International Journal of Obesity (2009) 1–8

0307-0565/09 $32.00
www.nature.com/ijo

ORIGINAL ARTICLE

Excessive fructose intake induces the features of metabolic syndrome in healthy adult men: role of uric acid in the hypertensive response

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Background: Excessive fructose intake causes metabolic syndrome in animals and can be partially prevented by lowering the uric acid level. We tested the hypothesis that fructose might induce features of metabolic syndrome in adult men and whether this is protected by allopurinol.
Methods: A randomized, controlled trial of 74 adult men who were administered 200 g fructose daily for 2 weeks with or without allopurinol. Primary measures included changes in ambulatory blood pressure (BP), fasting lipids, glucose and insulin, homeostatic model assessment (HOMA) index, body mass index and criteria for metabolic syndrome.
Results: The ingestion of fructose resulted in an increase in ambulatory BP (7 ± 2 and 5 ± 2 mm Hg for systolic (SBP) and diastolic BP (DBP), $P<0.004$ and $P<0.007$, respectively). Mean fasting triglycerides increased by 0.62 ± 0.23 mmol l^{-1} (55 ± 20 mg per 100 ml), whereas high-density lipoprotein cholesterol decreased by 0.06 ± 0.02 mmol l^{-1} (2.5 ± 0.7 mg per 100 ml), $P<0.002$ and $P<0.001$, respectively. Fasting insulin and HOMA indices increased significantly, whereas plasma glucose level did not change. All liver function tests showed an increase in values. The metabolic syndrome increased by 25–33% depending on the criteria. Allopurinol lowered the serum uric acid level ($P<0.0001$) and prevented the increase in 24-h ambulatory DBP and daytime SBP and DBP. Allopurinol treatment did not reduce HOMA or fasting plasma triglyceride levels, but lowered low-density lipoprotein cholesterol relative to control ($P<0.02$) and also prevented the increase in newly diagnosed metabolic syndrome (0–2%, $P=0.009$).
Conclusions: High doses of fructose raise the BP and cause the features of metabolic syndrome. Lowering the uric acid level prevents the increase in mean arterial blood pressure. Excessive intake of fructose may have a role in the current epidemics of obesity and diabetes.
International Journal of Obesity advance online publication, 22 December 2009; doi:10.1038/ijo.2009.259

Keywords: fructose; high-fructose corn syrup; sucrose; metabolic syndrome; uric acid; allopurinol

Introduction

The metabolic syndrome consists of a syndrome of insulin resistance, dyslipidemia, abdominal obesity and elevated blood pressure (BP), and often precedes the development of diabetes (Table1).[1] One proposed cause of metabolic syndrome is excessive intake of fructose, primarily from table sugar (sucrose) and high-fructose corn syrup.[2,3] Fructose intake correlates closely with the epidemics of obesity, diabetes and hypertension.[2,3] Animals fed high doses of fructose develop metabolic syndrome, which is not observed in rats fed equivalent calories of dextrose.[4] Humans administered fructose also develop the features of metabolic syndrome, especially hypertriglyceridemia insulin resistance and intra-abdominal fat accumulation; these effects are not observed with glucose- or starch-based diets.[5–7] Chronic fructose ingestion also causes leptin resistance in rats,[8] which could be an additional mechanism causing weight gain.

Fructose is distinct from glucose on account of to its metabolism. Unlike glucose, the phosphorylation of fructose by fructokinase is poorly regulated, and ATP depletion commonly occurs, resulting in the production of inflammatory mediators.[9–11] The breakdown of adenine nucleotides results in a transient increase in intracellular and serum uric

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Received 24 July 2009; revised 21 October 2009; accepted 25 October 2009

Table 1 Metabolic syndrome definitions

NCEP-ATP III criteria (three of the following five criteria)[36]
Waist circumference of >102 cm (40 inches) in men and > 88 cm (35 inches) in women
Fasting plasma triglycerides >1.7 mmol l^{-1} (150 mg per 100 ml)
HDL cholesterol <1.04 mmol l^{-1} (40 mg per 100 ml) in men and <1.3 mmol l^{-1} (50 mg per 100 ml) in women
BP ⩾130/85 mm Hg
Fasting plasma glucose ⩾5.55 mmol l^{-1} (100 mg per 100 ml)
IDF criteria (central obesity plus two of four criteria)[37]
Central obesity (> 94 cm in men or >80 cm in women in Europeans), or BMI >30 and two of the four criteria
Raised triglycerides
>11.7 mmol l^{-1} (150 mg per 100 ml) or specific treatment for this lipid abnormality
Reduced HDL cholesterol
<1.04 mmol l^{-1} (40 mg per 100 ml) in men and <1.3 mmol l^{-1} (50 mg per 100 ml) in women or specific treatment for this lipid abnormality
Raised blood pressure
⩾130 mm Hg SBP
⩾85 mm Hg DBP
Or treatment of previously diagnosed hypertension
Raised fasting plasma glucose
Fasting plasma glucose ⩾5.55 mmol l^{-1} (100 mg per 100 ml)
Previously diagnosed type 2 diabetes

Abbreviations: BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; IDF, International Diabetes Federation; NCEP-ATP III, Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III); SBP, systolic blood pressure.

acid.[12] Although it is historically considered to be a waste product, recent studies suggest that uric acid may have a role in insulin resistance owing to its effect on the adipocyte and vascular endothelium.[3,4,13,14] Lowering the uric acid level partially prevents fructose-induced metabolic syndrome in rats.[4,14] Lowering the uric acid level with allopurinol was also reported to improve the BP in hypertensive adolescents.[15]

We tested the hypothesis that excessive fructose intake can induce the features of metabolic syndrome, and whether lowering the uric acid level can prevent these findings. As the trial was limited in length (lasting only 2 weeks), a relatively high dose (200 g per day) of fructose was used.

Materials and methods

Study design

This was a randomized trial approved by the Institutional Review Board for Mateo Orfila Hospital and the Ethics Committee of Balearic Island (IB-850/07 PI). Informed consent was obtained by the principal investigators (SEP and JLL) in face-to-face interviews in which the study hypothesis and possible risks from ingesting excessive fructose were discussed.

After enrollment, participants were administered fructose 200 g daily, administered as two 1-l bottles of 10% fructose. They were recommended to sip from the solutions all day rather than to ingest rapidly, as the latter has been associated with diarrhea. The participant's adherence to the prescribed fructose consumption was verified by collecting the empty fructose containers three times a week at clinical visits to the hospital.

During the study, all participants were instructed to consume their usual diet, but to avoid alcohol or sugar-sweetened beverages. In addition, they were randomized based on a random number from QuickCalcs (Online Calculators for Scientists) to receive allopurinol (300 mg daily). The investigators and staff knew which participants were receiving allopurinol. All participants were seen in the clinic three times every week. Participants also underwent a 24-h ambulatory BP measurement before initiation of the study and at the final end point. A fasting blood sample was collected before initiation of the study and also at the final visit, and the serum was immediately frozen and stored at −80°C.

Participants

Participants were recruited from the community and within the Mateo Orfila Hospital in Minorca (Balearic Islands), Spain between March and October 2008. All participants underwent screening by clinical history, physical examination and routine laboratory studies. Inclusion criteria were male, age 40–65 years old and non-smokers. Exclusion criteria were high BP noted by casual BP testing or the use of antihypertensive agents, the presence of diabetes, history of cardiovascular disease, gout, cancer, allopurinol allergy, psychiatric disorder, use of statins, alcoholism, illicit drug use, and a history of fructose intolerance.

The study was viewed as a pilot study, as the expected effect of this dose of fructose on the features of metabolic syndrome was not known. We did predict that allopurinol would result in a reduction in fructose-mediated effects by about 25%. The target enrollment was aimed at 60 participants and there was no interim analysis. The number of participants recruited was 293, of which 83 fulfilled the inclusion criteria and were entered into the study. Nine participants did not complete the study because of fructose-induced diarrhea and abdominal cramping, leaving 74 participants for analysis.

Food frequency questionnaire

Each person underwent a dietary intake assessment before initiation of the study and at the final end point using a validated food frequency questionnaire[16] consisting of 135 questions that provided information about total energy, major pyramid food groups, as well as added sugars and discretionary fats. The results were processed by the Department of Preventive Medicine and Public Health in the Medical School at the University of Navarra (Pamplona, Spain).

Blood pressure
BP was measured by trained personnel using calibrated sphygmomanometers (SureSigns VS3 Patient Monitor from Philips Medical Systems, Lakewood, CO, USA) based on the recommendations of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII). BP was measured in the sitting position after a 10-min rest period. Cuff size was selected based on task force recommendations. Each BP value was based on the mean of four measurements. Twenty-four hour ambulatory BP monitoring was performed using monitors Oscar2 24-HR ABPM with Accu Win Pro v3 from Sun Tech Medical Inc-Morrisville (NC, USA), at the time of study screening and again during the last day. The monitors measured the BP every 15 min from 0800 to 2200 hours and every 30 min from 2200 to 0800 hours.

Weight
Body mass index (BMI) was calculated as weight (kilograms)/height (m^2). Weight was measured with a digital balance Model Seca from GmbH & Co. (Nuremberg, Germany) and height was measured by using a metal measuring tape to the nearest 0.5 cm.

Laboratory analyses
Serum lipids (low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, serum triglycerides), glucose, liver aminotransferases, gamma glutamyl transferase and serum uric acid were measured in the laboratory of Mateo Orfila Hospital using the Autoanalyzer Architect C-8000 from Abbott Diagnostics (Santa Clara, CA, USA). Fasting serum insulin was measured by immunochemiluminescence using the Immulite-2000 autoanalyzer (Siemens Medical Solutions Diagostics, NY, USA). The homeostatic model assessment (HOMA) index was calculated as fasting insulin (in IU ml^{-1}) $\times$ fasting glucose (in mg per 100 ml)/22.5.

Adverse events
At each visit the participant was screened for side effects, including headache, rash, itching, fever, abdominal pain or cramping, flatulence, hepatomegaly, jaundice, and diarrhea.

Statistical analysis
Paired *t*-tests were used to estimate the presence of changes in study parameters for each study arm individually (for those participants treated with allopurinol and for those not treated with allopurinol), assuming equal variances. In addition, the absolute changes (the difference between post-treatment values and pre-treatment values) were tested between groups using independent group *t*-tests. The distribution of changes was evaluated for normality assumptions using graphical assessment, and the qualitative result of the tests was examined with exclusion of potential outliers. In addition, in order to estimate the effects independent of any significant baseline levels, a linear regression model for the post-treatment level was generated adjusted for the baseline level of the parameter of interest.

Results

Patient characteristics
Seventy four participants completed the study (36 controls and 38 allopurinol-treated participants). Despite randomization, some differences were noted in baseline uric acid levels and blood pressure (Table 2).

Energy intake and macronutrient composition
At baseline, the total energy intake was in the range of 2400–2600 kcal per day, with a mean carbohydrate intake of 52%, protein intake of 17% and fat intake of 31% (Table 3). Dietary intake of fructose was approximately 55 g per day (of which 24 g was derived from sucrose). A dietary

Table 2 Baseline characteristics of subjects

	Control (n = 36)	*Allopurinol (n = 38)*	P-*value*
Age	51 ± 1.3	51 ± 1.3	NS
Weight (kg)	84.3 ± 2.3	83.6 ± 2.1	NS
BMI	29.0 ± 0.6	28.0 ± 0.6	NS
Waist circumference (cm)	99 ± 2	98 ± 1	NS
Waist hip ratio (cm/cm)	0.97 ± 0.01	0.95 ± 0.01	NS
Ambulatory BP			
SBP	126 ± 2	131 ± 2	<0.04
DBP	75 ± 2	80 ± 1	<0.04
Daytime BP			
SBP	128 ± 2	135 ± 2	<0.04
DBP	78 ± 2	83 ± 1	<0.03
Nocturnal BP			
SBP	117 ± 2	121 ± 3	NS
DBP	69 ± 2	71 ± 2	NS
Pulse rate	50 ± 1	52 ± 1	NS
Plasma triglycerides (mmol l^{-1})	1.54 ± 0.17	1.81 ± 0.21	NS
Plasma cholesterol (total) (mmol l^{-1})	5.49 ± 0.13	5.57 ± 0.13	NS
HDL (mmol l^{-1})	1.20 ± 0.04	1.25 ± 0.04	NS
LDL (mmol l^{-1})	3.37 ± 0.15	3.51 ± 0.13	NS
VLDL (mmol l^{-1})	0.70 ± 0.08	0.82 ± 0.1	NS
Glucose (mmol l^{-1})	5.59 ± 0.17	5.55 ± 1.13	NS
Insulin (pmol l^{-1})	48.8 ± 4.9	56.3 ± 6.3	NS
HOMA index	1.7 ± 0.2	2.1 ± 0.2	NS
Uric acid (μmol l^{-1})	309 ± 12	357 ± 12	0.01
Creatinine (μmol l^{-1})	88.4 ± 2.65	88.4 ± 1.77	NS
Liver tests			
GGT (U l^{-1})	36 ± 3	45 ± 7	NS
AST (U l^{-1})	20 ± 0.6	23 ± 1.4	0.06
ALT (U l^{-1})	23 ± 1.3	30 ± 3.4	0.06

Abbreviations: AST, aspartate aminotransferase; ALT, alanine transaminase; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; GGT, gamma glutamyl transferase; HDL, high-density lipoprotein; HOMA, homeostatic model assessment; LDL, low-density lipoprotein; NS, not significant; SBP, systolic blood pressure. Values shown are mean ± s.e.m.

Table 3 Energy intake during the study

	Control	*Allopurinol*	P-*value*
Baseline energy intake			
Total energy (kcal per day)	2414 ± 101	2529 ± 107	NS
Carbohydrate (g per day)	326 ± 13	338 ± 15	NS
Protein diet (g per day)	103 ± 3	108 ± 4	NS
Fat (g per day)	84 ± 5	89 ± 5	NS
Final energy intake (not including supplemental fructose)			
Total energy (kcal per day)	2242 ± 77	2361 ± 107	NS
Carbohydrate (g per day)	280 ± 12	289 ± 15	NS
Protein diet (g per day)	101 ± 3	105 ± 4	NS
Fat (g per day)	88 ± 3	94 ± 5	NS

Abbreviation: NS, not significant.

questionnaire administered at the end of the study documented a reduction in dietary calories of approximately 175 kcal (7%) in both groups, with a relatively greater reduction in carbohydrate intake (14%) than in protein (2–3%). In contrast, a slight increase in fat intake (5–6%) was observed in both groups. Fructose intake decreased by 8–10 g in both groups. As participants were ingesting 200 g per day of fructose in addition to their normal diet, the net energy intake at the end of the study was 2992 kcal in the control group and 3111 kcal in the allopurinol group, representing a 578 kcal per day net increase in the control group and 582 kcal in the allopurinol group, with a total fructose intake of approximately 245–250 g per day. As shown in Table 3, there were no differences in energy intake or macronutrient composition in the control and allopurinol groups at baseline or completion of the study.

Effects of fructose on the controls

Effect on body weight and BMI. At the end of 2 weeks, participants receiving fructose alone gained 0.6 ± 0.17 kg, with an increase of 0.2 U of BMI ($P = 0.003$).

Blood pressure. Fructose ingestion was associated with a significant increase in ambulatory BP compared with the baseline. 24-h Ambulatory systolic BP (SBP) increased by 7 ± 2 mm Hg and diastolic BP (DBP) by 5 ± 2 mm Hg ($P < 0.004$ and 0.007, respectively). BP increased by 5.5–7.1% with slightly greater increases in DBP during the day (Table 4). By applying the criteria for metabolic syndrome of casual BP $\geqslant$130/85 mm Hg, the number of participants who fit the criteria at baseline was 9 and that afterwards was 21 (International Diabetes Federation (IDF) criteria).

Triglycerides. Fructose ingestion resulted in a mean increase in fasting triglycerides of 0.62 ± 0.23 mmol l^{-1} (55 ± 20 mg per 100 ml) compared with the baseline ($P < 0.001$). The median increases in patients $\leq$48 years and in patients >48 years were 0.26 mmol l^{-1} (23 mg per 100 ml) and 0.95 mmol l^{-1} (84 mg per 100 ml), respectively. The differences in changes between age groups, however, did not reach significance ($P = 0.12$).

Table 4 Effect of fructose on metabolic parameters (% change)

	Control (n = *36*)	*Allopurinol* (n = *38*)	P-*value*
Weight change (kg)	0.6 ± 0.2 (0.7%)	0.7 ± 0.2 (0.8%)	NS
BMI change (kg m^{-2})	0.2 ± 0.1 (0.7%)	0.2 ± 0.1 (0.7%)	NS
Ambulatory BP (change mm Hg)			
24 h SBP	6.9 ± 2.3 (5.5%)	2.1 ± 1.2 (1.5%)	0.06
24 h DBP	4.7 ± 1.6 (6.3%)	1.0 ± 0.8 (1%)	<0.02
Daytime BP			
SBP	7.2 ± 2.4 (5.6%)	1.5 ± 1.2 (1.1%)	<0.04
DBP	5.5 ± 1.8 (7.1%)	0.5 ± 0.8 (0.7%)	<0.02
Nighttime BP			
SBP	6.5 ± 2.1 (5.6%)	2.6 ± 2.1 (2.2%)	NS
DBP	3.9 ± 1.8 (5.7%)	1.4 ± 1.1 (2.0%)	NS
Mean arterial pressure (mm Hg)	5 ± 2 (5.4%)	1 ± 1 (1%)	<0.03
Pulse rate	4 ± 1 (8%)	0 ± 1 (0%)	<0.01
Triglycerides (change) (mmol l^{-1})	0.62 ± 0.23 (40.4%)	0.82 ± 0.26 (45.6%)	NS
Cholesterol (change) (mmol l^{-1})	0.26 ± 0.1 (4.7%)	0.26 ± 0.08 (4.6%)	NS
HDL (mmol l^{-1})	−0.06 ± 0.02 (−5.4%)	−0.09 ± 0.03 (−7.5%)	NS
LDL (mmol l^{-1})	0.18 ± 0.08 (5.4%)	−0.08 ± 0.08 (−2.2%)	0.02
VLDL (mmol l^{-1})	0.31 ± 0.09 (44.3%)	0.39 ± 0.12 (47%)	NS
Glucose (mmol l^{-1})	0.05 ± 0.06 (1%)	0.15 ± 0.06 (2.7%)	NS
Insulin (pmol l^{-1})	14.6 ± 3.5 (32%)	10.4 ± 4.9 (18.5%)	NS
HOMA index (change)	0.57 ± 0.16 (33.5%)	0.50 ± 0.19 (23.8%)	NS
Uric acid (μmol l^{-1})	65 ± 6 (21.2%)	−113 ± 12 (−31.7%)	<0.001
Liver tests			
GGT (U l^{-1})	13 ± 4 (36.1%)	6 ± 5 (13.3%)	NS
AST (U l^{-1})	3 ± 1 (15%)	9 ± 3 (39.1%)	<0.07
ALT (U l^{-1})	9 ± 5 (39.1%)	3 ± 1 (10%)	NS

Abbreviations: AST, aspartate aminotransferase; ALT, alanine transaminase; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; GGT, gamma glutamyl transferase; HDL, high-density lipoprotein; HOMA, homeostatic model assessment; LDL, low-density lipoprotein; NS, not significant; SBP, systolic blood pressure. The *P*-value compares the change in the control group with the change in the allopurinol group. Values shown are mean ± s.e.m.

HDL cholesterol. Fructose administration resulted in a reduction in HDL cholesterol of 0.06 ± 0.02 mmol l^{-1} (2.5 ± 0.7 mg per 100 ml) compared with the baseline ($P < 0.001$). This decrease was not significantly different by BMI or age group. There was a doubling in the number of participants with HDL cholesterol meeting the criteria for metabolic syndrome as compared with the baseline (increase from 3 to 6 patients). LDL levels increased by 0.18 ± 0.08 mmol l^{-1} (7 ± 3 mg per 100 ml), but this was not significant ($P < 0.07$).

Glucose, insulin and HOMA index

There was no significant change in glucose (Table 4). However, there was an increase in the number of patients with fasting glucose levels meeting the criteria for metabolic syndrome when compared with the baseline (>5.5 mmol l^{-1}

(100 mg per 100 ml)) from 45 to 55%. There was also a significant increase in fasting plasma insulin 14.58 ± 3.5 pmol l^{-1} (2.1 ± 0.5 IU ml^{-1}, $P<0.001$) and an increase in the HOMA index (0.57 ± 0.16 U, $P<0.005$). There were three patients with HOMA levels ≥3.8 afterwards as compared with one patient at baseline.

Liver function tests. All liver function tests worsened with fructose ingestion. Gamma glutamyl transferase increased by 13 U l^{-1} ($P<0.001$), Aspartate aminotransferase (AST) increased by 9 U l^{-1} ($P<0.001$) and Alanine transaminase (AST) increased by 3 U l^{-1} ($P<0.01$) compared with the baseline.

Uric acid and serum creatinine
Fructose ingestion was associated with a 65 ± 6 μmol l^{-1} (1.1 mg per 100 ml) increase in fasting uric acid levels compared with the baseline (309 ± 12 μmol l^{-1}, $P<0.0001$). Serum creatinine did not change during the study (data not shown).

Effect of allopurinol on fructose-induced metabolic effects
Allopurinol treatment resulted in a significant decrease in serum uric acid (−113 μmol l^{-1} or −1.9 mg per 100 ml from the baseline, $P<0.001$). Allopurinol-treated participants did not show any significant increase in SBP or DBP compared with the baseline. Compared with the control group receiving fructose alone, allopurinol prevented the increase in both 24 h ambulatory DBP and daytime SBP and DBP induced by fructose (Figure 1 and Table 4). Allopurinol treatment also prevented the increase in mean arterial pressure ($P<0.03$) and in pulse rate ($P<0.01$) (Table 4).

Allopurinol did not prevent the fructose-induced increase in plasma triglycerides, lowering of HDL cholesterol or insulin resistance (Table 4). However, allopurinol was associated with a reduction in LDL cholesterol as opposed to the increase observed in controls ($P=0.02$).

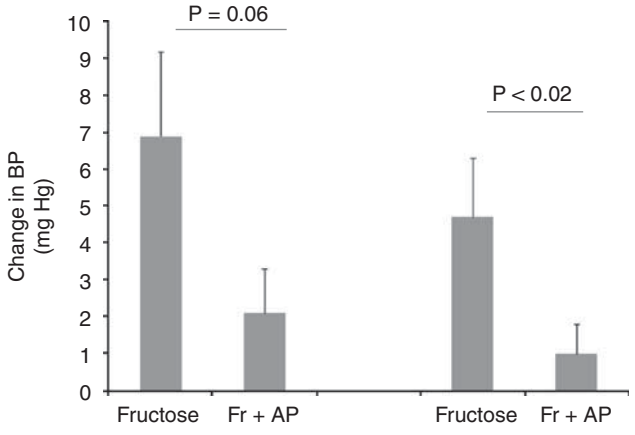

Figure 1 Changes in 24-h ambulatory SBP and DBP (mm Hg) in controls ingesting fructose and in participants ingesting fructose and allopurinol (Fr + AP). The difference in DBP was statistically significant ($P<0.02$). Values are mean ± s.e.m.

Metabolic syndrome
We determined the presence of metabolic syndrome using both the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATPIII) and IDF criteria (Table 1). Controls showed a significant increase in prevalence of metabolic syndrome following fructose ingestion, which increased from 19 to 44% by the NCEP-ATPIII criteria and from 25 to 58% by the IDF criteria (Figure 2). In participants receiving allopurinol and fructose, the increase in metabolic syndrome was not observed (from 32 to 34% by NCEP-ATPIII criteria and from 45 to 45% by IDF criteria) (Figure 2). If one compares the number of new cases of metabolic syndrome among participants who did not have metabolic syndrome at baseline, there was a significant difference when comparing the fructose alone group with the fructose plus allopurinol group ($P<0.009$).

Adverse effects
Nine participants developed diarrhea or abdominal cramps with the fructose and did not complete the study. Of the 74 participants who completed the study, limited episodes of diarrhea, abdominal cramps or flatulence occurred in 12 of the allopurinol-treated participants and 10 of the fructose-fed controls ($P=$NS). Three participant receiving allopurinol had pruritus, versus 0 in the fructose-alone treated group. No participant developed rash or jaundice.

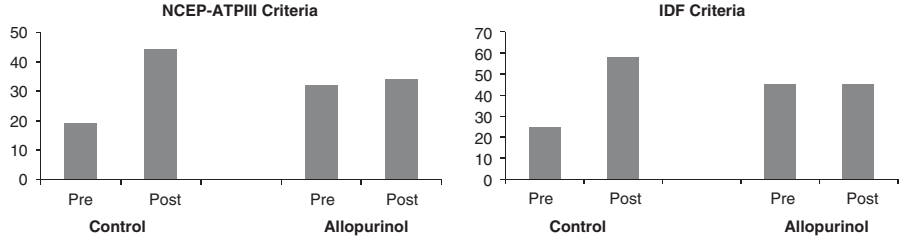

Figure 2 Percentage of participants with metabolic syndrome according to the NCEP-ATPIII and IDF criteria at baseline and at the end of the study in participants ingesting fructose alone, or fructose with allopurinol. The number of new cases of metabolic syndrome in participants without preexisting metabolic syndrome were significantly different between the control and allopurinol-treated groups ($P=0.009$ for each comparison).

Results from the model adjusted for baseline levels
The changes in the primary parameters of interest were additionally tested in a linear regression model adjusted for baseline levels. These models were generated to account for whether baseline levels influenced the results, as would be evident if the percentage change were important beyond the crude differences. For these models, the qualitative findings were consistent as those outlined above, with only marginal change in statistical significance.

Discussion

The administration of supplemental fructose (200 g per day = 750 kcal) for 2 weeks induced multiple features of the metabolic syndrome in healthy mostly overweight adult men. Fructose ingestion resulted in a significant increase in fasting serum triglycerides, a decrease in high-density lipoprotein cholesterol, an increase in serum insulin and HOMA index, an increase in ambulatory SBP and DBP, and an increase in BMI. Serum uric acid increased and liver function tests worsened. Although intake of fructose or sucrose (which contains 50% fructose) has been reported to cause features of the metabolic syndrome, including insulin resistance,[6] hypertriglyceridemia,[5,17] low high-density lipoprotein cholesterol,[18] and intra-abdominal fat accumulation,[6] this is the first study to show that excessive intake of fructose can cause almost all of the features of metabolic syndrome. Twenty-five to 33% of the participants developed new-onset metabolic syndrome according to standard criteria (Table 1).

Although the dose of fructose administered was higher than that currently ingested in the American diet, a recent study has suggested that the upper quintile of Americans consume more than 110 g fructose daily either as added sugar or as high-fructose corn syrup.[19] In another study of 1400 8th graders, more than 30% of all energy was found to be from added sugars, amounting to approximately 100 g fructose per day.[20] Another study found that 11–12% of preschoolers are ingesting more than 25% of their diet as added sugars.[21] Thus, although this study involved a higher dose, it is likely of clinical relevance, particularly because the changes could be induced in as short a time as 2 weeks.

A new finding in this study was the observation that fructose ingestion can raise the 24 h ambulatory BP in humans. Fructose is known to increase the BP in rodents, and the mechanism is thought to involve stimulation of the sympathetic nervous system, inhibition of endothelial nitric oxide production and activation of the renin–angiotensin system.[22] Fructose-induced hypertension appears to be greatest during the waking hours while animals are actively feeding.[23] The ability of fructose to increase BP in humans was also recently shown in a study in which the acute ingestion of fructose raised the BP for an hour immediately after perfusion.[24] Furthermore, soft drinks (a major source of fructose) have been linked with hypertension in adolescents.[25] Consistent with these findings, our study found a significant increase in BP that tended to be greatest during the day when the participants were actively ingesting their fructose. In a recent study by Stanhope *et al.*, an increase in clinic BP was not observed following the administration of fructose as 25% of the diet for 10 weeks. However, this study provided fructose only at meal times and did not measure 24-h ambulatory BP, and thus may have missed a postprandial BP increase.

Fructose-induced metabolic syndrome in laboratory animals is mediated in part by fructose-induced elevations in serum and intracellular uric acid.[4] It has been hypothesized that one of the reasons why laboratory rats require large doses of fructose (60% of the diet) to induce the metabolic syndrome is because rats express an enzyme (uricase) that blunts fructose-induced hyperuricemia.[3] In contrast, humans lack uricase and hence may be more sensitive to the effects of fructose.

We therefore investigated the effect of lowering the uric acid level in these participants. Fructose ingestion was associated with an increase in fasting serum uric acid ($65.4 \pm 6.0\,\mu mol\,l^{-1}$, $P<0.001$), and allopurinol not only prevented the increase but also lowered the levels below baseline ($-113.0 \pm 11.9\,\mu mol\,l^{-1}$). Allopurinol blocked the increase in both 24-h ambulatory DBP and daytime SBP and DBP. The observation that lowering the uric acid level can reduce BP has previously been reported in hypertensive obese adolescents.[15] In contrast, allopurinol did not improve other features of the metabolic syndrome, including triglycerides, high-density lipoprotein cholesterol or fasting glucose. LDL cholesterol, however, decreased in allopurinol-treated participants but increased in controls ($P=0.02$). Finally, the number of new cases of metabolic syndrome was dramatically reduced by allopurinol treatment ($P<0.003$), which was primarily because of the effect of allopurinol in preventing the increase in BP.

These studies suggest that the primary effect of lowering the uric acid level on the metabolic syndrome induced by fructose is to reduce the BP elevation. It remains possible that the lowering of uric acid level might be beneficial on lipids and insulin resistance if postprandial levels were targeted as opposed to fasting levels, as fructose is known to have its greatest effects at this time point[6] and most of the studies in rats using allopurinol were performed after only 4 h of fasting.[4,14] It is also possible that the effects of allopurinol may require a longer course of therapy, as the studies in rats typically were greater than 1 month in duration.

A limitation to this study is that we did not have a control group ingesting equivalent amounts of dextrose, and as such we cannot rule out the possibility that the changes in metabolic parameters simply relate to increased energy intake. However, the average weight gain was less than 1 kg, and therefore it seems unlikely to be responsible for the changes in HOMA, triglycerides or liver function tests. A change in weight of 1 kg results in only about 1 mm Hg change in SBP and DBP.[26] Other studies have reported that

hypertriglyceridemia, insulin resistance and intra-abdominal fat accumulation occur following ingestion of fructose diets as opposed to equivalent dextrose-based diets.[6,27] We have also shown in animals that fructose induces the features of metabolic syndrome independent of caloric intake when compared with starch-based diets,[4,14] and that it is possible to induce the features of metabolic syndrome with fructose when total energy intake is restricted.[28] Hence, although the effect of total energy intake cannot be completely ruled out, it is likely that fructose may have a unique ability to induce metabolic syndrome.

A second limitation is that the participants randomized to allopurinol had higher baseline uric acid values and BP and tended to have worse baseline features of metabolic syndrome. It is known that the effect of fructose in inducing the features of metabolic syndrome is greater in individuals who are overweight or hyperinsulinemic.[2,29] It is therefore possible that this blunted any effect of allopurinol on plasma lipids and insulin resistance. In addition, owing to uncertainty regarding the study effects and the variability of the relative impact of the treatment arms, this study was not explicitly powered for each defined end point. Although this clearly does not invalidate the primary results, which were statistically significant, we must caution against the inference of effects that did not reach statistical significance as they may not have been adequately powered in this pilot study.

A final limitation of this study is that it was performed only in adult men. Experimentally male animals are more prone to the effects of fructose, possibly because of the differential effects of sex hormones.[30,31] Given the fact that gender can affect fructose-related responses, we performed this initial study only in men. However, this does limit the generalizability of the findings.

The syndrome of impaired glucose tolerance, central obesity, elevated BP, dyslipidemia and hyperuricemia has been noted for almost 100 years.[32] Debate exists over whether this should be considered a disease entity, as some studies suggest that it represents multiple clusters of signs whereas others suggest that there may be one underlying pathway.[33–35] Our studies suggest that the syndrome may be a specific entity and that excessive intake of fructose may be one of its causes. We further show that lowering the uric acid level can prevent the increase in BP induced by fructose. These studies support the hypothesis that excessive fructose intake could have a causal role in the current epidemics of hypertension, obesity and diabetes.

Conflict of interest

Dr Richard Johnson and Dr Takahiko Nakagawa are listed as inventors on several patent applications on lowering uric acid as it relates to BP and metabolic syndrome. Dr Johnson is also author of the Sugar Fix (2008, Rodale, and 2009, Simon and Schuster). The remaining authors declare no conflict of interest.

Acknowledgements

We thank the volunteers and staff who participated in the study. Dr Enrique Perez-Pozo had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Trial registration: clinicaltrials.gov identifier number: NCT00639756. Support for this publication was provided by generous funds from the Mateo Orfila Foundation.

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