



Fructose intervention for 12 weeks does not impair glycemic control or incretin hormone responses during oral glucose or mixed meal tests in obese men

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Metabolic syndrome;
Mixed meal test;
Oral glucose tolerance test

Abstract *Background and aims:* Incretin hormones glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic polypeptide (GIP) are affected early on in the pathogenesis of metabolic syndrome and type 2 diabetes. Epidemiologic studies consistently link high fructose consumption to insulin resistance but whether fructose consumption impairs the incretin response remains unknown.

Methods and results: As many as 66 obese (BMI 26–40 kg/m²) male subjects consumed fructose-sweetened beverages containing 75 g fructose/day for 12 weeks while continuing their usual lifestyle. Glucose, insulin, GLP-1 and GIP were measured during oral glucose tolerance test (OGTT) and triglycerides (TG), GLP-1, GIP and PYY during a mixed meal test before and after fructose intervention. Fructose intervention did not worsen glucose and insulin responses during OGTT, and GLP-1 and GIP responses during OGTT and fat-rich meal were unchanged. Postprandial TG response increased significantly, $p = 0.004$, and we observed small but significant increases in weight and liver fat content, but not in visceral or subcutaneous fat depots. However, even the subgroups who gained weight or liver fat during fructose intervention did not worsen their glucose, insulin, GLP-1 or PYY responses. A minor increase in GIP response during OGTT occurred in subjects who gained liver fat ($p = 0.049$).

Conclusion: In obese males with features of metabolic syndrome, 12 weeks fructose intervention 75 g/day did not change glucose, insulin, GLP-1 or GIP responses during OGTT or GLP-1, GIP or

Abbreviations: AUC, area under incremental curve; AUC, area under curve; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; HDL, high density lipoproteins; LDL, low density lipoproteins; OGTT, oral glucose tolerance test; PYY, peptide YY; TG, triglyceride.

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PYY responses during a mixed meal. Therefore, fructose intake, even accompanied with mild weight gain, increases in liver fat and worsening of postprandial TG profile, does not impair glucose tolerance or gut incretin response to oral glucose or mixed meal challenge.

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Introduction

An increase in the prevalence in obesity and diabetes closely parallels the dramatic rise in sugar, especially fructose, intake due to consumption of sugar-sweetened beverages (SSBs) that accounts for nearly one-half of all added sugar intake in the U.S. [1]. Nowadays, fructose is a major sweetener in Western diets [2]. In the U.S., 50% of population consumes SSBs daily, and 25% obtains at least 200 kcal from these beverages [1].

The relationship between SSB and cardiometabolic diseases seen in epidemiological studies reflects potential combined effects of fructose and glucose or unique effects of fructose alone. The current data suggest a causative relationship between the intake of sweeteners, particularly fructose, and the increased prevalence of non-alcoholic fatty liver disease and dyslipidemia [1,3,4], especially postprandial plasma triglycerides (TG) [5].

Whether fructose consumption directly causes insulin resistance is much debated, and despite epidemiological evidence suggesting a link, data from intervention studies are inconsistent [4,6–13]. However, most studies included relatively small numbers of participants, a short intervention period or used only fasting insulin as a marker for insulin sensitivity. A 3-week consumption of fructose in 9 normal-weight young males impaired insulin sensitivity, measured as suppression of hepatic glucose production during a clamp, but did not change fasting insulin or glucose levels [13]. Insulin sensitivity, assessed from fasting insulin levels and deuterated glucose disposal, decreased after a 10-week fructose consumption in overweight/obese humans [12]. Studies assessing the effect of hypercaloric fructose consumption with respect to both liver fat and insulin resistance have mostly reported no change in insulin sensitivity, with varying effects on liver fat [6–10]. One study with 6–7 days intervention reported worsened insulin resistance together with increased liver fat [11].

Gut incretins, mainly glucagon-like peptide (GLP)-1 and glucose-dependent insulintropic polypeptide (GIP), mediate the insulintropic response to intraluminal nutrients [14]. Defects in either secretion or insulintropic actions of GLP-1 and GIP are early signs of acquired insulin resistance characterizing the metabolic syndrome [5,16]. Data on whether a single dose of fructose stimulates GLP-1 secretion in humans are inconsistent [17–19], whereas GIP secretion remains unaffected [17–19]. However, no data exists on the effect of longer fructose intervention on GLP-1 and GIP responses to nutritional stimuli.

Here, we test the hypothesis whether worsening of glycemic control induced by fructose consumption (75 g/day for 12 weeks served as a lemonade together with habitual *ad libitum* diet) may involve a gut incretin-dependent mechanism. Therefore, we studied the responses of GLP-1 and GIP in the fasting state and following a standard oral glucose tolerance test (OGTT) and the more physiological mixed meal test before and after fructose intervention in overweight male subjects who have high risk for future diabetes.

Methods

Study cohort

We recruited 82 obese healthy men to the Fructose intervention study (Clinical Trials NCT01445730) at four centers including in Quebec, Canada; Helsinki, Finland; Naples, Italy; and Gothenburg, Sweden. Two subjects discontinued the intervention study: one due to skin rash which was considered as possible allergic reaction to flavoring. The rash disappeared after the discontinuation. The other subject discontinued the study in response to his dentist's advice. In addition, the data from magnetic resonance examinations at baseline or after the fructose intervention were not sufficient from 9 subjects to allow the analyses of different fat depots and the incretin measurements after OGTT or mixed meal were lacking from 5 subjects for technical reasons. Thus, 66 subjects completed the full study protocol except for one subject, who lacked insulin measurements during OGTT. Subjects were recruited via newspaper advertisements. Inclusion criteria were the following; men with large waist circumference (>96 cm), body mass index (BMI) between 27 and 40 kg/m² [2], and stable weight (± 3 kg) for at least the last 3 months, LDL-C < 4.5 mmol/l and TG < 5.5 mmol/l. Exclusion criteria were: age <20 years or >65 years, BMI or lipid levels outside the inclusion ranges, smoking, alcohol consumption over 2 doses/day (i.e., 20 g pure alcohol), type 2 diabetes, cardiovascular disease, hormonal therapy, hepatic and renal diseases, gastroenterological, thyroid or hematological abnormalities, and any chronic disease requiring medication except for controlled hypertension. None of the subjects used any medication or hormones known to influence glucose or lipoprotein metabolism. The study design was approved by the local Ethics committees and each subject gave written informed consent before participation in the study. All the samples were collected in accordance with the Declaration of Helsinki.

Fructose intervention

Each subject underwent a 12-week fructose intervention period, during which they consumed 75 g of fructose daily. Fructose was administered as three daily 330 ml bottles equaling 990 ml and 303 kcal per day. The carbonated beverages were prepared as 7.6% (w/w) solutions and flavored with lemon aroma (specially produced for this study by Nokian Panimo Oy, Finland). Subjects were instructed to consume the beverages together with the three main meals while continuing their habitual *ad libitum* diet and physical activity during the intervention. The fructose-sweetened beverage was well tolerated. Each subject kept a 3-day food record (2 work days and 1 day off) before the fructose intervention period and again within 2 weeks before completing the intervention period. A qualified nutritionist gave detailed verbal and written instructions for filling in the food records and contacted the participants every 1–2 weeks to assure compliance with fructose intervention and lifestyle.

Study design

The subjects participated in 3 separate study visits within 2 weeks before the fructose intervention period: 1) oral glucose tolerance test (OGTT), 2) mixed meal test, and 3) magnetic resonance imaging. These visits were repeated within 2 weeks before completing the 12-week fructose intervention period. The OGTT (75 g) was performed after an overnight fast. Subjects consumed 75 g of glucose and blood sampling was done before and at 5, 10 and 30 min, and 1, 1.5, 2, 3 and 4 h. The standardized mixed meal test was performed at each center after an overnight fast. The subjects received a mixed meal test consisting of bread, butter, cheese, ham, boiled eggs, fresh red pepper, low fat (1%) milk, orange juice and tea or coffee (63 g carbohydrates, 56 g fat and 40 g protein). The fat-rich meal contained 927 kcal. Blood samples were drawn before and at 0.5, 1, 2, 3, 4, 6, and 8 h after the meal. During the test, only water was allowed *ad libitum* and the subjects remained physically inactive. The participants abstained from alcohol and physical exercise for two days before each examination.

Determination of liver, subcutaneous and visceral fat depots

Proton magnetic resonance spectroscopy was performed with a 1.5 T whole-body device to determine liver fat content [20]. A standardized protocol was used at all centers, and all analyses of the imaging results were performed by one person (AH). Subjects were advised to fast for 4 h before imaging.

Biochemical analyses

TG and cholesterol concentrations in total plasma were analyzed by automated enzymatic methods using the

Konelab 60i analyzer (Thermo Fisher Scientific Inc., Espoo, Finland). Concentrations of glucose (hexokinase method, Roche Diagnostic Gluco-quant, Mannheim, Germany). Insulin (electrochemiluminescence with Roche sandwich immunoassay on a Cobas autoanalyzer) was measured during OGTT.

GLP-1 and GIP plasma concentrations were measured after ethanol extraction (70% vol/vol, final concentration) using C-terminally directed assays, which detect both the intact peptide and the primary (N-terminally truncated) metabolite; such assays therefore can be designated as “total”, and the results can be interpreted to reflect the rate of secretion [21]. For GIP [22], we used antiserum code # 80867, which reacts fully with GIP 3–42, but not with GIP 8000, whose chemical nature and relationship to GIP secretion is uncertain. Plasma concentrations of GLP-1 were measured [23] using antiserum code no. 89390, which is specific for the amidated C-terminus of GLP-1. PYY concentrations were measured during mixed meal (Fasting and 4 h) with Elisa method (Merck, Darmstadt, Germany).

Statistical analyses and calculations

Statistical analyses were performed using IBM SPSS Statistics (Version 22, NY, USA). Data are presented as mean \pm SEM or standard deviation and range. HOMA-IR indices were calculated as described previously [24]. A web-based calculator was used to calculate Matsuda Index and Insulinogenic Index during OGTT (<http://mmatsuda.diabetes-smc.jp/MIndexsi.html>). Comparisons between before and after fructose intervention were evaluated with paired nonparametric tests (the Wilcoxon Matched-Pair Signed-Rank test to continuous data when comparing two specified variables and Friedman's 2-Way ANOVA by Ranks to continuous data when comparing more than 2 specified variables). In case of significant differences in 2-Way ANOVA, post hoc analysis was done with Scheffe's method. The area under curve (AUC) and incremental AUC (*i.e.*, the AUC above the fasting concentration; Δ AUC) for postprandial variables were calculated according to the trapezoid rule. Correlations were calculated using Spearman's rank test. A p value < 0.05 was considered statistically significant.

Results

Baseline characteristics

The study subjects were on average 48 years old and had a BMI of 30.6 kg/m². Their characteristics are summarized in Table 1. Before the OGTT or mixed meal, fasting concentrations of glucose, insulin, GLP-1 and GIP were essentially similar. There were no correlations between fasting concentrations of GLP-1 or GIP with BMI, liver fat, subcutaneous or visceral fat nor with concentrations of fasting glucose or insulin. Only fasting GLP-1 correlated with HOMA-IR ($r = 0.245$, $p = 0.049$).

Table 1 Subject characteristics before and after the fructose intervention period. Data are mean \pm standard error of mean and range.

	Before			After			p-value
	Mean	SEM	Range	Mean	SEM	Range	
Age, y	49.0	1.2	21–65				
BMI, kg/m ²	30.6	0.3	26.5–38.2				
Weight, kg	99.2	1.4	65.2–135	100.0	1.5	66.8–136	0.002
fP-Glucose, mmol/l	5.45	0.06	4.50–6.50	5.54	0.07	4.30–7.00	0.090
fP-Insulin, pmol/l	98.3	7.0	19.0–293.0	98.2	7.4	13.0–358.0	0.987
HOMA-IR	4.0	0.3	0.9–13.7	4.1	0.3	0.5–15.1	0.710
HOMA-S	143.2	9.2	20.4–408.4	135.7	9.4	21.3–453.6	0.216
Matsuda Index	3.43	0.23	0.85–9.42	3.61	0.30	0.70–13.55	0.961
Insulinogenic Index	1.25	0.12	–1.28 to 4.72	1.25	0.12	–0.02 to 7.09	0.645
fP-GLP-1 (OGTT), pmol/l	13.8	0.7	4.0–31.0	13.7	0.6	6.0–29.0	0.767
fP-GLP-1 (mixed meal), pmol/l	13.5	0.7	3.0–37.0	13.6	0.7	4.0–31.0	0.051
fP-GIP (OGTT), pmol/l	13.9	2.3	3.0–154.0	12.3	0.6	3.0–27.0	0.322
fP-GIP (mixed meal), pmol/l	11.1	0.6	3.0–29.0	12.2	0.7	2.0–27.0	0.070
fS-TG, mmol/l	1.56	0.11	0.34–4.52	1.66	0.11	0.46–4.25	0.032
Liver fat, %	6.9	0.8	0.3–24.8	7.5	0.8	0.6–27.7	0.021
Visceral fat, cm ³	2487	117	538–5434	2513	111	612–5198	0.621
Subcutaneous fat, cm ³	4223	169	1820–8491	4243	176	1832–8389	0.131
fP-PYY, pg/ml	107.7	7.8	28.3–369.2	100.1	6.4	32.8–247.3	0.220
P-PYY 4 h, pg/ml	164.6	9.4	31.1–496.9	165.5	8.5	54.1–384.7	0.856

Fructose intervention does not modify indexes of insulin sensitivity or secretion or responses of glucose, insulin or incretins during OGTT

During the standard OGTT, the responses (both AUC and AUIC) of glucose, insulin, GLP-1 and GIP were essentially similar before and after fructose intervention (Fig. 1). In accordance, fasting HOMA-IR Matsuda Index, Insulinogenic

Index or Disposition Index did not change significantly during fructose intervention (Table 1).

Fasting or postprandial PYY concentrations are not affected by fructose intervention

PYY concentrations rose similarly by 65 and 60% ($p < 0.001$) from fasting to 4 h during mixed meal before

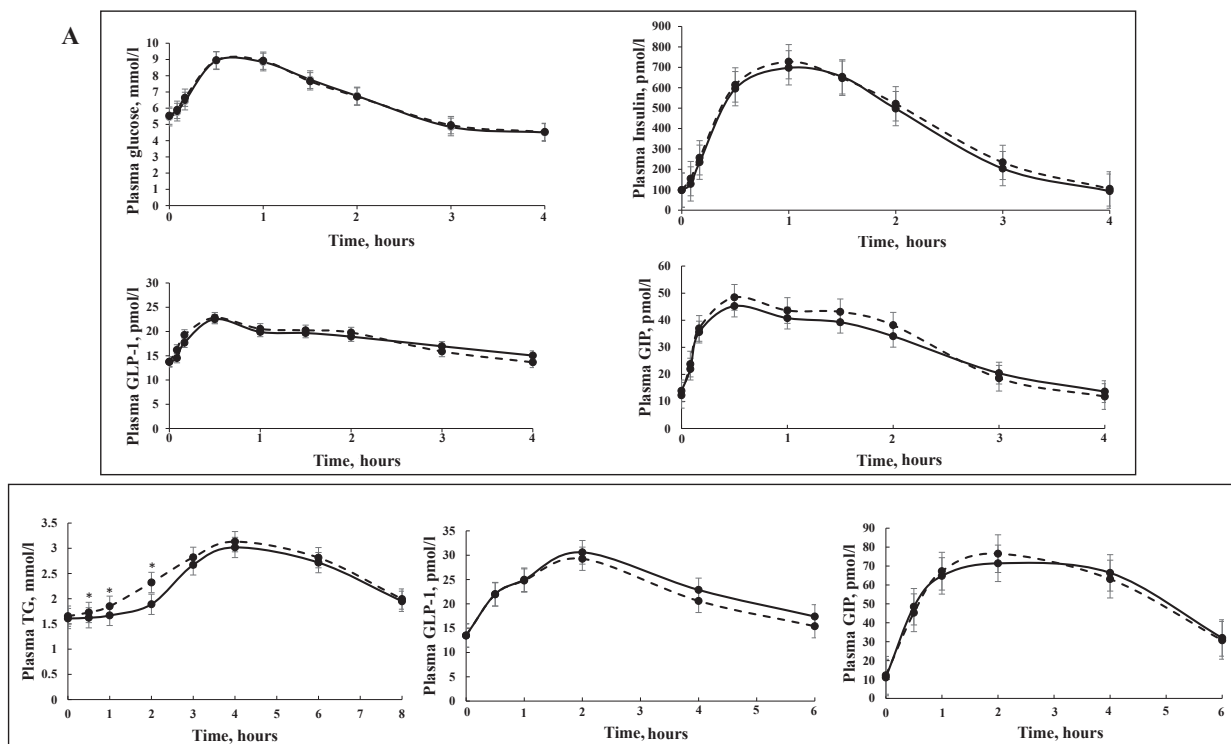


Figure 1 Panel A. Responses of glucose, insulin, GLP-1 and GIP after OGTT before (solid line) and after fructose intervention (dashed line). Panel B. Responses of triglycerides, GLP-1 and GIP after mixed meal test before (solid line) and after fructose intervention (dashed line). Data show mean \pm SEM.

and after fructose intervention, respectively. The 12 weeks fructose intervention did not have an impact on PYY levels. The data are presented in [Table 1](#).

Fructose intervention increases postprandial responses of triglycerides but not that of incretins during mixed meal

Fructose intervention increased fasting TG concentration slightly but significantly ([Table 1](#)). The postprandial TG responses differed before and after fructose intervention, with the response of plasma TG being higher after fructose intervention ([Table 2](#)). The difference was due to higher plasma TG values at 0, 0.5, 1 and 2 h after the fructose intervention ([Table 1](#), [Fig. 1](#)). The AUC or AUIC responses of GLP-1 and GIP during the mixed meal did not differ before or after fructose intervention, but peak concentrations for both GLP-1 and GIP occurred later during the mixed meal (at 2 h) as compared to peak at 0.5 h during the OGTT.

Impact of fructose intervention on diet composition, body weight, liver fat and fat depots

Based on 3-day food records, the subjects adjusted their diets and the increase in energy intake during the fructose intervention was small (only 58 kcal) and did not reach statistical significance. Fructose intake at baseline was 14.5 ± 1.0 g/day and increased to 85.7 ± 0.8 g/day during the fructose intervention. The proportion of energy from total carbohydrates was higher, but that of sucrose, protein, total fat, and saturated and unsaturated fatty acids was lower during the fructose intervention period. The detailed intake of energy and macronutrients are shown in [Supplementary Table 2](#).

Table 2 Glucose, insulin and incretin responses after OGTT and incretin and TG responses after a mixed meal test. Areas under curve (AUC) and areas under incremental curve (AUIC) are given before and after 12 weeks fructose intervention. Data are mean \pm standard error of mean. The given p-value shows differences between before and after fructose measurement (Wilcoxon signed rank test).

	Before		After		p
	Mean	SEM	Mean	SEM	
OGTT					
Glucose AUC, mmol/l h	1574	33	1583	34	0.740
Glucose AUIC, mmol/l h	266	28	254	26	0.496
Insulin AUC, pmol/l h	96,640	7896	101,409	8839	0.722
Insulin AUIC, pmol/l h	73,050	6987	77,849	7929	0.801
GLP-1 AUC, pmol/l h	4401	182	4405	139	0.535
GLP-1 AUIC, pmol/l h	1099	115	1110	113	0.587
GIP AUC, pmol/l h	7293	357	7611	372	0.067
GIP AUIC, pmol/l h	3955	455	4662	291	0.126
Mixed meal					
TG AUC, mmol/l h	1128	73	1238	74	0.004
TG AUIC, mmol/l h	379	30	441	35	0.025
GLP-1 AUC, pmol/l h	8525	358	8321	326	0.522
GLP-1 AUIC, pmol/l h	3671	254	3418	305	0.305
GIP AUC, pmol/l h	20,848	1023	21,522	1144	0.387
GIP AUIC, pmol/l h	16,860	973	17,125	1065	0.814

In general, 12 weeks fructose intervention increased the weight slightly, but statistically significantly from 99.2 to 100.0 kg ($p < 0.002$). The relative increase of liver fat was 9.2% (absolute increase from 6.9% to 7.5%, $p = 0.021$) during fructose intervention. However, fructose intervention did not change the subcutaneous ($p = 0.131$) or visceral ($p = 0.526$) fat depots ([Table 1](#)).

Impact of weight and liver fat changes on incretin response during fructose intervention

Because weight and liver fat changes are important determinants of glycemic control, we divided the study population to three subgroups according to 1) weight change and 2) liver fat change. Weight groups were: weight stable group ($n = 30$) with 0–1 kg change, weight gain group ($n = 27$) with ≥ 1 kg increase and weight loss group ($n = 9$) with ≥ 1 kg decrease in body weight during the fructose intervention. Liver fat groups were: Stable liver fat group with no or minimal change from 3.7% to 4.1% ($n = 17$), increased liver fat group with liver fat gain from 8.7% to 11.3% ($n = 27$) and reduced liver fat group with decrease in liver fat from 7.1% to 5.4% ($n = 22$).

In the whole study group, fructose intervention did not alter any measurement of glucose metabolism but we wanted to exclude the effect of weight on OGTT responses. We therefore analyzed the weight stable, weight gain and weight loss groups separately but the results remained unchanged with no statistical difference between glucose, insulin or GIP AUC or AUIC before vs. after fructose intervention in any of the weight change groups (see [Fig. 2](#) for AUC data). Likewise, the incretin responses as well as PYY responses during mixed meal test were similar before and after fructose in each weight group but the TG AUC was significantly higher in the weight gain group (data not shown).

Because the liver fat content is closely linked to insulin sensitivity and a predictor of diabetes, we wanted to exclude the possibility that subjects with liver fat gain respond to fructose intervention differently compared to subjects who do not increase or even decreased liver fat during fructose intervention. The metabolic characteristic including liver fat changes are given in [Supplementary Table 1](#). These three groups did not show any statistically difference in weight, fasting glucose, visceral fat, subcutaneous fat or fasting TG at baseline or after fructose intervention. However, in the liver fat increase group, fasting insulin and HOMA-IR were higher than in the other two groups and these changes persisted during fructose intervention. Despite the diverse liver fat responses and 5.9% difference in liver fat after the fructose intervention between liver fat decrease and liver fat increase groups, there were no differences in glucose, insulin or GLP-1 responses during OGTT, although the GIP AUC increased slightly in the increased liver fat group ($p = 0.049$, [Fig. 3](#)). During mixed meal test there were no changes in 4 h PYY concentrations or GLP-1 and GIP AUCs during fructose intervention, but as expected the TG AUC increased, which was statistically significant in the liver fat increase group ($p = 0.015$).

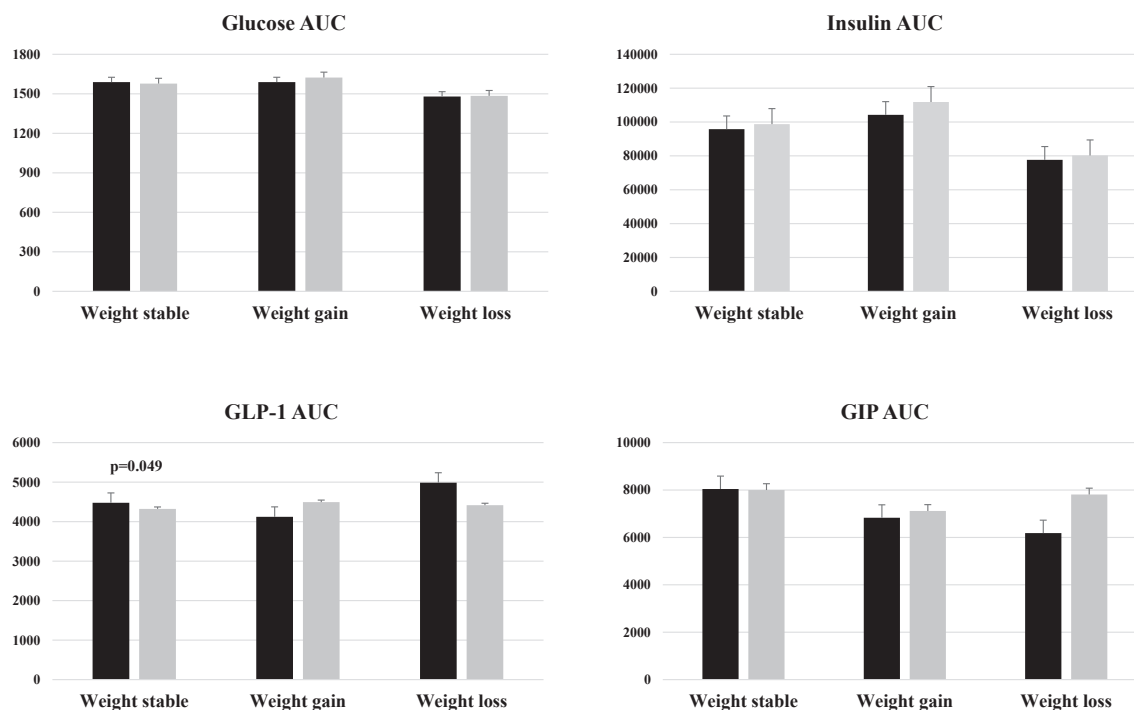


Figure 2 AUC responses of glucose, insulin, GLP-1 and GIP after OGTT by weight group. Weight stable $n = 30$, weight gain $n = 27$, weight loss $n = 9$. Data are mean \pm SEM. The given p-value shows differences between before and after fructose measurement, all other variables did not change significantly (Wilcoxon signed rank test).

Discussion

This is the first study to report the effect of fructose consumption in obese non-diabetic males on incretin responses following both OGTT and mixed meal. We show

that despite mild but significant weight and liver fat gain accompanied with fasting and postprandial TG increase, fructose consumption had no impact on either glycemic control or GLP-1 and GIP responses. Furthermore, although subgroups who gained either weight or liver fat had worse

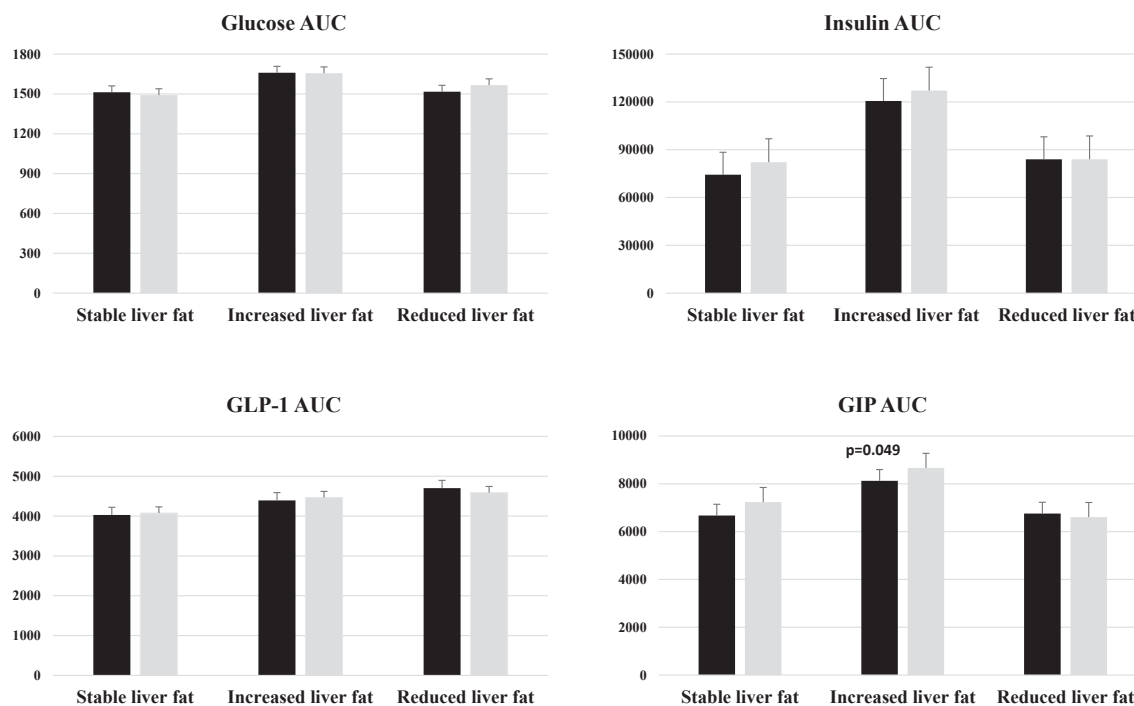


Figure 3 AUC responses of glucose, insulin, GLP-1 and GIP after OGTT by liver fat group. Stable liver fat $n = 17$, increased liver fat $n = 27$, reduced liver fat $n = 22$. Data are mean \pm SEM. The given p-value shows differences between before and after fructose measurement, all other variables did not change significantly (Wilcoxon signed rank test).

TG profiles, this was not associated with worsening of HOMA-IR, glucose tolerance during 4 h OGTT or GLP-1 or GIP responses measured either during OGTT or mixed meal. As expected, the energy intake was slightly hypercaloric during fructose intervention. However actual change of caloric intake was not significant as the subjects adjusted their caloric intake from other food and drinks and also fasting and postprandial PYY concentrations reflecting satiety remained stable. So our results suggest that daily fructose intake of 75 g consumed with a close to weight-maintaining diet does not in itself alter glycemia, but has adverse effects on lipid metabolism.

Our study population was obese, with a large waist circumference, and 41% had elevated screening TG concentrations, and as such, consisted of a high diabetes risk population that should be more prone to develop acquired insulin resistance. The present findings are in contradiction with strong, positive epidemiologic associations reported between fructose intake and components of the metabolic syndrome, insulin resistance and diabetes [1,25]. On the other hand, clinical trials have not been as consistent. Although fructose consumption increases liver fat, fasting TG, and systolic blood pressure and decreases HDL [26], not all studies report impaired glycemic variables. A recent meta-analysis of 29 published studies described effects of fructose in 1005 normal-weight and overweight or obese non-diabetic participants, and concluded that isocaloric or hypercaloric fructose impairs hepatic insulin sensitivity but not peripheral or muscle insulin sensitivity [27]. The included studies were shorter than 8 weeks except for 3 studies, had lower numbers of participants, except for 2 studies, and mostly measured only fasting glucose and insulin. Our results from a 12 weeks fructose intervention in a rather large study population are in agreement with the results from the meta-analysis regarding fasting insulin and HOMA-IR, and extend the findings to glycemic control and incretin responses in 4 h OGTT.

The concentration curves for glucose, insulin, GLP-1 and GIP before and after the intervention are almost superimposable (Fig. 1), and consistent with a stable glycemia also confirmed by calculation of Matsuda and Insulino-genic indexes. Whether previous findings of deleterious effects of fructose on insulin sensitivity are due to direct metabolic effects of fructose itself or a result of increased energy intake and weight gain remains unanswered. We have previously reported a defective GLP-1 response in acquired obesity with liver fat accumulation in young twins [16]. In contrast, in our current study population, the overall weight increase was minor, less than 1 kg, but even when the data were analyzed according to the weight change during the intervention, we did not find that weight gain was associated with impaired glycemic control or incretin responses. Thus, results from studies conducted in free-living conditions may be modulated by metabolic adaptations to nutrient and caloric intake [28,29].

We observed a range of liver fat changes during the fructose intervention, although the average absolute increase was only 0.6 percentage points, from 6.9% to 7.5%

but a clear increase in postprandial TG AUC and AUC. Therefore, we analyzed more closely if liver fat gain during fructose is a key determinant of abnormal glucose and lipid metabolism. However, when data were analyzed according to changes in liver fat, even the group with the greatest increase (fat from 8.7% to 11.3%) had no changes in glucose, insulin or GLP-1 responses during OGTT, with only marginally significant increases in GIP AUC despite the worse cardiometabolic profile. The postprandial incretin responses after the mixed meal were also not related to changes in liver fat, although the group with increased liver fat did have a significant increase in TG AUC response. This may indicate a disconnect between pathways of lipid and glucose metabolism. The concept of pathway-selective insulin resistance and responsiveness [30] is consistent with the results in our population.

We have previously shown that in obese males, GLP-1, GLP-2 and GIP responses to a mixed meal test are greater than following an OGTT. However, the contribution of these hormones to the variance in postprandial TG was minor [31]. This also is in concordance with our present results showing that incretin responses do not correlate significantly to impairment of lipid metabolism in obese non-diabetic males and that fructose intervention leading to increased TG response does not have any modulating effect on gut incretins during a mixed meal. We conclude that in these subjects, fructose consumption has little effect on the gut incretin–pancreas pathway or glucose tolerance.

Our study has some strengths and limitations. The time frame of 12 weeks is longer than in earlier acute or short-term mechanistic studies [27]. A longer intervention trial assessing insulin sensitivity with simple measurements in young adults [32] did not find differences between the effects of glucose and fructose. With respect to the findings that changes in the incretin system are early signs of altered glucose and insulin [15,16], we assume that changes in gut–pancreas axis would be detectable at the same time when changes in lipid metabolism are seen. Taken into account that our intervention period is substantially shorter than follow-up in previous epidemiologic studies that demonstrate impaired glucose tolerance and risk for diabetes with fructose consumption, our results may not be extrapolated to habitual and life-long use of excess fructose. Other limitations include lack of measurement of incretin-induced insulin secretion, lack of control group and standardized background diet, use liquid fructose beverage rather than naturally occurring sucrose and no measure of the absorption of fructose. However, our in our study the amount of fructose and the way it was served were chosen to mimic a behavior which is prevalent in Western societies [29].

In summary, our data show that 75 g daily fructose from SSBs for 12 weeks does not impair gut incretin response or glucose tolerance in obese males, even in the presence of moderate weight- or liver fat gain. Based on our results, the impairment of hepatic lipid handling and dyslipidemia in non-diabetic obese men due to fructose consumption may represent an early metabolic dysfunction in the metabolism of fructose. Our results

show that these early adverse changes are not linked to worsening of glucose tolerance or dysregulation of gut incretins in subjects in high risk for diabetes, at least within the dose and time frame studied here.

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Disclosures

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Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.numecd.2017.03.003>.

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