.05 ± 2.77	.56
Systolic BP (mm/Hg)	108.9 ± 1.12	109.1 ± 1.13	.92
Diastolic BP (mm/Hg)	69.01 ± 0.63	69.64 ± 0.64	.49
Fat (%)	41.46 ± 0.90	39.49 ± 0.90	.12
Wrist (cm)	15.57 ± 0.14	15.50 ± 0.14	.72
Waist to hip ratio	0.87 ± 0.08	1.01 ± 0.08	.23
Waist (cm)	97.13 ± 1.29	96.91 ± 1.30	.90
BMI (kg/m^2)	32.89 ± 0.55	31.81 ± 0.56	.17
Insulin (IU)	17.95 ± 1.26	18.07 ± 1.27	.95
sICAM (ng/dL)	4.44 ± 0.11	4.37 ± 0.11	.63
Urine creatinine (mg/dL)	176.8 ± 11.87	172.1 ± 11.77	.78
Urine microalbumin (μg/mg)	1.98 ± 0.42	1.68 ± 0.42	.63
Insulin resistance (HOMA)	2.28 ± 0.13	2.15 ± 0.13	.45
Uric acid (mg/dL)	5.53 ± 0.14	5.54 ± 0.14	.95
Cholesterol (mg/dL)	188.3 ± 4.29	196.2 ± 4.32	.19
Triglycerides (mg/dL)	180.6 ± 10.47	174.7 ± 10.55	.69
HDL (mg/dL)	40.36 ± 1.47	39.41 ± 1.51	.65

Data reported as least squares means ± SE. BP indicates blood pressure.

calibrated mechanical scale and an electric impedance scale (TANITA BF-681, WA, USA) that was used to calculate percentage of body fat. Body mass index was calculated with the formula weight (kilograms)/height (square meters). Waist and hip circumferences were measured by the same person with a Gulick glass fiber anthropometric tape. Measures were taken with the patient in a standing position, using the costal edge, iliac crest, and coxofemoral articulation as reference. To evaluate consistency of measurement, randomized measures were done blinded by a person external to the trial. Blood pressure was measured with a mercury sphygmomanometer (Tycos Welch Allyn, NY, USA) that was previously calibrated by the center. Blood pressure was recorded weekly with the patient seating. Three blood pressure measurements were recorded with 5-minute intervals after having the patient at rest for 10 minutes.

Concentration levels of serum glucose, uric acid, total cholesterol, HDL cholesterol, triglycerides, and microalbumin were measured at baseline and at the end of follow-up using the VetACE analyzer (Alfa Wassermann, West Caldwell, NJ). For triglycerides, an enzymatic glycerol phosphate oxidase assay was used. Creatinine was determined by the alkaline picrate (Jaffe reaction).Uric acid was analyzed by the uricase method. Cholesterol was analyzed by the esterase/oxidase assay. The phosphotungstic acid–Mg^{2+} precipitation procedure was used to precipitate apolipoprotein B–containing lipoproteins before quantifying HDL cholesterol. Glucose analysis used the hexokinase assay. High-sensitivity microalbumin for urine was determined by the immunoturbidimetric assay. Insulin in human serum was measured by a sandwich-type immunoassay in a 96-well plate format (ALPCO Diagnostics, Salem NH). Standards and serum samples were assayed in duplicate as per the manufacturers protocol. The HOMA, which is an estimate of steady-state β-cell function and insulin sensitivity, was determined using the online HOMA calculator (www.dtu.ox.ac-uk/index.php?maindoc=/homa/index.php).

Human soluble intercellular adhesion molecule–1 (sICAM-1) was determined by enzyme-linked immunosorbent assay in a 96-well plate format (Invitrogen, Camarillo, CA). Standards and serum samples were assayed in duplicate as per the manufacturer's protocol.

2.4. *Quality of life scores*

A validated quality of life questionnaire using 12 questions (SF-12) [13] was applied to all participants before randomization and at the end of follow-up. The main aspects evaluated by the questionnaire were perception of general health, ability to perform moderate activities, going up a few flights of stairs, overall productivity and general performance, physical limitation, ability to concentrate and perform their job thoroughly, feeling of peace and calmness, physical limitation secondary to pain, feeling of sadness and depression, and overall energy status.

2.5. *Statistical analyses*

The primary outcome of the study was the change in body weight over a period of 6 weeks; and the secondary outcomes were the changes in waist circumference, blood pressure, triglycerides, HDL cholesterol, insulin resistance, uric acid, sICAM-1, and quality of life scores (SF-12). Unadjusted independent-samples *t* tests were used to examine baseline characteristics of the low-fructose diet and the moderate natural fructose diet. Baseline data are presented as mean ± SD. Analysis of covariance (ANCOVA) adjusted for baseline values of each characteristic was used to compare the change in each variable at 6 weeks

Table 2 – Differences in diet compositions at baseline and among intervention groups

	Baseline energy intake (kcal) total cohort	%	Low-fructose diet 1500 kcal	%	Moderate-fructose diet 1500 kcal	%	Low-fructose diet 1800 kcal	%	Moderate-fructose diet 1800 kcal	%	Low-fructose diet 2000 kcal	%	Moderate-fructose diet 2000 kcal	%
Pyramid food groups														
Protein	416.4	14	264	18	227	15	308	17	272	15	344	17	296	15
Fat	764.3	26	427.5	29	441	29	508.5	28	504	28	571.5	29	625.5	32
Carbohydrate	1818.9	61	796	54	832	56	971	54	1014	57	1062	54	1104	56
Major food groups														
Dairy products	363.9	13	220	15	220	15	220	12	110	6	220	11	220	11
Fruits	528.1	17	60	4	480	32	60	3	540	30	60	3	540	27
Animal products	228.3	7	225	15	225	15	225	13	300	17	300	15	300	15
Vegetables	178.5	6	100	7	100	7	100	6	50	3	87.5	4	75	4
Leguminous products	99.9	3	60	4	60	4	120	7	240	13	120	6	180	9.1
Cereals	899.2	30	665	45	280	19	770	43	280	16	875	44	350	18
Fat	154.6	6	157.5	11	135	9	292.5	16	270	15	315	16	315	16
Candies	71.7	2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Juices and soft drinks	263.8	9	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Snacks	154.8	4	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Added sugars	56.8	3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Average caloric intake	2999.7	100	1487.5	100	1500.0	100	1787.5	100	1790.0	100	1977.5	100	1980.0	100

"%" refers to the percentage of calories from each food group.

Table 3 – Within- and between-group changes in the low-fructose group and the moderate-fructose group with natural fruit supplements

Δ = final – baseline	Low fructose		Moderate natural fructose		Comparison between intervention groups
	Δ Mean ± SD	*P* value	Δ Mean ± SD	*P* value	*P* value
Weight (kg)	−2.94 ± 2.18	<.0001	−4.07 ± 2.39	<.0001	.002
Systolic BP (mm/Hg)	−9.46 ± 7.77	<.0001	−7.85 ± 8.73	<.0001	.09
Diastolic BP (mm/Hg)	−5.17 ± 4.69	<.0001	−6.04 ± 5.40	<.0001	.57
Fat (%)	−2.09 ± 6.32	.02	−2.89 ± 6.33	.002	.10
Waist to hip ratio	−0.03 ± 0.02	<.0001	−0.18 ± 1.04	.21	.41
BMI (kg/m^2)	−1.18 ± 0.82	<.0001	−1.57 ± 1.08	<.0001	.02
Uric acid (mg/dL)	−0.24 ± 0.60	.004	−0.22 ± 0.56	.01	.90
sICAM (ng/dL)	−0.28 ± 0.78	.01	−0.42 ± 0.67	<.0001	.19
Urine microalbumin (μg/mg)	0.19 ± 7.70	.85	−0.42 ± 1.84	.11	.32
Total cholesterol (mg/dL)	−9.75 ± 24.4	.004	−12.76 ± 33.31	.01	.95
Triglycerides (mg/dL)	−23.50 ± 69.2	.01	−31.76 ± 55.36	<.0001	.48
HDL (mg/dL)	−0.75 ± 19.67	.79	0.107 ± 12.36	.95	.93
Insulin resistance (HOMA)	−0.29 ± 0.93	.02	−0.37 ± 0.57	<.0001	.12
Blood glucose (mg/dL)	−6.14 ± 30.83	.14	−6.96 ± 9.37	<.0001	.07

compared with baseline. Because subjects were assigned to different caloric intakes, ANCOVA was then performed, adjusting for baseline and caloric intake. Data from ANCOVA are reported as adjusted least square means ± SE. Paired t tests were used to compare within-group changes from baseline to 6 weeks. The data were analyzed first for completers of the study because those who dropped out tended to drop out after the baseline visit and second as intention to treat. The study was powered to detect an effect size of 0.5 kg (difference in 1 kg between groups as an effect of the fructose content on each diet with a 2-kg standard deviation). The number of patients required to have a power of 80% was 64 patients in each arm.

3. Results

3.1. *Participants*

A total of 107 (82%) of the 131 subjects recruited into the study completed the trial, with baseline characteristics shown in Table 1. Nine patients from the low-fructose arm and 13

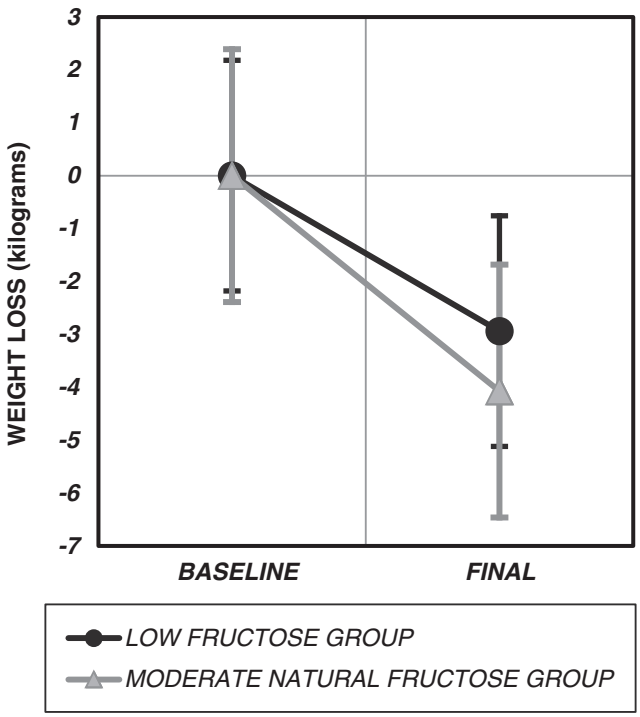

Fig. 2 – Weight changes for each diet intervention group.

patients from the moderate natural fructose arm did not complete the trial. Most of the patients that withdrew from the trial were lost to follow-up after the first visit. Two patients admitted difficulty to adhering to the diet, and 3 patients felt weak and dizzy after starting the diet. Two patients were diagnosed with diabetes, 1 patient was diagnosed with hypothyroidism, and 1 patient withdrew after the diagnosis of pregnancy during the trial (Fig. 1). Patients that did not complete the trial were heavier and had more percentage of body fat, higher levels of sICAM, and microalbuminuria (data not shown). There was no difference with regard to adherence between the 2 diet groups.

3.2. *Baseline energy intake and macronutrient composition*

The average caloric intake for the cohort before initiating the diet was 3000 ± 2520 kcal/d, the average fructose intake was 141 ± 119 g/d, and the average fructose intake from added sugars (after removing natural fruits) was 77 ± 73 g/d (Table 2). There were no significant differences in the baseline macronutrients categories and energy consumption between both groups (data not shown).

3.3. *Primary outcome: weight loss*

The low-fructose diet and the moderate natural fructose diet were associated with significant weight loss compared with baseline (Table 3, Fig. 2). Compared with baseline, each intervention group was associated with a significant change in BMI and fat percentage (Table 3). The change in waist to hip ratio was significant only for the moderate natural fructose group ($P < .001$).

When the 2 diets were compared, weight loss was greater in the moderate natural fructose group (4.19 ± 0.30 kg) compared with the low-fructose group (2.83 ± 0.29 kg) at the end of 6 weeks (Fig. 2, $P = .002$) (Table 3). When analyzed as intention to treat, weight loss was still greater in the moderate natural fructose group (3.39 ± 2.51 kg) compared with the low-fructose group (2.54 ± 2.33) ($P = .047$). The change in BMI was also greater in the moderate natural fructose group ($P = .02$); however, the change in the waist to hip ratio was not significant between groups ($P = .41$).

3.4. *Secondary outcomes: metabolic syndrome parameters*

Each intervention diet was associated with an improvement in the parameters of metabolic syndrome. Both the low-fructose diet and the moderate natural fructose diet resulted in significant changes in blood pressure, total cholesterol, triglycerides, insulin resistance (measured by HOMA index), and uric acid (Table 3). There was no significant change in HDL cholesterol levels in either group. A trend for a greater reduction of systolic blood pressure was observed in the subjects on the low-fructose diet compared with the diet with natural fruit supplements, although this did not reach statistical significance ($P = .09$). There was also a trend towards higher glucose reduction in the moderate natural fructose group ($P = .07$). There was no difference between both diets in relationship to reduction of total cholesterol, triglycerides, insulin resistance, and uric acid (Table 3).

3.5. *Exploratory end points: inflammatory markers*

Each diet was also associated with a significant reduction of sICAM-1 levels (–0.26 ± 0.09 and –0.44 ± 0.09, for the low-fructose and the moderate natural fructose diet, respectively). The absolute reduction of sICAM-1 was not statistically significant between the 2 intervention groups.

3.6. *Quality of life scores*

There was a substantial percentage of patients from both groups that had improvement in their quality of life scores (SF-12), especially in relation to perception of general health and emotional health. There was no difference in the baseline and follow-up scores between the 2 groups (data not shown).

4. Discussion

We report a pilot study using a low-fructose diet to determine its effects on weight loss and metabolic syndrome. The main finding of our study was that both the low-fructose diet and the moderate natural fructose diet were associated with significant weight loss, blood pressure reduction, and changes in the metabolic syndrome parameters, in addition to improved inflammatory markers and some aspects of quality of life scores, in a 6-week follow-up period. When both diets were compared, the moderate natural fructose diet was associated with greater weight loss than the low-fructose diet. There was no difference between both diets in relation to any other parameters.

Our primary hypothesis was that restricting fructose in the diet would result in weight loss and improvement of features of the metabolic syndrome. The potential role for fructose as a cause of metabolic syndrome is best known from animal models [1-3] and is supported by several clinical studies [4-8,14]. Fructose has also been reported to alter satiety responses in humans [15], to induce leptin resistance in rats [16], and to have effects on the hypothalamus in rats that all encourage increased food intake [17]. Nevertheless, to date, no studies have been reported on the effect of modifying the fructose intake in the diet on weight or features of metabolic syndrome. Although our main hypothesis was that the lowering of fructose in the diet would be beneficial by reducing weight and features of the metabolic syndrome, we also compared 2 different fructose diets based on the rationale that the fructose present in natural fruits might not be as deleterious as fructose present in added sugars. First, natural fruits are known to contain many antioxidants, including vitamin C, resveratrol, and flavonols. Some studies suggest that these antioxidants can block the effects of fructose to induce metabolic syndrome in animals [14]. In addition, uric acid is a major byproduct of fructose metabolism and may be responsible for some of its metabolic effects; and vitamin C and antioxidants can also block many of the proinflammatory effects of uric acid on various cell types [18]. Thus, the antioxidants in fruits, along with the high potassium and fiber content, may outweigh the

negative consequences of having relatively high fructose content. The possibility that natural fruits may be a healthy source of fructose is also supported by epidemiological studies that show that fructose from added sugars (with the exclusion of natural fruits) is associated with an increased risk for elevated blood pressure [10], whereas in a study in which subjects had high natural fruit intake, the association of fructose with blood pressure was not observed [19].

A key strength of our study was that the restriction of carbohydrate was limited to fructose. Total carbohydrate percentage was not restricted significantly in either diet. All added sugars were eliminated from both groups; total calorie intake was equal and contained the same percentage of macronutrients. Compared with baseline ingestion, both groups had a total reduction of fructose intake from added sugars.

One of the major findings was that, although both diets were effective at improving metabolic syndrome, the moderate natural fructose diet was actually associated with greater weight loss. There are few potential hypotheses to explain this finding. As mentioned, the moderate natural fructose diet was rich in natural fruits that contain many beneficial antioxidants. In addition, patients in the very low fructose diet had a higher glycemic index and glycemic load, as this was necessary to maintain equivalent carbohydrate content. Diets with high glycemic load result in higher postprandial insulin concentration, which has been associated with hunger and overeating [20]. In our study, glycemic load was confounded with diet groups and caloric intake; and therefore, it was not possible to discern its specific effects.

A second major finding of the study was that, in addition to weight loss, both diets were associated with dramatic improvement in most metabolic syndrome parameters. A striking finding was that the improvement in metabolic syndrome parameters was greater than expected for the degree of weight loss. For example, in comparison to a published study examining the effect of 4 different diets (ie, low fat–average protein, low fat–high protein, high fat–average protein, and high fat–high protein) [21], we observed an almost 2-fold greater decrease in cholesterol, 3-fold greater fall in systolic and diastolic blood pressure, and 50% to 2-fold better improvement in blood glucose levels despite a mean change in weight that was only 60% to 70% of the other diets.

Some of the benefits shown in our study from both low-fructose diets are similar nonetheless to those reported with low-carbohydrate ketogenic diets, especially in relation to change in triglycerides, glucose levels, and blood pressure [22-24]. However, in contrast to our results, it is recognized that total cholesterol and low-density lipoprotein cholesterol do not improve and may even worsen in carbohydrate-restricted diets [25]. In addition, the proportion of patients that can adhere to a low-carbohydrate ketogenic diet is low [21,26]; and there is high pattern of weight loss and regain [26], with only 13% of the subjects having urinary ketones as a marker of adherence present after 48 weeks of enrollment in one randomized study [22]. Our findings raise the possibility that the beneficial effects previously reported with low-carbohydrate regimens may have been due to the concomitant restriction of fructose rather than due to carbohydrate restriction.

One of the other major findings from our trial was that fructose restriction was able to significantly reduce blood pressure. Fructose is known to increase blood pressure in rodents, and the mechanism has been reported to be due to the increase in intracellular and serum uric acid [27,28]. The administration of fructose, but not glucose, raises blood pressure acutely in humans [29]. In a recent clinical study, the administration of fructose to healthy adult men resulted in significant increases in blood pressure, an effect that was not observed in a separate group that received the same diet but with the uric-acid–lowering drug allopurinol [7]. These data suggest that fructose may be a cause of elevated blood pressure and are consistent with a recent study from the National Health and Nutrition Examination Survey cohort that demonstrated that high fructose intake in the form of added sugar is independently associated with higher blood pressure levels in a population with no previous history of hypertension [10]. In addition, a prospective study that evaluated the effect of reduction of sugar-sweetened beverages on blood pressure found that reducing the intake of one sugar-sweetened beverage serving per day had a significant impact on blood pressure among healthy adults, an effect that was independent of weight loss [30]. Our results are consistent with these previous studies, as reducing all added sugars in both diets was reflected in a reduction of -9.66 ± 0.81 and -7.64 ± 0.85 mm Hg for the low-fructose diet and the moderate natural fructose diet, respectively, a change that appears superior to what is expected with weight loss alone and may even be greater to other dietary modifications or the addition of one antihypertensive agent.

Our study has several limitations. First, we recognize that the effects of this trial cannot be attributed exclusively to the effects of fructose reduction and are not fully independent from energy restriction. From the ethical standpoint, energy restriction was essential for a weight loss trial. Furthermore, we did not directly compare these diets with standard diets. However, as mentioned above; the changes in the metabolic parameters appear superior when compared with the historical effects of weight loss alone using other diets that include caloric but not carbohydrate restriction. In addition, we have a relatively short period of follow-up; and therefore, we cannot be certain that these changes in weight loss would be sustained. Nevertheless, the positive changes in blood pressure and other metabolic syndrome features achieved in such a short-term follow-up are relevant and point out the importance of limiting the consumption of fructose. Finally, our population has an unequal sex distribution; and therefore, we cannot extrapolate our findings to men. However, because the effects of fructose are almost universally greater in men than women [31], this limitation may have been more likely to lead to lesser changes than would have been observed if more men had been included in the study.

In conclusion, diets low in fructose from added sugars result in a significant improvement in weight, blood pressure, metabolic syndrome parameters, serum sICAM-1, and quality of life scores. For weight loss achievement, a moderate natural fructose diet was superior to a low-fructose diet. Such a diet may offer greater benefits than other energy-restriction diets, as it does not entail the restriction of total carbohydrate intake and hence may be more sustainable. Based on the results of this pilot study, larger studies in other populations with longer follow-up periods are warranted to evaluate the impact of low-fructose diets on body weight and to explore the potential

of such diets as a therapeutic measure to reduce the frequency of obesity and metabolic syndrome.

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Conflict of interest

Disclosure statement: Dr R Johnson has patent applications related to lowering uric acid in the treatment of metabolic syndrome. Dr Johnson also has a book, *The Sugar Fix* (Rodale, 2008; and Simon and Schuster, 2009), that discusses the potential role of fructose in the obesity epidemic. None of the other authors have any conflicts of interest.

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