Clinical Nutrition xxx (xxxx) xxx

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Effect of a high fructose diet on metabolic parameters in carriers for hereditary fructose intolerance

François-Guillaume Debray [a], Kevin Seyssel [b], Marjorie Fadeur [c], Luc Tappy [b], Nicolas Paquot [c], Christel Tran [d, *]

[a] Department of Medical Genetics, Metabolic Unit, University Hospital Liège, Liège, Belgium
[b] Department of Biomedical Sciences, University of Lausanne, 1005 Lausanne, Switzerland
[c] Division of Diabetes, Nutrition and Metabolic Diseases, Department of Medicine CHU Sart-Tilman and GIGA I3, Immunometabolism and Nutrition Unit, University of Liège, Liège, Belgium
[d] Center for Molecular Diseases, Division of Genetic Medicine, University of Lausanne, Lausanne, Switzerland

ARTICLE INFO

Article history:
Received 16 October 2020
Accepted 17 January 2021

Keywords:
Hereditary fructose intolerance
Healthy carriers
Fructose
Insulin
Uric acid

SUMMARY

Background & aims: Hyperuricemia is an independent risk factor for the metabolic syndrome and cardiovascular disease. We hypothesized that asymptomatic carriers for hereditary fructose intolerance (OMIM 22960) would have increased uric acid and altered component of the metabolic syndrome when exposed to fructose overfeeding.

Methods: Six heterozygotes for HFI (hHFI) and 6 controls (Ctrl) were studied in a randomized, controlled, crossover trial. Participants ingested two identical test meals containing 0.7 g kg^{-1} glucose and 0.7 g kg^{-1} fructose according to a cross-over design, once after a 7-day on a low fructose diet (LoFruD, <10 g/d) and on another occasion after 7 days on a high fructose diet (HiFruD, 1.4 g kg^{-1} day^{-1} fructose + 0.1 g kg^{-1} day^{-1} glucose). Uric acid, glucose, and insulin concentrations were monitored in fasting conditions and over 2 h postprandial, and insulin resistance indexes were calculated.

Results: HiFruD increased fasting uric acid ($p < 0.05$) and reduced fasting insulin sensitivity estimated by the homeostasis model assessment (HOMA) for insulin resistance ($p < 0.05$), in both groups. Postprandial glucose concentrations were not different between hHFI and Ctrl. However HiFruD increased postprandial plasma uric acid, insulin and hepatic insulin resistance index (HIRI) in hHFI only (all $p < 0.05$).

Conclusions: Seven days of HiFruD increased fasting uric acid and slightly reduced fasting HOMA index in both groups. In contrast, HiFruD increased postprandial uric acid, insulin concentration and HIRI in hHFI only, suggesting that heterozygosity for pathogenic Aldolase B variants may confer an increased susceptibility to the effects of dietary fructose on uric acid and hepatic insulin sensitivity.

This trial was registered at the U.S. Clinical Trials Registry as NCT03545581.

1. Introduction

Overweight and obesity have been estimated to affect close to 40% individuals worldwide, with parallel rises in the prevalence of non-communicable diseases [1]. Among other factors, there is much concern that fructose consumed as added sugars (mainly sucrose and high fructose corn syrup) may be involved in the pathogenesis of cardiometabolic diseases [2]. This is mainly supported by short-term intervention studies, which showed that consumption of a high fructose diet caused hepatic insulin resistance and increased intrahepatic triglyceride (IHTG) in healthy human subjects [3–5]. Some studies have also reported that fructose increased blood uric acid concentration, and that this

Abbreviations: AMP, Adenosine monophosphate; ATP, Adenosine triphosphate; AUC, Area under the curve; DNL, De novo lipogenesis; F-1-P, Fructose-1-phosphate; G-6-P, Glucose-6-phosphate; GKRP, Glucokinase regulatory protein; GSD, Glycogen storage disease; HFI, Hereditary fructose intolerance; HOMA, Homeostatic model assessment; HIRI, Hepatic insulin resistance index; IHTG, Intrahepatic triglyceride; IMP, Inosine monophosphate; IR, Insulin resistance; Pi, Inorganic phosphate.

* Corresponding author. Center for Molecular Diseases, Lausanne University Hospital, Division of Genetic Medicine, Beaumont-02/248, Lausanne CH-1011, 1011 Lausanne, Switzerland.
E-mail address: christel.tran@chuv.ch (C. Tran).

https://doi.org/10.1016/j.clnu.2021.01.026

Please cite this article as: F.-G. Debray, K. Seyssel, M. Fadeur *et al.*, Effect of a high fructose diet on metabolic parameters in carriers for hereditary fructose intolerance, Clinical Nutrition, https://doi.org/10.1016/j.clnu.2021.01.026

metabolite may play a role of secondary messenger to cause dyslipidemia and insulin resistance [6–8].

Hereditary fructose intolerance (HFI; OMIM #229600), is an inborn error of fructose metabolism caused by biallelic variants in the gene coding for aldolase B *(ALDOB)* [9–12]. Ingestion of fructose in HFI immediately triggers symptoms as nausea and vomiting accompanied by hypoglycemia, acute hepatic and tubular renal dysfunction. This is due to the rapid accumulation of fructose-1-P in hepatocytes and proximal tubular renal cells expressing aldolase B, associated with ATP and inorganic phosphate consumption and cellular energy depletion. ATP depletion is also associated with purine catabolism and increased production of uric acid. HFI subjects remain symptom-free when consuming a fructose-free diet, but recent evidence indicates that they nonetheless may present some alterations of hepatic lipid metabolism [13–16].

Extrapolated HFI prevalence is reported to be between 1:18,000 and 1:31,000in European countries [17–19] and at 1:60,000 in the United States [20]. Based on this, a carrier frequency is predicted between 1:55 and 1:122 worldwide making it relatively common [20,21]. A more accurate carrier frequency is difficult to estimate given that a large number of children with HFI are undiagnosed in the general population [22]. HFI carriers are generally considered to have normal fructose metabolism since ~50% level of ALDOB activity is presumed to be sufficient for adequate function, however they were reported to have enhanced uric acid responses to large intravenous and/or oral fructose loads [10,23] and in some cases, even clinical manifestations of gout [24]. Since uric acid is generally associated with the majority of the components of metabolic syndrome, we wondered whether HFI carriers would also be at risk of developing this syndrome [25]. Previously, we observed that heterozygous carriers for HFI had no major alteration of postprandial glucose homeostasis or fructose metabolism after ingestion of a fructose containing meal. They did, however, had a slight but significant increase in postprandial uric acid concentrations [26]. Since the dose of fructose was relatively small (~25 g) and the exposure limited to one single test meal challenge, we cannot exclude that this was insufficient to elicit all metabolic effects of fructose in HFI carriers. In the current study, we increased the dose of fructose in the test meal (~35–60 g), and evaluated the effect of a chronic high fructose vs low fructose diets on uric acid, glucose and lipid metabolism in HFI carriers.

2. Materials and methods

2.1. Participants

Six participants heterozygous for HFI (4 women, 2 men; hHFI) and 6 age-, sex- and weight-matched control participants (4 women, 2 men; Ctrl) were included in the study. The hHFI participants were parents of children with HFI followed in the Department of Medical Genetics at the University Hospital of Liège/CHU Sart Tilman, Liège. The *ALDOB* genotype was established in heterozygous participants as part of the routine assessment and follow-up and for genetic counseling purposes. Control participants were recruited from the general healthy population aged 18–65 y and were matched for gender, age and weight to heterozygous participants for HFI. Control participants were genotyped in the same department to confirm the absence of variants in the gene *ALDOB*. The participants were currently not taking any medication, and had no history of diabetes, dyslipidemia or renal insufficiency. For women, they used effective methods of birth controls. Before inclusion, they underwent a physical examination to ensure that they were in good physical health and a blood test to confirm that they had a fasting plasma glucose <7.0 mmol/l and fasting plasma triglycerides <4.0 mmol/l. Initially the main investigators planned to recruit patients on both sites (Switzerland and Belgium) to ensure that a sufficient number of participants would be included in the study considering that HFI is a rare disease and finding HFI carriers might be difficult. Indeed the experimental protocol was then submitted and approved by the Ethics Committee of the University Hospitals of Liège (Belgium) and Lausanne (Switzerland). The trial was registered at the US Clinical Trials Registry as NCT03545581. Appropriate informed consent for study participation and genetic testing was obtained from all individuals.

2.2. Study design

All participants' diet and anthropometric characteristics were assessed prior to the experiments. Each hHFI and Ctrl participants were then instructed to follow two 7-day dietary conditions in a randomized, crossover-controlled order, once on a low fructose diet (LoFruD, <10 g day^{-1} fructose) and once on a high fructose diet (HiFruD, 1.4 g kg^{-1} day^{-1} fructose + 0.1 g kg^{-1} day^{-1} glucose). For the low fructose diet, participants received a list of foods and their fructose content and were instructed on which foods were allowed during the study and which ones were prohibited. For the high fructose diet, participants continued to follow the instructions of the low-fructose diet and, at the same time, received fructose supplementation in the form of ready-to-drink prepared beverages. The day after each dietary conditions, hHFI and Ctrl reported to the Clinical Research Center to measure their postprandial response to a test meal containing 0.7 g kg^{-1} of glucose and 0.7 g kg^{-1} fructose (Fig. 1). The co-ingestion of glucose and fructose was chosen as dietary fructose is mainly present in fructose-containing caloric sweeteners, fruits and honey, which all contain roughly equimolar amounts of fructose and glucose. The dose of fructose in the test meal and the HiFruD were chosen to have a known sufficient amount to generate metabolic disturbances across different metabolic phenotypes (~50–100 g/d) and also on liver insulin sensitivity based on literature in human (200–300 g/d) [27,28].

2.3. Metabolic test

Each of the 12 participants was studied at the Clinical Research Center of CHU Sart Tilman, Liège. Overnight-fasted participants were first weighed. Their blood pressure and heart rate were then measured using an automated device (Omron 907). Body composition was measured using bioelectrical impedance analysis

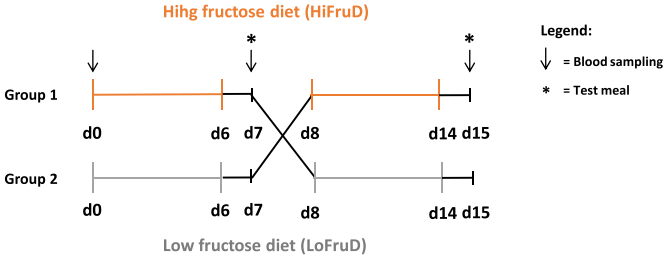

Fig. 1. Experimental setting of the metabolic test. Each subject received on two occasions 2 different diets during a 7-d period (from day 0 to day 6 and from day 8 to day 14) and was asked not to consume alcohol or caffeine-containing beverages. The diets were administered in a randomized order and consisted of 2 diets: low fructose diet (fructose < 10 g/d) or high fructose diet enriched with three drinks containing 0.1 g glucose/kg/d and 1.4 g fructose/kg/d for 7 days. On day 7 and 15, overnight fasted subjects remained on bed to assess their postprandial response to a test meal containing 0.7 g kg^{-1} glucose and 0.7 g kg^{-1} fructose. Baseline samples were obtained prior to meal ingestion and repeated sequentially thereafter (for details, see Methods). Abbreviation: d, day.

(Biacorpus, MediCAL RX 4000). The participants were asked to come with a bottle containing their urine for the last 24 h. A catheter was inserted into a vein of the right forearm for blood sampling. Blood samples were collected at day 0, day 7 and day 15 after a 12-h fast. Participants were randomized to follow either a low fructose diet (<10 g day^{-1}) or a low fructose diet (<10 g day^{-1}) enriched with three drinks containing 0.1 g kg^{-1} day^{-1} of glucose and 1.4 g kg^{-1} day^{-1} fructose for 7 days to which 0.1 g kg^{-1} day^{-1} of glucose was added to improve gut fructose absorption [29]. Participants consumed these two diets «ad libitum». At the end of this period (day 0 to day 6), participants were crossed over to the other intervention for 7 days (D-8 to D-14). A washout period between the two diets was not deemed necessary since metabolic adaptations to changes in dietary fructose content were shown to occur after 4 days already [30]. At the end of each dietary condition (day 7 and day 15), the participants were asked to come to the Clinical Research Center after an overnight fast and ingested a test meal containing 0.7 g kg^{-1} of glucose and 0.7 g kg^{-1} fructose. Blood samples were collected at baseline and after 30, 60, 90 and 120 min after the test meal to measure concentrations of glucose, insulin, non-esterified fatty acid, total triglycerides, lactate, fructose and uric acid. Plasma concentrations of creatinine, urea, cystatin, liver function tests, glucagon, phosphate sodium and potassium were measured at baseline only of day D-0, D-7 and D-15. The experimental protocol for the oral fructose loading experiment is shown in Fig. 1.

2.4. Dietary assessment

In a 3-day dietary diary, individuals recorded each food and beverages consumed from day D-3 to D-1 (before the experiment), from day D-4 to D-6 and from day D-12 to D-14 (during the LoFruD and the HiFruD). A registered dietitian estimated from the records of each diary fructose and energy intake before and during the experiment.

2.5. Analytic procedures

For plasma metabolites, plasma was immediately separated from blood by centrifugation at 1230 relative centrifugal force for 10 min at 4 °C and stored at −20 °C. Plasma metabolites glucose, lactate, triglycerides, uric acid, urea, creatinine, urea were measured using enzymatic methods (COBAS®8000, Roche). Commercial radioimmunoassay kits were used for determination of plasma insulin and glucagon. Cystatin C was measured by immunoassay. Plasma fructose was measured by gas chromatography−mass spectrometry (GC−MS). Two-point-three micromole 1,2,3 $^{13}C_3$d-fructose was added to 250 mL plasma as an internal standard. Plasma was thereafter deproteinized using the ZnSO4−$Ba(OH)_2$ method [31], partially purified over anion- and cation-exchange resins and derivatized with acetic anhydride and pyridine. Samples were then dried under a stream of nitrogen and resuspended in 60 μL ethyl acetate, and 1 μL was analyzed by GC−MS (Agilent Technologies, Santa Clara, CA, USA) in electron impact mode, with selected monitoring of *m/z* 275 and 277. The fructose concentration in samples was determined from the ratio of *m/z* 277 to *m/z* 275 by means of an unlabeled pure fructose standard curve.

Urine samples after 7-days of HiFruD were assayed for the level of specific amino acids-cystine, lysine, threonine, serine, glycine, alanine, valine, tyrosine, phenylalanine and histidine-with a Beckman autoanalyzer using liquid chromatography. These amino acids were selected due to stability in urine when kept at −20° [32].

2.6. Calculations

The degree of insulin resistance (IR) was estimated with the HOMA-IR and HOMA2-IR calculator [33]. The HOMA2-β calculator was used to assess β-cell function. The hepatic insulin resistance index (HIRI) was calculated as the square root of the product of the glucose area under the curve (AUC; mg/min^{-1}/dL) and insulin (pmol/min^{-1}/mL) during the first 30 min after the test meal, and expressed as arbitrary units [34].

2.7. Statistical analysis

Based on previous work [26,35] a sample size of 12 participants was estimated (1-b: 90%; a = 0.05) to detect a 10% difference in uric acid concentrations between Ctrl group (n = 6) and hHFI group (n = 6). Distributions were first inspected, then distribution normality and homoscedasticity were assessed with the use of Shapiro−Wilk and Bartlett's tests, and data were log-transformed when appropriate (HOMA-IR, HOMA-β). Baseline participants' groups' characteristics were compared using an unpaired Student's *t* test. Significance of changes was determined with the use of mixed-models analysis, with fixed effects of participant's group (Group effect: hHFI vs. Ctrl) and diet (Diet effect: LoFruD vs. HiFruD), and random effects for participant-specific intercepts and slopes. The Group × Diet (G × D) interaction and dietary allocation order were included in the models whenever goodness of fit was improved. Post-hoc Tukey comparisons were finally performed on paired time points for data presented in figures. Analyzes were performed with R, version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria) and the Jamovi module. Data are presented as mean ± SEM with a level of significance set as 2-tailed p = 0.05.

3. Results

3.1. Baseline participant's characteristics and variant analysis

At inclusion, Ctrl and hHFI participants did not differ in anthropometric, plasma substrates and hormones variables (Table 1). Absence of mutation in the *ALDOB* (OMIM #229600) coding sequence was confirmed in Ctrl (*n* = 6). Heterozygosity for the most common pathogenic variants in the *ALDOB* gene was identified in the 6 hHFI participants (c.448G>C, p.Ala150Pro; ExAC frequency 0.2% in 5 participants and the c.548T>C, p.Leu183Pro pathogenic variant in 1 participant).

3.2. Dietary records at baseline and during HiFruD and LoFruD

A 3-day dietary record in free-living conditions (pre-experimental period) indicated that Ctrl and hHFI participants had similar daily energy intake, and that carbohydrate (and specifically fructose), lipids and protein contents did not differ between groups prior to dietary conditions (Table 2; all p > 0.05). Participants then followed the experimental diets, and their records of the last 3-days indicated that lipids and protein intake did not differ between conditions, in both groups (all p > 0.05). Energy intake however was higher in hHFI during the HiFruD in comparison to Ctrl with a significant increase of carbohydrate and fructose intake (Diet effect: all p < 0.001).

3.3. Blood metabolites in the fasting state

After 7 days of HiFruD vs LoFruD, no difference in blood metabolites variables was observed between hHFI and Ctrl fasting participants (Table 3; Group effect: all p > 0.05). Compared to LoFruD, HiFruD tended however to increase fasting plasma glucose

Table 1
Anthropometric variables, plasma substrates and hormones at baseline.

	Ctrl	hHFI
Age [y]	40.93 ± 2.21	40.68 ± 2.5
Weight [kg]	72.78 ± 8.75	71.52 ± 7.22
Body mass index [kg·m^{-2}]	24.93 ± 2.45	25.02 ± 2.18
Body fat [%]	30.15 ± 3.37	30.75 ± 2.98
Lean body mass [%]	69.85 ± 3.37	69.25 ± 2.98
Systolic blood pressure [mmHg]	120 ± 6.9	121.33 ± 8.64
Diastolic blood pressure [mmHg]	84.67 ± 4.93	78.33 ± 4.45
Heart rate [beats·min^{-1}]	69.17 ± 3.2	65.5 ± 4.57
Glucose [mmol·l^{-1}]	5.15 ± 0.07	5.29 ± 2.16
Insulin [pmol·l^{-1}]	59.45 ± 8.83	36.66 ± 1.04
Glucagon [pg·ml^{-1}]	158.69 ± 20.98	152.97 ± 19.87
NEFAs [mmol·bsp;l^{-1}]	0.61 ± 0.1	0.56 ± 0.09
Total TG [mmol·l^{-1}]	1.36 ± 0.34	1.03 ± 0.35
Lactate [mmol·l^{-1}]	1.07 ± 0.22	0.79 ± 0.07
Fructose [μmol·l^{-1}]	20.74 ± 0.86	18.34 ± 0.46
Uric acid [μmol·l^{-1}]	264.97 ± 23.52	277.07 ± 37.42
Creatinine [μmol·l^{-1}]	77.66 ± 4.96	70.44 ± 5.17
Urea [mmol·l^{-1}]	9.34 ± 0.94	9.7 ± 1.02
Cystatin [mg·dl^{-1}]	0.98 ± 0.04	0.82 ± 0.04
Phosphate [mmol·l^{-1}]	0.86 ± 0.03	18.73 ± 1.38
AST [U·l^{-1}]	21.43 ± 4.04	19.53 ± 1.38
ALT [U·l^{-1}]	23.42 ± 6.01	16.95 ± 2.38

Data presented as mean ± SEM (n = 6 per condition). Statistics: p = N.S. for all variables (unpaired Student's T-test). Abbreviation: AST, aspartate aminotransferase; ALT, alanine aminotransferase; Ctrl, control participants; hHFI, heterozygotous for hereditary fructose intolerance participants, SEM, standard error of measurement.

(Diet effect: p = 0.0528), increased uric acid (Diet effect: p = 0.0106), and lowered urea concentrations (Diet effect: p = 0.0318), yet similarly between both groups (both G × D effect: p > 0.1). HiFruD also decreased circulating AST (Diet effect: p = 0.0175) and tended to decrease ALT concentrations (Diet effect: p = 0.0623) compared to LoFruD (both G × D effect: p > 0.1). Fasting plasma sodium, potassium, calcium and chlorine concentrations were similar in hHFI and Ctrl participants (data not shown, all p > 0.05).

3.4. Post-prandial blood concentrations and insulin sensitivity indexes

Systemic fructose concentrations rapidly increased after ingestion of the test meal, but no difference was observed between hHFI and Ctrl or dietary conditions (Fig. 2A–B, p > 0.05). Interestingly, there was however a significant group effect for plasma uric acid, that increased only in hHFI during the 2 h postprandial period (Fig. 2C–D + Group effect: p = 0.014). Further analysis in hHFI participants showed that HiFruD produced a greater increase than LoFruD (Tukey post-hoc: p = 0.042). No significant effect (all p > 0.05) was found for blood triglycerides (Fig. 2E–F).

Plasma glucose, insulin and lactate concentrations peaked between times 30–60 min postprandial and then decreased in both conditions (Fig. 3). No difference was observed between hHFI and Ctrl participants (Group effect: all p > 0.05). However, hHFI and Ctrl presented different insulin response across dietary conditions (Diet × Group interaction: p = 0.001). Post-hoc analysis indicated that times 30 and 60 min postprandial insulin responses were increased by HiFruD only in hHFI (both p < 0.01). Blood creatinine, phosphate and urea were not statistically different in hHFI and Ctrl, and not affected by dietary conditions (data not shown; all p > 0.05).

Calculation of insulin sensitivity indexes after 7-days on LoFruD or HiFruD (Table 4) indicated that HOMA-IR was increased in HiFruD compared to LoFruD (Diet effect: p = 0.0210), and that HOMA-β was not statistically different between group or diet (all p > 0.05). Calculation of HIRI during the first 30 min during the test meal was increased in hHFI only. HIRI increased from 24.38 ± 3.58 on LoFruD to 33.91 ± 3.56 on HiFruD in hHFI vs 31.44 ± 5.51 on LoFruD to 28.45 ± 3.06 on HiFruD in Ctrl (Group × Diet interaction: p = 0.005).

3.5. Electrolytes and urinary metabolites after a-7 day of a low fructose diet or high fructose diet

Urinary concentrations of creatinine and urea over 24 h did not differ between conditions (Table 5). In contrast urinary uric acid tended to be higher in hHFI than in Ctrl (Group effect: p = 0.064), while phosphate in urine were lowered in HiFruD compared to LoFruD in both groups (Diet effect: p = 0.017). Tests of proximal tubular function included the measurement of urinary aminoaciduria and glycosuria after the 7-days of HiFruD. Urine amino acids and glucose were similar in hHFI and Ctrl participants except for three amino acids (cystine, valine and phenylalanine) which were higher in hHFI (data not shown).

4. Discussion

The data confirm that blood uric acid concentration increased after the acute ingestion of a fructose-containing meal (~35–60 g) in hHFI, but not in Ctrls. Conversely, a 7-days consumption of a HiFruD increase fasting uric acid concentration in both groups [23,36]. Since all hHFI subjects displayed loss of function ALDOB alleles, it is tempting to attribute this acute effect to a deficiency of

Table 2
Dietary characteristics at baseline and during the experimental low-fructose (LoFruD) and high-fructose (HiFruD) diets.

	Ctrl		hHFI	
	LoFruD	HiFruD	LoFruD	HiFruD
Pre-experimental 3-day record				
Energy intake [kcal·day^{-1}]	1743.36 ± 134.69		1682.44 ± 104.8	
Carbohydrates [g·day^{-1}]	189.36 ± 18.99		176.99 ± 11.81	
Fructose [g·day^{-1}]	23.17 ± 4.61		12.16 ± 1.97	
Lipids [g·day^{-1}]	69.91 ± 6.76		69.66 ± 6.39	
Protein [g·day^{-1}]	71.99 ± 5.84		77.51 ± 5.5	
Experimental period				
Energy intake [kcal·day^{-1}]	1331.66 ± 114.82	1761.19 ± 118.45*	1670.17 ± 107.12	2013.18 ± 109.95*
Carbohydrates [g·day^{-1}]	110.52 ± 9.99	221.48 ± 13.80*	149.44 ± 10.47	251.87 ± 13.99*
Fructose [g·day^{-1}]	3.84 ± 0.63	103.80 ± 6.42*	3.43 ± 0.44	101.58 ± 5.25*
Lipids [g·day^{-1}]	66.08 ± 6.98	60.84 ± 5.71	78.90 ± 6.67	78.95 ± 6.36
Protein [g·day^{-1}]	73.64 ± 7.69	79.76 ± 8.94	90.56 ± 7.0	75.07 ± 6.50

Data presented as mean ± SEM (n = 6 per condition). Statistics: p = N.S. for all variables (Group × Diet mixed-model analysis and unpaired Student's T-test); *p < 0.001 for Diet effect. Abbreviation: Ctrl, control participants; hHFI, heterozygotous for hereditary fructose intolerance participants; SEM, standard error of measurement, SEM, standard error of deviation.

Table 3
Fasting plasma concentrations of substrates and hormones after 7-days on a low fructose diet (LoFruD) or a high fructose diet (HiFruD).

	Ctrl		hHFI	
	LoFruD	HiFruD	LoFruD	HiFruD
Glucose [mmol·l^{-1}]	5.08 ± 0.63	5.22 ± 0.43	4.94 ± 0.71	5.24 ± 0.84
Insulin [pmol·l^{-1}]	50.93 ± 79.8	52.84 ± 58.43	36.46 ± 47.86	42.77 ± 91.03
Glucagon [pg·ml^{-1}]	173.87 ± 24.11	173.93 ± 13.45	150.76 ± 21.62	140.97 ± 16.47
NEFAs [mmol·l^{-1}]	0.82 ± 0.11	0.62 ± 0.15	0.56 ± 0.1	0.56 ± 0.12
Total TG [mmol·l^{-1}]	1.02 ± 0.08	1.31 ± 0.24	0.75 ± 0.1	0.93 ± 0.19
Lactate [mmol·l^{-1}]	0.89 ± 0.13	0.99 ± 0.11	0.83 ± 0.1	0.92 ± 0.14
Fructose [μmol·l^{-1}]	19.28 ± 0.05	20.17 ± 0.06	17.11 ± 0.06	17.59 ± 0.07
Uric acid [μmol·l^{-1}]	271.02 ± 30.02	280.74 ± 28.6*	240 ± 21.67	273.7 ± 27.68*
Creatinine [μmol·l^{-1}]	80.17 ± 7.48	81.79 ± 5.93	66.9 ± 4.5	67.49 ± 4.27
Urea [mmol·l^{-1}]	11.96 ± 1.31	10.06 ± 1.1*	11.48 ± 1.27	10.53 ± 1.51*
Cystatin [mg·dl^{-1}]	0.86 ± 0.03	0.87 ± 0.03	0.82 ± 0.03	0.81 ± 0.03
Phosphate [mmol·l^{-1}]	1.01 ± 0.05	1.09 ± 0.04	1.04 ± 0.06	1.03 ± 0.04
AST [U·l^{-1}]	18.73 ± 2.41	16.6 ± 2.12*	19.42 ± 1.69	17.15 ± 1.45*
ALT [U·l^{-1}]	21.98 ± 4.78	17.02 ± 2.83	18.05 ± 2.76	15.27 ± 2.34

Data presented as mean ± SEM (n = 6 per condition). Statistics: *p < 0.05 for Diet effect (Subject × Diet mixed-model analysis). Abbreviations: Ctrl, control subjects; hHFI, heterozygotous for hereditary fructose intolerance subjects; NEFA, non-esterified fatty acids; AST, aspartate aminotransferase; ALT, alanine aminotransferase; SEM, standard error of measurement.

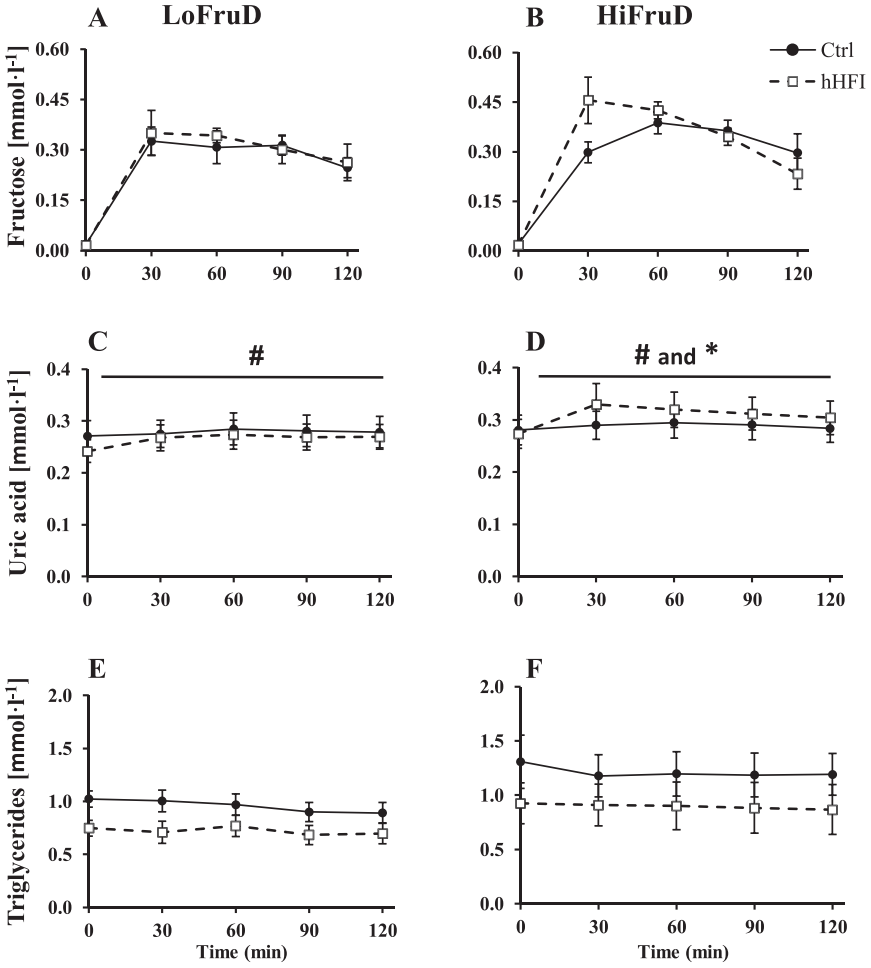

Fig. 2. Fructose, uric acid and triglycerides kinetics during 120 min after the test meal. Data presented as mean ± SEM (n = 6 per condition). Symbols: Ctrl, control participants; hHFI, heterozygotous for hereditary fructose intolerance participants; LoFruD, low-fructose diet; HiFruD, high-fructose diet. A–B: no difference was observed for plasma fructose concentrations (Group effect: p = 0.242; Diet effect: p = 0.100; Group × Diet interaction: p = 0.632). C–D: a significant Group effect was observed for plasma uric acid concentrations (Group effect: p = 0.014; Diet effect: p = 0.161; Group × Diet interaction: p = 0.208). E–F: no difference was observed for plasma triglycerides concentrations (Group effect: p = 0.359; Diet effect: p = 0.774; Group × Diet interaction: p = 0.585). #p < 0.05 for Group effect (Group × Diet mixed-model analysis); *p < 0.05 for Diet effect (Tukey post-hoc comparisons). Abbreviations: SEM, standard error of measurement.

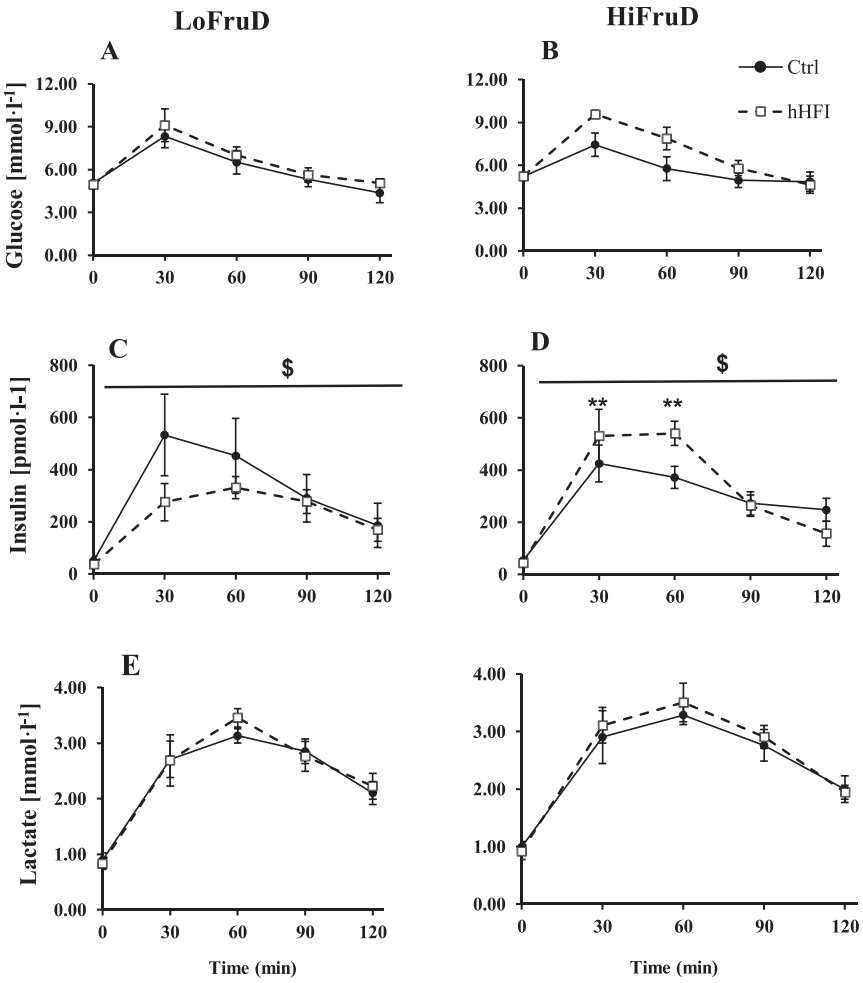

Fig. 3. Glucose, insulin and lactate kinetics during 120 min after the test meal. Data presented as mean ± SEM (n = 6 per condition). Symbols: Ctrl, control participants; hHFI, heterozygotous for hereditary fructose intolerance participants; LoFruD, low-fructose diet; HiFruD, high-fructose diet; A–B: no difference was observed for plasma glucose concentrations (Group effect: p = 0.137; Diet effect: p = 0.437; Group × Diet interaction: p = 0.342). C–D: a significant Group × Diet interaction effect was observed for plasma insulin concentrations (Group effect: p = 0.836; Diet effect: p = 0.114; Group × Diet interaction: p = 0.001). E–F: no difference was observed for plasma lactate concentrations (Group effect: p = 0.492; Diet effect: p = 0.700; Group × Diet interaction: p = 0.297). $p < 0.05 for Group × Diet interaction (Group × Diet mixed-model analysis); **p < 0.01 for Diet effect (Tukey post-hoc comparisons). Abbreviations: SEM, standard error of measurement.

Table 4
Insulin sensitivity indexes after 7-days on a low fructose diet (LoFruD) or a high fructose diet (HiFruD).

	Ctrl		hHFI	
	LoFruD	HiFruD	LoFruD	HiFruD
HOMA-IR	1.63 ± 0.53	1.80 ± 0.47 *	1.19 ± 0.27	1.45 ± 0.19*
HOMA-β	1.00 ± 0.35	0.88 ± 0.16	0.74 ± 0.07	0.71 ± 0.04
HOMA2-IR	0.95 ± 0.30	1.00 ± 0.24 *	0.69 ± 0.13	0.81 ± 0.09*
HOMA2-β	0.88 ± 0.20	0.84 ± 0.10	0.74 ± 0.04	0.74 ± 0.02
HIRI	31.44 ± 5.51$	28.45 ± 3.06$	24.38 ± 3.58$	33.91 ± 3.56$

Data presented as mean ± SEM (n = 6 per condition). Statistics: *p < 0.05 for Diet effect; $p < 0.05 for Subject × Diet effect (Subject × Diet mixed-model analysis). Abbreviations: Ctrl, control subjects; hHFI, heterozygotous for hereditary fructose intolerance subjects; HOMA-IR, homeostatic model for assessment of insulin resistance; HOMA-β, homeostatic model for assessment of β-cells function; HIRI, hepatic insulin resistance index; SEM, standard error of measurement.

aldolase B causing transient intrahepatocellular fructose-1-phosphate (F-1-P) accumulation. Considering that aldolase B knockout mice exposed to a massive fructose load had elevated urate concentrations altogether with reduced intrahepatocellular ATP levels [37], it was proposed that F-1-P build-up may cause liver phosphate depletion. In turn, lowered ATP concentrations would increase the activities of adenosine deaminase and xanthine oxidase, leading to rapid uric acid formation [38]. Using ^{31}P Magnetic Resonance Spectroscopy, previous studies have shown that depletion of liver inorganic phosphate (Pi) was induced by acute oral or intravenous fructose in hHFI and was inversely correlated to plasma uric acid concentration [23,39].

Acute ATP deficiency could be expected to have an impact on glucose and lactate levels or renal tubular function. However, in this work, these variables were not changed, nor were the triglyceride levels, raising the question of whether other mechanisms for increasing uric acid concentration may be involved. To answer this question, it may be of interest to focus on other inherited metabolic diseases in which hyperuricemia is observed, such as in glucose-6-phosphatase deficiency (glycogen storage diseases type I; GSD-I). The similarity between blood chemistry of patients with GSD-I and healthy subjects infused with fructose (hypertriglyceridemia, lactacidaemia, hypophosphatemia, hyperuricaemia) prompted the hypothesis that the mechanism for hyperuricemia in these two conditions might be analogous [40]. Hyperuricemia in GSD-I has been shown to result from at least two mechanisms: (*a*) decreased urinary excretion due to chronic elevation of lactic acid [41] and (*b*)

Table 5
24 h urinary collections of substrates after 7-days on a low fructose diet (LoFruD) or a high fructose diet (HiFruD).

	Ctrl		hHFI	
	LoFruD	HiFruD	LoFruD	HiFruD
Creatinine [g·day^{-1}]	1.24 ± 0.08	1.15 ± 0.09	1.43 ± 0.21	1.41 ± 0.17
Urea [g·day^{-1}]	21.41 ± 1.10	17.28 ± 1.63	28.90 ± 5.61	25.28 ± 6.24
Uric acid [g·day^{-1}]	0.44 ± 0.04	0.44 ± 0.06	0.60 ± 0.08	0.63 ± 0.07
Sodium [g·day^{-1}]	137.54 ± 27.4	122.91 ± 24.6	139.47 ± 54.6	128.30 ± 45.3
Phosphate [g·day^{-1}]	2.66 ± 0.3	2.21 ± 0.21*	3.03 ± 0.46	2.68 ± 0.61*

Data presented as mean ± SEM (n = 6 per condition). Statistics: *p < 0.05 for Diet effect (Subject × Diet mixed-model analysis). Abbreviations: Ctrl, control subjects; hHFI, heterozygotous for hereditary fructose intolerance subjects; SEM, standard error of measurement.

increased production of uric acid [42–45]. The second mechanism has not been clearly defined but may include two steps. First step, accumulation of glucose-6-phosphate (G-6-P) in hepatocytes during glycogenolysis and excess glycolysis induced by hypoglycemia, leading to depletion of ATP and Pi. Depletion of ATP and Pi favored degradation of AMP to IMP, as previously mentioned, which is further degraded to uric acid. This mechanism has been studied extensively by number of investigators who demonstrated the rapid phosphorylation of large amounts of fructose [35,46,47]. Second step, GSD-I is associated with *de novo* overproduction of purine synthesis contributing to hyperuricemia. It is postulated that in the absence of glucose-6-phosphatase, there may be an increase of phosphoribosyl pyrophosphate due to diversion of G-6-P to the pentose phosphate pathway. An overabundance of this substrate may then accelerate *de novo* synthesis of purines [44,48,49]. This is a plausible explanation as an increase in purine synthesis *de novo* was shown by an increase in labeled glycine incorporation into urinary uric acid [50]. Interestingly, fructose stimulates the rate of glucose phosphorylation of glucose to G-6-P in isolated hepatocytes. This effect is mediated by F-1-P, which releases the inhibition exerted by a regulatory protein on liver glucokinase. F-1-P antagonizes this inhibition by causing dissociation of the glucokinase regulatory protein (GKRP) complex, which cause migration of glucokinase toward cytosolic space, where it facilitates the conversion of glucose to G-6-P [51]. Overall, these observations suggest that G-6-P may play a pivotal role in *de novo* purine synthesis (Fig. 4).

Since it has been proposed that fructose-induced increase in uric acid concentration may be instrumental in causing whole-body insulin resistance [52–54], we next turned or attention to postprandial glucose homeostasis. Both groups presented similar glycemic responses to the test meal. Postprandial insulin responses were however lower in hHFI than Ctrl after LoFruD, indicating that hHFI were more insulin sensitive. This effect however reverted after HiFruD, since postprandial insulin responses nearly doubled in hHFI, suggesting that consumption of a fructose-rich diet significantly impaired their insulin sensitivity. Fasting indexes of pancreatic islet function (HOMA-IR) were elevated by the high fructose diet in both groups, while the specific index of hepatic insulin response (HIRI) was impaired by fructose only in hHFI. This is in contrast with our previous study where acute effect of fructose led to increased uric acid but no impairment of glucose homeostasis. Knowing that exposure to fructose for a few days can lead to significant alterations in hepatic insulin sensitivity [55], our present results therefore suggest that hHFI may confer an increased susceptibility to fructose-induced insulin resistance.

Aldolase B knockout mice and human with biallelic variants in the *ALDOB* gene were found to have increased intrahepatic triglyceride content and a decrease in glucose tolerance with no elevation of plasma TG concentration [15,37]. Subsequent detailed examination of the potential pathways involved in the pathogenesis of IHTG accumulation revealed upregulation of *de novo* lipogenesis (DNL) genes and increased cytosolic expression of glucokinase in aldo B^{-}/B^{-} mouse livers. This observation is

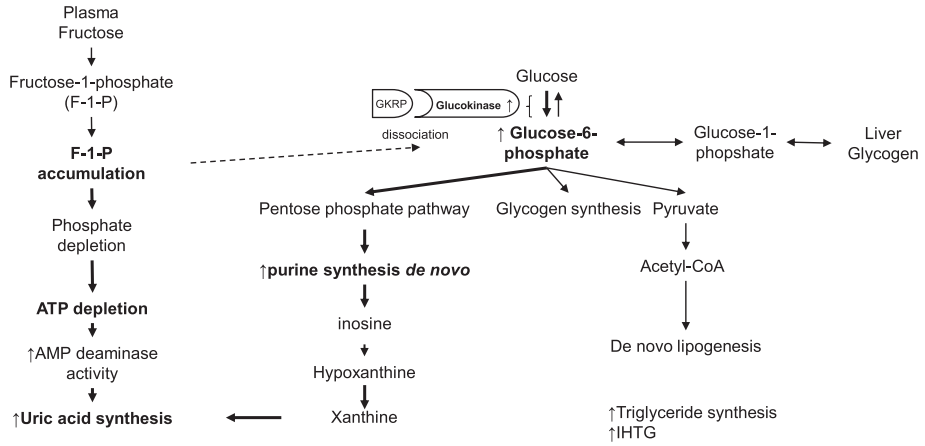

Fig. 4. Possible mechanisms involved in fructose-induced increased uric acid in carriers for hereditary fructose intolerance. Fructose causes transient fructose-1-phosphate accumulation leading to phosphate depletion. ATP depletion increases the activity of AMP-deaminase, leading to uric acid synthesis. In parallel, F-1-P releases the inhibition of the glucokinase by GKRP contributing to synthesis of glucose-6-phosphate. Glucose-6-phosphate is diverted to the pentose phosphate pathway leading to acceleration of purine synthesis *de novo* and finally uric acid synthesis. AMP, adenosine monophosphate; ATP, adenosine triphosphate; F-1-P, fructose-1-phosphate; GKRP, glucokinase–glucokinase regulatory protein; IHTG: intra-hepatic triglyceride.

consistent with the hypothesis that F-1-P may act as a trigger for glucokinase activity resulting in increased conversion of glucose to G-6-P. This may in turn increase downstream metabolism of G-6-P into, not only glycolysis, but also the pentose phosphate pathway (*de novo* purine synthesis) and DNL (Fig. 4). Whether this is contributing to fructose-induced hyperuricemia and to a decrease of insulin-sensitivity in human HFI carriers remains to be explored. The liver was long assumed to be the primary site of fructose metabolism, but recent evidence indicates that most ingested fructose is in fact first metabolized by the small intestine, which, similarly to the liver, expresses fructolytic and gluconeogenic enzymes. At higher levels of fructose intake, some fructose escapes gut metabolism and gets metabolized in the liver; in addition, part of fructose remains unabsorbed in the gut lumen and is further fermented to short-chain fatty acids in the colon. This bacterial fructose fermentation may indeed be instrumental in providing acetate as a lipogenic substrate to the liver [56,57]. It would be of interest to evaluate the contribution of this novel microbiota−hepatocyte−lipogenesis pathway to DNL in hHFI.

Our study has major limitations. First, the HiFruD was attained by adding an extra amount of fructose and glucose, while leaving dietary intake otherwise ad libitum. This resulted in a minor increase in total energy intake in control subjects due to suppression of their usual sugar intake during supplementation, and in a larger increase in energy intake in hHFI subjects who had a very low basal sugar intake. Indeed analysis of participant's dietary intakes indicated that energy, carbohydrate and fructose intake were higher during HiFruD in hHFI compared to Ctrl leading to relative overfeeding in hHFI. Overfeeding in hHFI during HiFruD may have contributed to reduction in insulin sensitivity relative to Ctrl. Second, HOMA is a global index-composite evaluation of hepatic and peripheral insulin sensitivity, and with much lower sensitivity than direct methods [58]. HIRI is more specific to hepatic IR. Since it has largely been established that a high fructose diet impair hepatic, but not peripheral insulin sensitivity [59], no effect on HOMA in both groups, and on HIRI in Ctrl most likely reflects low sensitivity compared to direct measures. The fact that HiFrD affected HIRI in hHFI nonetheless strongly supports that high fructose intake specifically impaired hepatic insulin sensitivity in hHFI. Metabolomics in plasma and urine was initially planned but was ultimately not realized, which should be added in future studies as it may better delineate a metabolic signature in hHFI and its relation with insulin-resistance. Third, we did not include a washout period between the two diets, but though unlikely to affect the results since changes in fructose intake have been shown to impact metabolic parameters within 4 days already [30].

In conclusion, these data illustrate the metabolic effect of a 7-days high fructose diet in carriers for ALDOB deficiency. This study confirms previous data with a slight but significant increase in fasting uric acid concentrations after a 7-day of fructose enriched diet in both groups. However, this increase was only observed in hHFI after a fructose containing meal. Likely, the accumulation of ALDOB's substrate such as F-1-P is contributing to increased uric acid in carriers for HFI. In addition, hHFI displayed significantly different postprandial insulin response in hHFI compared to Ctrl after 7-days of high fructose diet. This observation is suggestive of a reduced insulin sensitivity in hHFI when exposed to a chronic high fructose diet. Whether the chronic elevation of uric acid is associated with altered insulin response to fructose in hHFI remains to be further evaluated. While there is no evidence so far that hHFI have a clinical disadvantage because of their genetic status, the long-term impact of these metabolic anomalies, albeit subtle, on clinical outcome and cardiovascular risk deserve attention, especially if exposure to moderate doses of fructose is prolonged, typically as in Western diet.

Statement of authorship

C.T., L.T. and F.G.D. designed the study. C.T. and K.S analyzed the data. C.T. wrote the manuscript. F.G.D, K.S., L.T. and N.P. contributed to writing the manuscript. M.F. collected data and contributed to writing the manuscript. F.G.D, C.T. and N.P. supervised the study. C.T. supervised data collection and analysis, and manuscript preparation.

Conflict of interest

All authors state that they have no competing interests to declare. None of the authors accepted any reimbursements, fees or funds from any organization that may in any way gain or lose financially from the results of this study. The authors have not been employed by such an organization. The authors do not have any other competing interest.

Acknowledgments

We thank Valentine Rey and Nathalie Stefanoni (Department of Biomedical Sciences, University of Lausanne) for laboratory analysis. We sincerely thank Ariane Caris (dietician at the department of Medical Genetics, Metabolic Unit at the University Hospital of Liège) for having calculated dietary intake from dietary records. We also thank Andrea Superti-Furga for his critical and constructive review of the manuscript. Additionally, this is a study that was supported by the Fondation Raymond Berger, Switzerland and CT was supported by a "Pépinière" Grant form the University of Lausanne Faculty of Biology and Medicine, Switzerland. NP and MF were supported by a “Fonds d'investissement de recherche scientifique” Grant from the CHU of Liège.

References

[1] Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2014;384(9945):766−81.
[2] Soltani Z, Rasheed K, Kapusta DR, Reisin E. Potential role of uric acid in metabolic syndrome, hypertension, kidney injury, and cardiovascular diseases: is it time for reappraisal? Curr Hypertens Rep 2013;15(3):175−81.
[3] Tappy L, Le KA. Metabolic effects of fructose and the worldwide increase in obesity. Physiol Rev 2010;90(1):23−46.
[4] Taskinen MR, Packard CJ, Boren J. Dietary fructose and the metabolic syndrome. Nutrients 2019;11(9).
[5] Mai BH, Yan LJ. The negative and detrimental effects of high fructose on the liver, with special reference to metabolic disorders. Diabetes Metab Syndr Obes 2019;12:821−6.
[6] Tappy L, Lê KA. Metabolic effects of fructose and the worldwide increase in obesity. Physiol Rev 2010;90(1):23−46.
[7] Caliceti C, Calabria D, Roda A, Cicero AFG. Fructose intake, serum uric acid, and cardiometabolic disorders: a critical review. Nutrients 2017;9(4).
[8] Viazzi F, Garneri D, Leoncini G, Gonnella A, Muiesan ML, Ambrosioni E, et al. Serum uric acid and its relationship with metabolic syndrome and cardiovascular risk profile in patients with hypertension: insights from the I-DEMAND study. Nutr Metab Cardiovasc Dis 2014;24(8):921−7.
[9] Hollak CEM, Lachmann RH. Disorders of fructose metabolism. Inherited metabolic disease in adults. New York: Oxford; 2016. p. 25.
[10] Steinmann B, Gitzelmann R. The diagnosis of hereditary fructose intolerance. Helv Paediatr Acta 1981;36(4):297−316.
[11] Bouteldja N, Timson DJ. The biochemical basis of hereditary fructose intolerance. J Inherit Metab Dis 2010;33(2):105−12.
[12] Steinmann B, Gitzelmann R, Van Den Berghe D. Disorders of fructose metabolism. In: Scriver C, editor. The metabolic and molecular basis of inherited disease. New-York: McGraw-Hill; 2001. p. 1489−520.
[13] Buziau AM, Schalkwijk CG, Stehouwer CDA, Tolan DR, Brouwers M. Recent advances in the pathogenesis of hereditary fructose intolerance: implications for its treatment and the understanding of fructose-induced non-alcoholic fatty liver disease. Cell Mol Life Sci 2019;77:1709−19.
[14] Aldamiz-Echevarria L, de Las Heras J, Couce ML, Alcalde C, Vitoria I, Bueno M, et al. Non-alcoholic fatty liver in hereditary fructose intolerance. Clin Nutr 2019;39(2):455−9.

[15] Simons N, Debray FG, Schaper NC, Kooi ME, Feskens EJM, Hollak CEM, et al. Patients with aldolase B deficiency are characterized by an increased intrahepatic triglyceride content. J Clin Endocrinol Metab 2019;63(2):253–60.
[16] Aldamiz-Echevarria L, de Las Heras J, Couce ML, Alcalde C, Vitoria I, Bueno M, et al. Non-alcoholic fatty liver in hereditary fructose intolerance. Clin Nutr 2020;39(2):455–9.
[17] Santer R, Rischewski J, von Weihe M, Niederhaus M, Schneppenheim S, Baerlocher K, et al. The spectrum of aldolase B (ALDOB) mutations and the prevalence of hereditary fructose intolerance in Central Europe. Hum Mutat 2005;25(6):594.
[18] James CL, Rellos P, Ali M, Heeley AF, Cox TM. Neonatal screening for hereditary fructose intolerance: frequency of the most common mutant aldolase B allele (A149P) in the British population. J Med Genet 1996;33(10):837–41.
[19] Gruchota J, Pronicka E, Korniszewski L, Stolarski B, Pollak A, Rogaszewska M, et al. Aldolase B mutations and prevalence of hereditary fructose intolerance in a Polish population. Mol Genet Metabol 2006;87(4):376–8.
[20] Lazarin GA, Haque IS, Nazareth S, Iori K, Patterson AS, Jacobson JL, et al. An empirical estimate of carrier frequencies for 400+ causal Mendelian variants: results from an ethnically diverse clinical sample of 23,453 individuals. Genet Med 2013;15(3):178–86.
[21] Coffee EM, Yerkes L, Ewen EP, Zee T, Tolan DR. Increased prevalence of mutant null alleles that cause hereditary fructose intolerance in the American population. J Inherit Metab Dis 2010;33(1):33–42.
[22] Baker P, Ayres L, Gaughan S, Weisfeld-Adams J. Hereditary fructose intolerance. Seattle: University of Washington; 2015. Available from: https://www.ncbi.nlm.nih.gov/books/NBK333439/.
[23] Oberhaensli RD, Rajagopalan B, Taylor DJ, Radda GK, Collins JE, Leonard JV, et al. Study of hereditary fructose intolerance by use of 31P magnetic resonance spectroscopy. Lancet 1987;2(8565):931–4.
[24] Seegmiller JE, Dixon RM, Kemp GJ, Angus PW, McAlindon TE, Dieppe P, et al. Fructose-induced aberration of metabolism in familial gout identified by 31P magnetic resonance spectroscopy. Proc Natl Acad Sci U S A 1990;87(21):8326–30.
[25] Gitzelmann R, Baerlocher K, Prader A. Hereditary defects of fructose and galactose metabolism. Monatsschr Kinderheilkd 1973;121(5):174–80.
[26] Debray FG, Damjanovic K, Rosset R, Mittaz-Crettol L, Roux C, Braissant O, et al. Are heterozygous carriers for hereditary fructose intolerance predisposed to metabolic disturbances when exposed to fructose? Am J Clin Nutr 2018;108(2):292–9.
[27] Livesey G. Fructose ingestion: dose-dependent responses in health research. J Nutr 2009;139(6):1246S–52S.
[28] Macdonald IA. A review of recent evidence relating to sugars, insulin resistance and diabetes. Eur J Nutr 2016;55(Suppl. 2):17–23.
[29] Latulippe ME, Skoog SM. Fructose malabsorption and intolerance: effects of fructose with and without simultaneous glucose ingestion. Crit Rev Food Sci Nutr 2011;51(7):583–92.
[30] Egli L, Lecoultre V, Theytaz F, Campos V, Hodson L, Schneiter P, et al. Exercise prevents fructose-induced hypertriglyceridemia in healthy young subjects. Diabetes 2013;62(7):2259–65.
[31] Petersen KF, Laurent D, Yu C, Cline GW, Shulman GI. Stimulating effects of low-dose fructose on insulin-stimulated hepatic glycogen synthesis in humans. Diabetes 2001;50(6):1263–8.
[32] Bingham C, Ellard S, Nicholls AJ, Pennock CA, Allen J, James AJ, et al. The generalized aminoaciduria seen in patients with hepatocyte nuclear factor-1alpha mutations is a feature of all patients with diabetes and is associated with glucosuria. Diabetes 2001;50(9):2047–52.
[33] The Oxford Center for Diabetes, Endocrinology and Metabolism [Oxford University]. Available from: http://www.dtu.ox.ac.uk/homacalculator/.
[34] Muniyappa R, Tella SH, Sortur S, Mszar R, Grewal S, Abel BS, et al. Predictive accuracy of surrogate indices for hepatic and skeletal muscle insulin sensitivity. J Endocr Soc 2019;3(1):108–18.
[35] Woods HF, Eggleston LV, Krebs HA. The cause of hepatic accumulation of fructose 1-phosphate on fructose loading. Biochem J 1970;119(3):501–10.
[36] Kogut MD, Roe TF, Ng W, Nonnel GN. Fructose-induced hyperuricemia: observations in normal children and in patients with hereditary fructose intolerance and galactosemia. Pediatr Res 1975;9(10):774–8.
[37] Lanaspa MA, Andres-Hernando A, Orlicky DJ, Cicerchi C, Jang C, Li N, et al. Ketohexokinase C blockade ameliorates fructose-induced metabolic dysfunction in fructose-sensitive mice. J Clin Investig 2018;128(6):2226–38.
[38] de Oliveira EP, Burini RC. High plasma uric acid concentration: causes and consequences. Diabetol Metab Syndr 2012;4:12.
[39] Boesiger P, Buchli R, Meier D, Steinmann B, Gitzelmann R. Changes of liver metabolite concentrations in adults with disorders of fructose metabolism after intravenous fructose by 31P magnetic resonance spectroscopy. Pediatr Res 1994;36(4):436–40.
[40] Greene HL, Wilson FA, Hefferan P, Terry AB, Moran JR, Slonim AE, et al. ATP depletion, a possible role in the pathogenesis of hyperuricemia in glycogen storage disease type I. J Clin Investig 1978;62(2):321–8.
[41] Howell RR, Ashton DM, Wyngaarden JB. Glucose-6-phosphatase deficiency glycogen storage disease. Studies on the interrelationships of carbohydrate, lipid, and purine abnormalities. Pediatrics 1962;29:553–65.
[42] Fine RN, Strauss J, Donnell GN. Hyperuricemia in glycogen-storage disease type 1. Am J Dis Child 1966;112(6):572–6.
[43] Howell RR. The interrelationship of glycogen storage disease and gout. Arthritis Rheum 1965;8(5):780–5.
[44] Howell RR. Hyperuricemia in childhood. Fed Proc 1968;27(4):1078–82.
[45] Cohen JL, Vinik A, Faller J, Fox IH. Hyperuricemia in glycogen storage disease type I. Contributions by hypoglycemia and hyperglucagonemia to increased urate production. J Clin Investig 1985;75(1):251–7.
[46] Bode JC, Zelder O, Rumpelt HJ, Wittkamp U. Depletion of liver adenosine phosphates and metabolic effects of intravenous infusion of fructose or sorbitol in man and in the rat. Eur J Clin Investig 1973;3(5):436–41.
[47] Raivio KO, Kekomaki MP, Maenpaa PH. Depletion of liver adenine nucleotides induced by D-fructose. Dose-dependence and specificity of the fructose effect. Biochem Pharmacol 1969;18(10):2615–24.
[48] Kelley WN, Holmes EW, Van der Weyden MB. Current concepts on the regulation of purine biosynthesis de novo in man. Arthritis Rheum 1975;18(6 Suppl.):673–80.
[49] Alepa FP, Howell RR, Klinenberg JR, Seegmiller JE. Relationships between glycogen storage disease and tophaceous gout. Am J Med 1967;42(1):58–66.
[50] Jakovcic S, Sorensen LB. Studies of uric acid metabolism in glycogen storage disease associated with gouty arthritis. Arthritis Rheum 1967;10(2):129–34.
[51] van Schaftingen E, Vandercammen A, Detheux M, Davies DR. The regulatory protein of liver glucokinase. Adv Enzym Regul 1992;32:133–48.
[52] Johnson RJ, Nakagawa T, Sanchez-Lozada LG, Shafiu M, Sundaram S, Le M, et al. Sugar, uric acid, and the etiology of diabetes and obesity. Diabetes 2013;62(10):3307–15.
[53] Facchini F, Chen YD, Hollenbeck CB, Reaven GM. Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. J Am Med Assoc 1991;266(21):3008–11.
[54] Dawson J, Wyss A. Chicken or the egg? Hyperuricemia, insulin resistance, and hypertension. Hypertension 2017;70(4):698–9.
[55] Abdel-Sayed A, Binnert C, Le KA, Bortolotti M, Schneiter P, Tappy L. A high-fructose diet impairs basal and stress-mediated lipid metabolism in healthy male subjects. Br J Nutr 2008;100(2):393–9.
[56] Jang C, Hui S, Lu W, Cowan AJ, Morscher RJ, Lee G, et al. The small intestine converts dietary fructose into glucose and organic acids. Cell Metab 2018;27(2):351–361 e3.
[57] Zhao S, Jang C, Liu J, Uehara K, Gilbert M, Izzo L, et al. Dietary fructose feeds hepatic lipogenesis via microbiota-derived acetate. Nature 2020;579(7800):586–91.
[58] Sarafidis PA, Lasaridis AN, Nilsson PM, Pikilidou MI, Stafilas PC, Kanaki A, et al. Validity and reproducibility of HOMA-IR, 1/HOMA-IR, QUICKI and McAuley's indices in patients with hypertension and type II diabetes. J Hum Hypertens 2007;21(9):709–16.
[59] Ter Horst KW, Schene MR, Holman R, Romijn JA, Serlie MJ. Effect of fructose consumption on insulin sensitivity in nondiabetic subjects: a systematic review and meta-analysis of diet-intervention trials. Am J Clin Nutr 2016;104(6):1562–76.