Fructose- and sucrose- but not glucose-sweetened beverages promote hepatic de novo lipogenesis: A randomized controlled trial

Bettina Geidl-Flueck, Michel Hochuli, Ágota Németh, Anita Eberl, Nina Derron, Harald C. Köfeler, Luc Tappy, Kaspar Berneis, Giatgen A. Spinas, Philipp A. Gerber

PII: S0168-8278(21)00161-6

DOI: https://doi.org/10.1016/j.jhep.2021.02.027

Reference: JHEPAT 8167

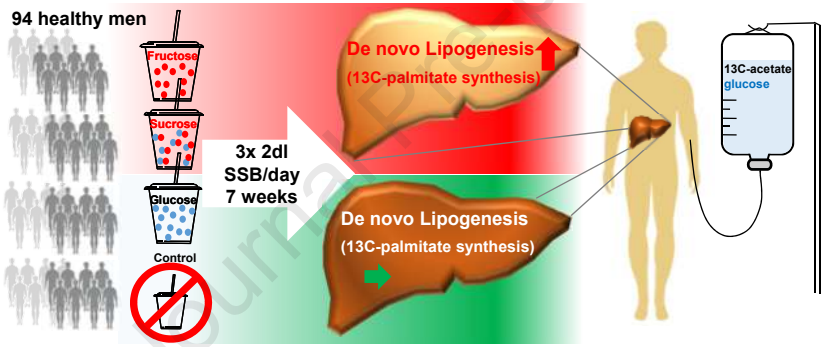
To appear in: *Journal of Hepatology*

Received Date: 17 June 2020

Revised Date: 3 February 2021

Accepted Date: 18 February 2021

Please cite this article as: Geidl-Flueck B, Hochuli M, Németh Á, Eberl A, Derron N, Köfeler HC, Tappy L, Berneis K, Spinas GA, Gerber PA, Fructose- and sucrose- but not glucose-sweetened beverages promote hepatic de novo lipogenesis: A randomized controlled trial, *Journal of Hepatology* (2021), doi: https://doi.org/10.1016/j.jhep.2021.02.027.



Fructose- and sucrose- but not glucose-sweetened beverages promote hepatic de novo lipogenesis: A randomized controlled trial

Bettina Geidl-Flueck[1*], Michel Hochuli[1,5], Ágota Németh[1], Anita Eberl[2], Nina Derron[1], Harald C. Köfeler[3], Luc Tappy[4], Kaspar Berneis†[1], Giatgen A. Spinas[1] and Philipp A. Gerber[1]

[1] Department of Endocrinology, Diabetes and Clinical Nutrition, University Hospital Zurich (USZ) and University of Zurich (UZH), Switzerland

[2] Institute for Biomedicine and Health Sciences, Joanneum Research, Graz, Austria

[3] Core Facility Mass Spectrometry, Medical University of Graz, Austria

[4] Department of Physiology, University of Lausanne, Switzerland

[5] Department of Diabetes, Endocrinology, Nutritional Medicine and Metabolism (UDEM), University Hospital Bern, Switzerland

*Corresponding author**.** Mailing address: University Hospital Zurich, Raemistrasse 100, 8091 Zurich, Switzerland. E-Mail: bettina.geidl@usz.ch, Tel.: +41-44-255-3620

Grant Support: This study was funded by the Swiss National Science Foundation (No. 144204), Vontobel Foundation, Rhyner Bangerter Foundation , Promedica Foundation, Uniscientia Foundation , Prof. Otto Beisheim- Foundation, Jubiläuumsstiftung Swiss Life, Philhuman Foundation and the Austrian Federal Ministry of Education (No. BMWFW-10.420/0005-WF/V/3c/2017).

The study has a trial registration number of NCT01733563 (www.clinicaltrials.gov).

Total word count: 6564 (6600 allowed)

Abstract: (255 words)

Number of tables: 2

Number of figures: 3

Data availability statement: All data, materials and methods in this study are available upon request from the authors.

Conflict of interest: The authors have declared that no conflicts of interest exist with regard to this study.

Author contributions

M.H., B.G., and K.B. designed the research; B.G., A.N., M.H., A.E., H.K., L.T., and P.A.G. conducted the research; B.G., N.D. and P.A.G., analyzed the data; B.G. and P.A.G wrote the manuscript, and A.N., M.H., A.E., H.K., L.T. and G.A.S. revised the manuscript; B.G. and P.A.G. had access to all data and had primary responsibility for the final content.

Abstract

Background & aims: Excessive fructose intake associates with increased de novo lipogenesis, blood triglycerides, and hepatic insulin resistance. Whether fructose-specific effects on lipid metabolism in healthy men exist independently from overfeeding needs clarification.

Methods: 94 subjects were studied in this double-blind, randomized trial. They were assigned to daily consumption of sugar-sweetened beverages (SSB) containing moderate amounts of fructose, sucrose (fructose-glucose disaccharide) or glucose (80g/day) in addition to their usual diet or SSB abstinence (control group) for seven weeks. De novo fatty acid (FA) and triglyceride (TAG) synthesis, lipolysis and plasma free FA (FFA) oxidation were assessed by tracer methodology.

Results: Daily intake of beverages sweetened with free fructose and fructose combined with glucose (sucrose) increased basal fractional secretion rates (FSR) of newly synthesized FA by the liver 2-fold compared to control (median FSR %/day: sucrose 20.8 (p=0.0015); fructose 19.7 (p=0.013); control 9.1). Conversely, the same amounts of glucose did not change FSR (median of FSR %/day 11.0 (ns)). Fructose intake did not change basal secretion of newly synthesized VLDL-TAG. It did neither alter rates of peripheral lipolysis nor total FA and plasma FFA oxidation. Total energy intake was similar across groups with SSB intake and controls.

Conclusions: Regular consumption of both fructose and sucrose sweetened beverages in moderate doses associated with stable caloric intake increases hepatic FA synthesis even in a basal state, whereas this effect is not observed after consumption of glucose. These findings support the hypothesis of an adaptative response of the liver to regular fructose exposure, i. e. habitual SSB consumption.

Keywords: sugar, carbohydrate, liver, stable isotopes, lipid metabolism

Lay summary

This study investigated the metabolic effects of daily sugar-sweetened beverage consumption for several weeks in healthy lean men. It revealed that beverages sweetened with the sugars fructose and sucrose (glucose and fructose combined), but not glucose, increase the ability of the liver to produce lipids. This change may pave the way for further unfavorable effects on metabolic health.

Introduction

How dietary habits impact human health is a highly debated issue with increasing incidence of obesity and associated diseases such as non-alcoholic fatty liver disease (NAFLD), type 2 diabetes and cardiovascular disease[1, 2]. Excessive energy intake from free sugars, and in particular from increased fructose intake associates with obesity, metabolic syndrome and NAFLD[3, 4]. Moreover, evidence exists that high-fructose intake increases hepatic de novo lipogenesis and hepatic fat content and decreases hepatic insulin sensitivity independently from weight gain[5]. Even consumption of SSB containing moderate amounts of fructose for a few weeks changes the serum FA profile and induces hepatic insulin resistance[6, 7].

Differences between hepatic fructose and glucose metabolism and fructose-specific mechanisms promoting metabolic disturbances are known[8]. Importantly, fructose-specific effects result from the fact that the liver plays the major role in fructose clearance[9]. Fructose consumption induces the hepatic master transcription factors regulating the expression of lipogenic enzymes e. g. fatty acid synthase and acetyl-CoA carboxylase more effectively than glucose[10-12]. Increased hepatic lipogenic capacity by upregulation of lipogenic gene expression may be an important mechanism enhancing hexose disposal and supporting metabolic homeostasis in response to the uptake of large carbohydrate (CHO) loads[13]. Furthermore, it may enhance lipogenesis from microbiota-derived acetate[14]. Increased lipogenic capacity may not only be an acute cellular response in order to process large loads of carbohydrates/lipogenic substrates, but be maintained by the liver for a prolonged period as a general metabolic adaptation to a diet rich in CHO[15]. Thus, amounts of CHO and possibly the type/composition of CHO of a diet modify substrate flux within the liver contributing to lipid and glucose homeostasis.

Apart from being a lipogenic substrate and an inducer for lipogenic gene expression in the liver, fructose may also affect other components of the FA metabolism such as peripheral

lipolysis and FA oxidation[7, 16]. It may promote ectopic fat deposition in the liver and muscle associated with insulin resistance[17-19].

However, so far it is neither known whether moderate amounts of sugar sustainably increase the flux of the FA synthesis pathway nor whether they dysregulate basal FFA delivery and oxidation. In particular, it is not known whether fructose exerts divergent effects on hepatic lipid metabolism when consumed alone or co-ingested with glucose i. e. as sucrose or high fructose corn syrup (HFCS). This is of importance because most commercially available sugar sweetened beverages are sweetened with HFCS (United States) or sucrose (Europe).

In this study, metabolic effects of moderate fructose, sucrose and glucose intake in a liquid form as SSB were investigated. Thus, the aim was 1) to identify hexose specific metabolic effects free from confounding factors i.e. CHO overfeeding or differences in the degree of complexity or ways of presentation of sugars and 2) to investigate the effects of fructose containing SSB possibly representing the most deleterious form of fructose administration since associated with incomplete intestinal catabolism allowing a high proportion of fructose passing to the liver [20]. First, we assessed whether a 6-week intervention with SSB containing moderate, but biologically relevant amounts (80g/day) of free fructose, fructose in combination with glucose (sucrose) or glucose or SSB abstinence differently affect hepatic FA synthesis using the method of mass isotopomer distribution analysis (MIDA) (primary outcome). It was postulated that highest effects on basal hepatic lipogenic activity would be elicited by free fructose containing SSB, whereas intermediate effects would be noted by sucrose containing SSB, and little effects after glucose SSB consumption. Secondly, effects on systemic FA flux were investigated measuring lipolysis and plasma FFA oxidation by stable isotope infusions (after 5-weeks SSB interventions). Thirdly, we assessed effects of SSB intake on macronutrient and caloric intake and on anthropometry.

Materials&Methods

Subjects and intervention

126 healthy male volunteers (age 18-30 years) with BMI>24kg/m^2 were recruited to be studied in this double-blind, randomized trial in the years 2013-2016. Study participation was limited to only one gender (male subjects) as there is evidence for divergent metabolic effects of fructose on male and female subjects. Furthermore, a body mass cut-off was defined to exclude subjects with a possibly increased liver fat content[21, 22]. Subject's eligibility was assessed by examination including medical history and blood biochemistry. Subjects with high SSB consumption (exceeding CHO 60g/day) or more than 3 hours of physical activity per week were excluded from the study.

Sample size (n=24 per group) was calculated based on previous studies showing changes in fractional de novo lipogenesis after fructose exposure[23]. Subjects were randomly assigned to one out of four dietary intervention groups by the Cantonal Pharmacy of Zurich (simple random allocation) and supplied with SSB (80g sugar/day) containing fructose, sucrose or glucose or abstained from SSB consumption (control) (Molkerei Biedermann AG, Bischofszell (provided SSB in coded containers), Swiss technology testing service, Dietikon (quality control)). As non-caloric sweeteners potentially affect human metabolism (e.g. appetite control, weight, microbiome composition), the present study did not use a placebo in the control group[24, 25]. The study (NCT01733563) was approved by the ethical committee (Canton Zurich, Switzerland). Informed consent was obtained from all subjects and all procedures were performed in compliance with the guidelines of the Declaration of Helsinki.

Study design

After 4-week SSB abstinence, subjects started a 7-week intervention with consumption of three times/day 2dL SSB containing 13.3g/dL of either fructose, sucrose or glucose with their

regular meals or continued SSB abstinence. At baseline and at the end of the study period (week 7), an oral glucose tolerance test (OGTT) was performed (Accu-Chek Dextrose O.G-T., Roche Pharma AG, 75g). At week 5 and 6, respectively, tracer based metabolic measurements were performed to assess plasma FFA oxidation (week 5), FA and triglyceride (TAG) synthesis (week 6) and lipolysis (week 5 and 6) (Supplemental Figure 1 and Figure 1). The days before examinations subjects abstained from strenuous physical activity. Examination started after a 12-hour overnight fast at the Clinical Trial Unit (University Hospital Zurich).

To assess compliance, subjects had to return empty SSB containers and not consumed SSB and to keep SSB records. To evaluate the impact of SSB on their dietary pattern, subjects had to keep 3-day food records before each examination day. Food records were analyzed using a software (EBISpro, University of Hohenheim, Hohenheim, Germany). Laboratory and anthropometric parameters were measured at each examination.

Metabolites and hormones

Blood glucose was measured from whole blood samples (BIOSEN C-line, EKF Diagnostic, Germany). Kits used in this study are indicated in the supplemental material. TAG, cholesterol and FFA were measured enzymatically in fresh serum. From frozen serum C-peptide was measured using IRMA, insulin using RIA and leptin using ELISA. Insulin sensitivity/beta cell function and adipose tissue resistance was calculated as described previously[26, 27].

Anthropometry

Weight was determined using a digital balance accurate to 0.1kg, and height was measured using a wall-mounted stadiometer. BMI was calculated as weight kg/height(m)^2. Waist and

hip circumference were determined using a measuring tape. Body fat percentage was measured by bioelectrical impedance (AKERN BIA 101, Pontassieve, Italy). Blood pressure was measured using an automated device (Omron M6).

Metabolic studies

During examinations, subjects remained at rest with an indwelling catheter placed in an antecubital vein for tracer infusion, and a sampling catheter inserted in a vein of the contralateral arm. All infusates were prepared by the Cantonal Pharmacy of Zurich with tracers from Cambridge Isotope Laboratory, Inc. Arterialized blood was obtained applying heated hand technique[28]. Baseline blood and breath samples were drawn to measure natural 13C/2H enrichments.

Measurement of peripheral lipolysis and plasma FFA and total fat oxidation (week 5)

Lipolysis represented as the rate of appearance (Ra) of glycerol was assessed by [2H5]glycerol infusion and regular measurements of plasma [2H5]glycerol enrichment[29].The tracer infusion protocols and blood samplings are indicated in Figure 1A. Glycerol derivatization/MS-analysis and calculations are described in the supplemental material.

Plasma FFA oxidation was assessed by [U-13C]palmitate/albumin infusion and measurement of breath 13CO2 enrichment and indirect calorimetry (Figure 1A) (Ergostik, Geratherm Respiratory GmbH, Germany). MS-analysis and calculations are described in the supplemental material.

Measurement of FA, VLDL-TAG synthesis/secretion and lipolysis (week 6)

Basal secretion of newly synthesized VLDL palmitate was assessed by [1,2-13C]acetate and glucose infusion and palmitate isotopomer distribution analysis (Figure 1B). Sample preparation/derivatization and calculations are described in the supplemental material.

Simultaneously, secretion of newly synthesized VLDL-TAG and lipolysis were assessed by primed constant [2H5]glycerol infusion (Figure 1B). [2H5]glycerol enrichment in VLDL-TAG was measured to assess TAG synthesis/secretion. Plasma [2H5]glycerol enrichment was measured to assess Ra of glycerol/ lipolysis [30]. Sample analysis/derivatization and calculations are described in the supplemental material.

sdLDL analysis

LDL size and subclasses were determined in frozen samples. For analysis of LDL size and subclasses, nondenaturing polyacrylamide gradient gel electrophoresis of plasma was performed and analyzed as described elsewhere[31].

Statistics

Data were tested for normal distribution and presented accordingly as means ± standard deviations or as medians with interquartile ranges. SSB groups and the control group were compared by ANOVA testing (parametric data) or Kruskal-Wallis test (nonparametric data). When means or medians were significantly different between groups, appropriate post hoc tests were made either with Tukey's or Dunn's multiple comparison's test or Mann-Whitney tests. In general, 2-tailed tests were performed. Only when one-sided hypotheses were explicitly formulated in advance, 1-tailed tests were performed. Paired t-test (parametric data) or Wilcoxon test (nonparametric data) were applied to compare parameters within one group (baseline vs after intervention). The significance level was set $p<0.05$ and was adjusted for

multiple comparisons by Bonferroni correction. Statistics were performed using GraphPad PRISM (Version 7.04) / IBM SSPS (Version 25).

Results

126 subjects were randomized to four different intervention groups, with either daily consumption of fructose-, sucrose- or glucose-sweetened beverages (80g sugar/day), or SSB abstinence (Control n=31, glucose n=32, fructose n=32, sucrose n=31). Subjects that completed the study (Control n=24, glucose n=24, fructose=23, sucrose=23) were included in the analysis. Data from 22-24 subjects per group could be analyzed, numbers of analyzed subjects are indicated in figures and tables. The data from the remaining 1-3 subjects per group could not be completely collected during the study visits for technical reasons or incompliance with the study protocol. At baseline, the subjects were on average 22.7±2.4 years old. Their mean body weight was 71.5±7.7 kg and their body mass index was normal (21.8±1.6 kg/m^2).

Caloric intake and composition of diet

Total energy intake did not differ significantly between baseline and after SSB interventions (week 7) in any of the groups (Supplemental Table 1). Macronutrient composition varied according to the dietary intervention: SSB consumption significantly increased % caloric intake from carbohydrates. Absolute sugar intake (g/day) was increased according to the assigned interventions. SSB consumption decreased partially sugar intake from fruits (i. e. fructose and sucrose group). Percentage of caloric intake from complex carbohydrates was significantly reduced during the fructose and sucrose SSB interventions. Percent caloric intake from protein was significantly lowered in all SSB groups. Similarly, % caloric intake from fat was significantly lowered in the groups consuming SSB containing fructose or glucose, and tended to be decreased in the sucrose group. SSB consumption increased *absolute* total carbohydrate intake and partially decreased the absolute intake of other

macronutrients (i.e. decreased fat intake in the glucose group and decreased protein intake in the sucrose group).

Anthropometry

The average body weight and percentage of body fat tended to increase during the SSB interventions in all groups (Table 1). However, this increase was only significant for the glucose SSB intervention (week 7 72.4±6.6 kg vs baseline 71.6±6.8 kg, p=0.009; 23.8±4.8 % body fat vs baseline 20.5±5.4 % body fat, p=0.007).

Vital parameters and laboratory parameters, glucose tolerance

Relevant vital and laboratory parameters are summarized in Table 1 and Supplemental Table 2. Systolic and diastolic blood pressure slightly decreased during the study in all groups. Neither fasting plasma TAG, glucose and insulin concentrations nor overall insulin (HOMA-IR) and adipose tissue insulin sensitivity (Adipo-IR) changed throughout the study. Furthermore, glucose tolerance assessed by an oral glucose tolerance test (75g glucose) was not changed by the dietary interventions. Fasting leptin concentrations significantly increased in the sucrose (p=0.019) and glucose (p=0.033) group, but not in the fructose group (p= 0.291).

Concentrations, pool sizes, and distributions (% of VLDL bound TAG of plasma TAG) of plasma triglycerides and palmitate pool sizes after 6-weeks dietary interventions are summarized in Supplemental Table 3 (fasting state). There were no significant differences between the dietary intervention groups. Fatty acid profiles of VLDL-TAGs are presented in Supplemental Table 4 (fasting state). Overall, SSB interventions did not change FA profiles. There was only a significant decrease in oleic acid (C18:1n9) in fructose group compared to

the control group (p=0.038). Accordingly, the saturation index C18:1n9/C18:0 was decreased in the fructose group compared to the control group (p=0.030).

Synthesis and secretion of VLDL-bound palmitate and VLDL-TAG (week 6)

We measured basal hepatic fractional and absolute secretion rates of newly synthesized VLDL-palmitate to assess the activity of the FA synthesis pathway during infusion of 2mg/kg/min glucose providing lipogenic substrate. Palmitate accounting for 75-85% of all newly synthesized FA by the liver represents a suitable proxy for newly synthesized FA [30]. The fractional secretion rate (FSR, defined as the fraction of the plasma VLDL-palmitate pool that is newly synthesized per unit of time) in the basal state was higher after both fructose and sucrose SSB interventions than after the glucose SSB intervention and control. Consumption of beverages containing fructose resulted in 2-fold increased basal FSR of newly synthesized FA compared to control (median FSR %/day: sucrose 20.8 (p=0.0015); fructose 19.7 (p=0.013); control 9.1) (Figure 2
A). In contrast, the same amounts of glucose did not change FSR (median of FSR %/day 11.0 p=0.16).

Similarly, absolute secretion rates of newly synthesized VLDL-palmitate, calculable from FSR and the VLDL-palmitate pool size, tended to be increased by the fructose intervention (p=0.055) and were significantly increased by the sucrose SSB intervention (p= 0.008) compared to control in the basal state (Supplemental Table 5). The total rate of secretion of VLDL-palmitate (de novo synthesized and preformed palmitate) also tended to be higher after the fructose and sucrose SSB interventions compared to control in the basal state, although this was below statistical significance. Parameters for calculation of the FSR of newly synthesized VLDL-palmitate are summarized in Supplemental Table 5.

For hepatic TAG synthesis and secretion, FA uptake from the plasma is of importance[32]. Thus, peripheral lipolysis, a source of FA for hepatic TAG synthesis, was also measured. SSB consumption did not impact basal peripheral lipolysis (Supplemental Table 6).

We also measured basal fractional and absolute secretion rates of newly synthesized VLDL-TAG with incorporated plasma glycerol. There were no differences of fractional or absolute rates of secretion of these VLDL-TAG between groups consuming SSB during 6 weeks and control (Figure 2B and supplemental table 6).

Whole-body fuel use (week 5)

Resting energy expenditure (REE), total fat and CHO oxidation as well as non-protein respiratory quotient (NPRQ) were measured after 5 weeks of SSB interventions by indirect calorimetry. There were no differences regarding REE, total fat and CHO oxidation as well as NPRQ between the groups (Supplemental Table 6). Energy expenditure ranged from 0.019±0.004 kcal/kg per min to 0.023±0.013/kg per min in the different groups. In the fasted state, total fat oxidation varied from 1.43±0.69 to 1.59±0.83 mg/kg per min and CHO oxidation from 0.78±0.77 to 1.20±0.88 mg/kg per min.

Figure 3 shows the analysis of different components of FA-metabolism. The basal rate of R_a glycerol reflecting lipolysis did not differ between the intervention groups (Figure 3A). Neither basal rates of plasma FFA oxidation nor total FA oxidation differed between the groups (Figure 3B,C). The percentage of infused U-13C-palmitate oxidized was not significantly different between the intervention groups (Figure 3D).

sdLDL

Large, buoyant LDL particles (subgroups I and IIa) tended to decrease at 7 weeks after all SSB interventions (Supplemental Table 7); this decrease was significant in the sucrose intervention group, with a decrease of large LDL particles (subgroup I) by >13% (p=0.012).

Similarly, small, dense LDL particles tended to increase after all interventions. The increase was significant in the sucrose group (LDL particles of subgroup IIIa, p=0.031).

Discussion:

This study demonstrates that daily consumption of beverages containing moderate amounts (comparable to those provided by commercial soft drinks/fruit juices) of either fructose or sucrose, but not glucose increases hepatic FA synthesis in healthy men in a basal state. SSB consumption (with ad libitum meals) influenced absolute macronutrient intake (i.e. decreased fat and protein intake) and did not increase total energy intake. Measurements of FA synthesis applying the MIDA approach revealed that consumption of fructose or the fructose-glucose-disaccharide sucrose (3 times 2dl SSB containing 13.3g sugar/dl) increased the FSR of newly synthesized palmitate even at a basal state, possibly reflecting a persisting reinforced lipogenic gene expression. This "metabolic switch" occurring in hepatocytes may enable them to quickly respond to recurrent fructose loads with an increased lipogenic capacity, but may also enhance lipogenesis fed by short chain fatty acids produced by bacterial fermentation i.e. acetate [14] . Contrasting with our hypothesis, fructose and sucrose likewise increase the FSR. This may result from facilitating effects of glucose ingestion important for the induction of lipogenic gene expression. Firstly, glucose strongly enhances intestinal fructose uptake and secondly, insulin is required for the maximal induction of SREBP1c and lipogenic gene expression[33, 34]. Moreover, fructose stimulates hepatic glucose uptake through glucokinase activation possibly enhancing glucose flux towards the liver and increasing abundance of glycolytic intermediates and lipogenic substrate [35, 36]. This is in line with the notion that the monosaccharide composition determines the extent of "monosaccharide flooding" of the liver and thus is a key determinant of lipogenic gene expression and therefore hepatic lipogenic activity.

Enhanced lipogenesis after both fructose and sucrose ingestion is seemingly contrary to our previous observation of an increased relative abundance of plasma palmitate only after daily consumption of SSBs containing fructose but not sucrose[7]. However, the MIDA approach

used in this study assesses the basal de novo FA synthesis whereas measurement of plasma palmitate reflects hepatic FA synthesis integrating postprandial and fasting states. The reported increased ratio of palmitic to linoleic acid after prolonged daily fructose consumption may therefore mainly reflect the importance of fructose as a lipogenic *substrate*. VLDL-TAG secretion was not increased at the basal state in this study, consistent with unchanged/normal fasting TAG levels after the dietary intervention. Nevertheless, a fructose-induced enhanced lipogenic activity may increase *postprandial* hepatic FA/TAG production and fat content[37] and contribute to postprandial hypertriglyceridemia after consumption of high-fructose loads (e.g. SSB). This may not be primarily due to accumulating newly synthesized FA after fructose intake feeding the TAG synthesis pathway, but rather due to concomitant downregulation of FA oxidation of preformed FA entering the liver and promoting re-esterification [36]. Thus preformed and newly synthesized FA as well copious glycerol from fructolysis may promote re-esterification and VLDL production[32, 38]. The effect of fructose consumption on hepatic fat content was not examined in this study. A recent study by Smajis et al. in healthy men demonstrated that a daily consumption of 150 g fructose over 8 weeks did not result in a net fat retention in the liver[39]. However, the authors did not specify whether fructose was consumed in liquid form or solid food rendering it difficult to compare the two studies. Thus, it remains an open question whether fructose *in the form of SSB* with fast fructose absorption and significant overflow to the liver increases hepatic fat content in the long term when possible compensatory mechanisms such as increased VLDL-TAG secretion may be exhausted beyond the limits. Nevertheless, our data demonstrates that fructose consumed as SSB is a potent stimulator of de novo lipogenesis (DNL) which is recognized per se as a risk factor for NAFLD and diabetes[40, 41]. An increased hepatic lipogenic activity and a concurrently increased intestinal fructose absorption and hepatic clearance capacity may increase the susceptibility to liver-related pathologies[42]. Moreover,

a recent study demonstrated that acetate generated by microbial fermentation of fructose also feeds hepatic lipogenesis pointing out possible interactions between fructose and dietary sources of acetate such as ethanol and fermentable fibers[14].

VLDL-TAG synthesis and secretion is also determined by the FA flux towards the liver[32]. Accordingly, we measured rates of peripheral lipolysis during the measurement of FA synthesis, when substrate for FA synthesis was provided by a glucose infusion inducing an insulin response. Rates of peripheral lipolysis did not differ between the groups indicating that SSB consumption during several weeks does not induce adipose tissue insulin resistance. This is in contrast to a study reporting impaired insulin-induced suppression of adipose tissue lipolysis already after 6 days of high-fructose overfeeding (3g/kg of body weight fructose provided as 20% fructose solutions)[23]. Notably, our study investigated the metabolic effects of SSB consumption close to a real life setting instead of sugar overfeeding.

Impaired FA utilization may play a role in the etiology of skeletal muscle and hepatic insulin resistance [43]. We measured plasma FFA oxidation to assess whether regular SSB consumption is a primary factor that decreases basal FA oxidation. Plasma FFA oxidation was not impaired by moderate SSB consumption. Replacement of lipid energy substrate in the skeletal muscle by metabolites generated from fructose i.e. lactate or glucose may spare lipids from oxidation and increase intramuscular fat content, which is supposed to decrease muscular FFA uptake and oxidation[43, 44]. A decreased FFA utilization by the skeletal muscle is supposed to increase FFA flux to the liver which could in combination with an impaired hepatic FA oxidation due to regular fructose consumption promote hepatic fat deposition and insulin resistance[16, 43].

Diet composition impacts whole body fuel selection. Lipolysis as well as the proportion of released FA oxidized correlate inversely with CHO intake[45]. 5 days high-CHO overfeeding (type of CHO not specified) impacts whole body fuel selection even at an overnight fasted

state in healthy men. It induces an insulin resistant state with increased hepatic glucose production and oxidation despite of increased serum insulin concentrations[45]. To test whether daily SSB consumption increases carbohydrate oxidation in the fasted state we measured CHO and total fat oxidation rates by indirect calorimetry. Unlike subjects overfed with carbohydrates for 5 days, subjects with prolonged moderate intakes of SSB containing fructose, sucrose or glucose for several weeks did not show increased fasting CHO oxidation[45].

Not only fat deposition per se but also fat distribution, independently of obesity, is of particular importance for the development of type 2 diabetes[46]. However, determination of subcutaneous, intramuscular or hepatic fat deposition was beyond the scope of this study. Overall SSB interventions tended to increase body weight and fat. It might be hypothesized that the significant increase of % body fat and fasting leptin concentrations after the glucose intervention were caused by an increase of mainly subcutaneous adipose tissue, which was observed to produce higher leptin amounts than visceral fat.[47].

This study confirmed that SSB consumption containing fructose changes LDL composition as described previously[48]. In the intervention group with added sucrose, there was a significant change of the LDL particle distribution towards smaller, more atherogenic particles associated with cardiovascular disease[49].

To our knowledge, this is the first study that applied tracer-based methodology to quantify metabolic changes induced by interventions with SSBs with moderate fructose, sucrose or glucose content with the habitual diet and thus provides findings most relevant for our everyday life. The finding that regular consumption of fructose containing beverages increases hepatic basal lipogenic activity is well in accordance with mechanistic animal studies that showed that fructose and sucrose are more potent inducers of lipogenic gene expression than glucose[10].

This study bears some limitations. Inherent problems of this type of study remain i) little control for compliance to the protocol of individual subjects and ii) unknown intestinal capacities (fructose tolerability) of the subjects to take up fructose. Accordingly, intersubject variability may reflect individual compliance and differences in the intestinal fructose uptake. Though a valuable tool for tracing in vivo kinetics of human metabolism, tracer based methodology provides only estimations of kinetics as it is based on various assumptions and possibly simplifications and mathematical models. Thus, in the present study the use of 13C-acetate as tracer and MIDA may have led to an underestimation of de novo fatty acid synthesis [50]. We measured the synthesis and secretion of VLDL-TAG formed from plasma glycerol which represents a fraction of total VLDL-TAG. The contribution of VLDL-TAG with glycerol originating from the glyceroneogenic or glycolytic pathway has not been assessed in the study [51].

Conclusions:

In summary, our study provides evidence that daily consumed fructose-containing beverages induce profound alterations in the hepatic lipid metabolism manifested as an increased basal lipogenic capacity (increased FSR of newly synthesized FA). Very interestingly, pure fructose (80g fructose/day) and sucrose (40g fructose plus 40g glucose/day) increased basal hepatic FA synthesis comparably. Other features of the metabolic syndrome, i.e. fasting hypertriglyceridemia, hyperglycemia, hyperinsulinemia, peripheral/adipose tissue insulin resistance were not observed in this study of seven weeks duration. This indicates that an increased basal hepatic FA synthesis is probably the first metabolic change induced by regular SSB consumption containing fructose. We hypothesize that this switch of the liver metabolism by fructose intake towards a higher lipogenic activity may pave the way to further changes affecting metabolic health.

Acknowledgements

We thank Isabelle Herter-Aeberli (ETH Zurich), Patrick Schrauwen and Ellen Blaak (Maastricht University, Netherlands) for scientific input in the study design, the personal of the Clinical Trial Unit (University Hospital Zurich) for medical assistance, Cornelia Zwimpfer (University Hospital Zurich), Valentine Rey, Philippe Schneiter (University of Lausanne) and Stefanie Rappold (Medical University Graz, Austria) for their laboratory work and Marc Liechti and Andreas Klaus for assistance with data collection. In particular, we thank all volunteers for participating in our study.

References:

Author names in bold designate shared co-first authorship

[1] Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology (Baltimore, Md) 2016;64:73-84.10.1002/hep.28431

[2] Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nature Reviews Endocrinology 2017;14:88.10.1038/nrendo.2017.151

[3] Jensen T, Abdelmalek MF, Sullivan S, Nadeau KJ, Green M, Roncal C, et al. Fructose and sugar: A major mediator of non-alcoholic fatty liver disease. Journal of hepatology 2018;68:1063-1075.10.1016/j.jhep.2018.01.019

[4] Stanhope KL, Schwarz JM, Keim NL, Griffen SC, Bremer AA, Graham JL, et al. Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. The Journal of clinical investigation 2009;119:1322-1334.10.1172/jci37385

[5] Schwarz JM, Noworolski SM, Wen MJ, Dyachenko A, Prior JL, Weinberg ME, et al. Effect of a High-Fructose Weight-Maintaining Diet on Lipogenesis and Liver Fat. The Journal of clinical endocrinology and metabolism 2015;100:2434-2442.10.1210/jc.2014-3678

[6] Aeberli I, Hochuli M, Gerber PA, Sze L, Murer SB, Tappy L, et al. Moderate amounts of fructose consumption impair insulin sensitivity in healthy young men: a randomized controlled trial. Diabetes care 2013;36:150-156.10.2337/dc12-0540

[7] **Hochuli M, Aeberli I**, Weiss A, Hersberger M, Troxler H, Gerber PA, et al. Sugar-sweetened beverages with moderate amounts of fructose, but not sucrose, induce Fatty Acid synthesis in healthy young men: a randomized crossover study. The Journal of clinical endocrinology and metabolism 2014;99:2164-2172.10.1210/jc.2013-3856

[8] Geidl-Flueck B, Gerber PA. Insights into the Hexose Liver Metabolism-Glucose versus Fructose. Nutrients 2017;9.10.3390/nu9091026

[9] Hannou SA, Haslam DE, McKeown NM, Herman MA. Fructose metabolism and metabolic disease. The Journal of clinical investigation 2018;128:545-555.10.1172/jci96702

[10] Janevski M, Ratnayake S, Siljanovski S, McGlynn MA, Cameron-Smith D, Lewandowski P. Fructose containing sugars modulate mRNA of lipogenic genes ACC and FAS and protein levels of transcription factors ChREBP and SREBP1c with no effect on body weight or liver fat. Food & function 2012;3:141-149.10.1039/c1fo10111k

[11] **Kim MS, Krawczyk SA**, Doridot L, Fowler AJ, Wang JX, Trauger SA, et al. ChREBP regulates fructose-induced glucose production independently of insulin signaling. The Journal of clinical investigation 2016;126:4372-4386.10.1172/jci81993

[12] Koo HY, Wallig MA, Chung BH, Nara TY, Cho BH, Nakamura MT. Dietary fructose induces a wide range of genes with distinct shift in carbohydrate and lipid metabolism in fed and fasted rat liver. Biochimica et biophysica acta 2008;1782:341-348.10.1016/j.bbadis.2008.02.007

[13] Solinas G, Borén J, Dulloo AG. De novo lipogenesis in metabolic homeostasis: More friend than foe? Mol Metab 2015;4:367-377.10.1016/j.molmet.2015.03.004

[14] 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;579:586-591.10.1038/s41586-020-2101-7

[15] Hudgins LC, Hellerstein M, Seidman C, Neese R, Diakun J, Hirsch J. Human fatty acid synthesis is stimulated by a eucaloric low fat, high carbohydrate diet. The Journal of clinical investigation 1996;97:2081-2091.10.1172/jci118645

[16] Softic S, Meyer JG, Wang GX, Gupta MK, Batista TM, Lauritzen H, et al. Dietary Sugars Alter Hepatic Fatty Acid Oxidation via Transcriptional and Post-translational Modifications of Mitochondrial Proteins. Cell metabolism 2019;30:735-753.e734.10.1016/j.cmet.2019.09.003

[17] Chavez JA, Summers SA. Characterizing the effects of saturated fatty acids on insulin signaling and ceramide and diacylglycerol accumulation in 3T3-L1 adipocytes and C2C12 myotubes. Archives of biochemistry and biophysics 2003;419:101-109.10.1016/j.abb.2003.08.020

[18] Kumashiro N, Erion DM, Zhang D, Kahn M, Beddow SA, Chu X, et al. Cellular mechanism of insulin resistance in nonalcoholic fatty liver disease. 2011;108:16381-16385.10.1073/pnas.1113359108 %J Proceedings of the National Academy of Sciences

[19] Petersen MC, Shulman GI. Roles of Diacylglycerols and Ceramides in Hepatic Insulin Resistance. Trends Pharmacol Sci 2017;38:649-665.10.1016/j.tips.2017.04.004

[20] Jang C, Wada S, Yang S, Gosis B, Zeng X, Zhang Z, et al. The small intestine shields the liver from fructose-induced steatosis. Nature metabolism 2020;2:586-593.10.1038/s42255-020-0222-9

[21] Couchepin C, Lê KA, Bortolotti M, da Encarnaçao JA, Oboni JB, Tran C, et al. Markedly blunted metabolic effects of fructose in healthy young female subjects compared with male subjects. Diabetes care 2008;31:1254-1256.10.2337/dc07-2001
[22] Pasanta D, Tungjai M, Chancharunee S, Sajomsang W, Kothan S. Body mass index and its effects on liver fat content in overweight and obese young adults by proton magnetic resonance spectroscopy technique. World J Hepatol 2018;10:924-933.10.4254/wjh.v10.i12.924
[23] Faeh D, Minehira K, Schwarz JM, Periasamy R, Park S, Tappy L. Effect of fructose overfeeding and fish oil administration on hepatic de novo lipogenesis and insulin sensitivity in healthy men. Diabetes 2005;54:1907-1913
[24] Suez J, Korem T, Zeevi D, Zilberman-Schapira G, Thaiss CA, Maza O, et al. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. Nature 2014;514:181-186.10.1038/nature13793
[25] Fowler SP, Williams K, Resendez RG, Hunt KJ, Hazuda HP, Stern MP. Fueling the obesity epidemic? Artificially sweetened beverage use and long-term weight gain. Obesity (Silver Spring) 2008;16:1894-1900.10.1038/oby.2008.284
[26] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-419.10.1007/bf00280883
[27] Abdul-Ghani MA, Molina-Carrion M, Jani R, Jenkinson C, Defronzo RA. Adipocytes in subjects with impaired fasting glucose and impaired glucose tolerance are resistant to the anti-lipolytic effect of insulin. Acta diabetologica 2008;45:147-150.10.1007/s00592-008-0033-z
[28] McGuire EA, Helderman JH, Tobin JD, Andres R, Berman M. Effects of arterial versus venous sampling on analysis of glucose kinetics in man. Journal of applied physiology 1976;41:565-573.10.1152/jappl.1976.41.4.565
[29] Horton TJ, Miller EK, Bourret K. No effect of menstrual cycle phase on glycerol or palmitate kinetics during 90 min of moderate exercise. Journal of applied physiology (Bethesda, Md : 1985) 2006;100:917-925.10.1152/japplphysiol.00491.2005
[30] Aarsland A, Wolfe RR. Hepatic secretion of VLDL fatty acids during stimulated lipogenesis in men. Journal of lipid research 1998;39:1280-1286
[31] Krauss RM, Burke DJ. Identification of multiple subclasses of plasma low density lipoproteins in normal humans. Journal of lipid research 1982;23:97-104
[32] Aarsland A, Chinkes D, Wolfe RR. Contributions of de novo synthesis of fatty acids to total VLDL-triglyceride secretion during prolonged hyperglycemia/hyperinsulinemia in normal man. The Journal of clinical investigation 1996;98:2008-2017.10.1172/JCI119005
[33] **Haas JT, Miao J**, Chanda D, Wang Y, Zhao E, Haas ME, et al. Hepatic insulin signaling is required for obesity-dependent expression of SREBP-1c mRNA but not for feeding-dependent expression. Cell metabolism 2012;15:873-884.10.1016/j.cmet.2012.05.002
[34] Rumessen JJ, Gudmand-Hoyer E. Absorption capacity of fructose in healthy adults. Comparison with sucrose and its constituent monosaccharides. Gut 1986;27:1161-1168.10.1136/gut.27.10.1161
[35] Watford M. Small amounts of dietary fructose dramatically increase hepatic glucose uptake through a novel mechanism of glucokinase activation. Nutrition reviews 2002;60:253-257.10.1301/002966402320289377
[36] Topping DL, Mayes PA. Comparative effects of fructose and glucose on the lipid and carbohydrate metabolism of perfused rat liver. Br J Nutr 1976;36:113-126.10.1079/bjn19760062
[37] **Dusilova T, Kovar J**, Drobny M, Sedivy P, Dezortova M, Poledne R, et al. Different acute effects of fructose and glucose administration on hepatic fat content. Am J Clin Nutr 2019;109:1519-1526.10.1093/ajcn/nqy386
[38] Chong MF, Fielding BA, Frayn KN. Mechanisms for the acute effect of fructose on postprandial lipemia. Am J Clin Nutr 2007;85:1511-1520.10.1093/ajcn/85.6.1511
[39] Smajis S, Gajdosik M, Pfleger L, Traussnigg S, Kienbacher C, Halilbasic E, et al. Metabolic effects of a prolonged, very-high-dose dietary fructose challenge in healthy subjects. Am J Clin Nutr 2019.10.1093/ajcn/nqz271
[40] Lambert JE, Ramos-Roman MA, Browning JD, Parks EJ. Increased de novo lipogenesis is a distinct characteristic of individuals with nonalcoholic fatty liver disease. Gastroenterology 2014;146:726-735.10.1053/j.gastro.2013.11.049
[41] Ma W, Wu JH, Wang Q, Lemaitre RN, Mukamal KJ, Djousse L, et al. Prospective association of fatty acids in the de novo lipogenesis pathway with risk of type 2 diabetes: the Cardiovascular Health Study. Am J Clin Nutr 2015;101:153-163.10.3945/ajcn.114.092601

[42] Sullivan JS, Le MT, Pan Z, Rivard C, Love-Osborne K, Robbins K, et al. Oral fructose absorption in obese children with non-alcoholic fatty liver disease. Pediatric obesity 2015;10:188-195.10.1111/ijpo.238
[43] Blaak EE, van Aggel-Leijssen DP, Wagenmakers AJ, Saris WH, van Baak MA. Impaired oxidation of plasma-derived fatty acids in type 2 diabetic subjects during moderate-intensity exercise. Diabetes 2000;49:2102-2107
[44] 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;100:393-399.10.1017/s000711450789547x
[45] Schwarz JM, Neese RA, Turner S, Dare D, Hellerstein MK. Short-term alterations in carbohydrate energy intake in humans. Striking effects on hepatic glucose production, de novo lipogenesis, lipolysis, and whole-body fuel selection. Journal of Clinical Investigation 1995;96:2735-2743
[46] Tatsukawa Y, Misumi M, Kim YM, Yamada M, Ohishi W, Fujiwara S, et al. Body composition and development of diabetes: a 15-year follow-up study in a Japanese population. European journal of clinical nutrition 2018;72:374-380.10.1038/s41430-017-0077-7
[47] Van Harmelen V, Reynisdottir S, Eriksson P, Thorne A, Hoffstedt J, Lonnqvist F, et al. Leptin secretion from subcutaneous and visceral adipose tissue in women. Diabetes 1998;47:913-917.10.2337/diabetes.47.6.913
[48] **Aeberli I, Gerber PA**, Hochuli M, Kohler S, Haile SR, Gouni-Berthold I, et al. Low to moderate sugar-sweetened beverage consumption impairs glucose and lipid metabolism and promotes inflammation in healthy young men: a randomized controlled trial. Am J Clin Nutr 2011;94:479-485.10.3945/ajcn.111.013540
[49] Ip S, Lichtenstein AH, Chung M, Lau J, Balk EM. Systematic review: association of low-density lipoprotein subfractions with cardiovascular outcomes. Annals of internal medicine 2009;150:474-484.10.7326/0003-4819-150-7-200904070-00007
[50] Puchowicz MA, Bederman IR, Comte B, Yang D, David F, Stone E, et al. Zonation of acetate labeling across the liver: implications for studies of lipogenesis by MIDA. The American journal of physiology 1999;277:E1022-1027.10.1152/ajpendo.1999.277.6.E1022
[51] Kalhan SC, Bugianesi E, McCullough AJ, Hanson RW, Kelley DE. Estimates of hepatic glyceroneogenesis in type 2 diabetes mellitus in humans. Metabolism: clinical and experimental 2008;57:305-312.10.1016/j.metabol.2007.10.003

Table 1. Anthropometric and vital parameters

	Control		Glucose		Fructose		Sucrose	
n	24		22		23		23	
	Baseline	Week 7	Baseline	Week 7	Baseline	Week 7	Baseline	Week 7
Weight[1](kg)	70.4±8.1	70.6±8.0	71.6±6.8	72.4±6.6[A]	69.2±7.7	69.5±7.4	75.5±7.3	76.00±7.0
BMI(kg/m^2)[2]	21.0(2.8)	21.3(1.8)	22.0(2.3)	22.4(2.6)[A]	21.2(2.3)	21.5(2.4)[A]	22.9(1.4)[B]	22.9(2.0)[C]
WHR[1]	0.88±0.03	0.89±0.04	0.85±0.04[B]	0.85±0.04[C]	0.87±0.05	0.87±0.04	0.87±0.04	0.88±0.06
Body fat(%)[1]	21.0±5.5	21.9±4.2	20.5±5.4	23.8±4.8 [A]	20.5±5.5	21.7±5.1	21.4±6.8	22.5±4.7
Muscle(%)[1]	56.7±5.1	53.6±3.7[A]	56.6±4.9	54.0±3.9[A]	56.3±4.2	55.3± 5.1	55.5±5.4	55.1±4.3
Systolic blood pressure (mm Hg) [1]	127.0±10.7	122.9±9.3	125.7±9.0	125.6±11.3	122.6±8.8	121.5± 6.5	126.2±7.2	123.1±9.2
Diastolic blood pressure (mm Hg) [1]	69.7±10.1	66.1±8.5	71.6±8.6	66.7±9.55	67.3±11.8	65.2±8.7	67.2±8.1	63.8±6.5[A]

[1]Arithmetic means±SDs
[2]Medians (Interquartile range)
[A]Significant differences between baseline and after 7-weeks SSB interventions ($p < 0.05$) (Paired t-test or Wilcoxon)
[B]Significant differences between SSB intervention groups and control at baseline ($p < 0.05$) (ANOVA with Tukey's multiple comparisons test or Kruskal-Wallis with Dunn's multiple comparison's test).
[C]Significant differences between groups after 7-weeks SSB interventions ($p < 0.05$) (ANOVA with Tukey's multiple comparisons test or Kruskal-Wallis with Dunn's multiple comparison's test).

Table 2: Indirect calorimetry (Week 5), fasting condition

	Control	Glucose	Fructose	Sucrose
n	23	24	23	22
REE (kcal/kg/min)	0.0229±0.0130	0.02102±0.0046	0.0194±0.0038	0.0195±0.0029
NPRQ	0.76±0.09	0.76±0.10	0.74±0.08	0.76±0.08
Fat oxidation (mg/kg/min)	1.45±0.60	1.59±0.83	1.56±0.64	1.43±0.69
CHO oxidation (mg/kg/min)	1.20±0.88	1.13±1.43	0.78±0.77	1.10±1.00

Arithmetic means±SD
No significant differences between SSB interventions and control (ANOVA)
REE=resting energy expenditure; NPRQ=non-protein respiratory quotient

Fig. 1: Tracer examinations. (A) Day 1 for determination of the acetate recovery factor; day 3 for measurement of fat oxidation and lipolysis at week 5 (B) Measurement of FA synthesis, VLDL-TAG kinetics and lipolysis at week 6.

Fig. 2. Fractional secretion rates (FSR) of newly synthesized palmitate and newly synthesized VLDL-TAG containing plasma glycerol after 6-week SSB interventions. (A) FSR of newly synthesized palmitate are significantly increased in the fructose and sucrose group compared to the control group (fructose p=0.013; sucrose p=0.0015; glucose p=0.16). Fructose n= 23; Glucose n=23; Sucrose n=23; Control n=23. (B) FSR of newly synthesized TAG are not significantly different between the SSB groups and control. Fructose n=23; Glucose n=23; Sucrose n=22; Control n=21. Kruskal-Wallis test for comparison of SSB intervention groups vs control, Mann-Whitney test (one-tailed) for comparison of fructose vs control and sucrose vs control. Significance level P=0.017 (Bonferroni corrected)).

Fig. 3. Lipolysis, percentage infused U-13C-palmitate oxidized, oxidation of plasma FFA and total FA after 5-weeks SSB interventions. (A) Rate of appearance of glycerol representing lipolysis. No significant differences between the groups. Fructose n= 23; Glucose n= 24; Sucrose n= 23; Control n= 23. (B) Percentage of infused tracer oxidized. No significant differences between the groups. Fructose n= 23; Glucose n= 24; Sucrose n= 23; Control n= 23. (C) Oxidation rates of plasma FFA. No significant differences between the groups. Fructose n= 22; Glucose n=24; Sucrose n=23; Control n=23. (D) Total FA oxidation. No significant differences between the groups. Fructose n= 22; Glucose n=24; Sucrose n=24; Control n=23. Kruskal-Wallis test for comparison of SSB intervention groups vs control.

Figure 1

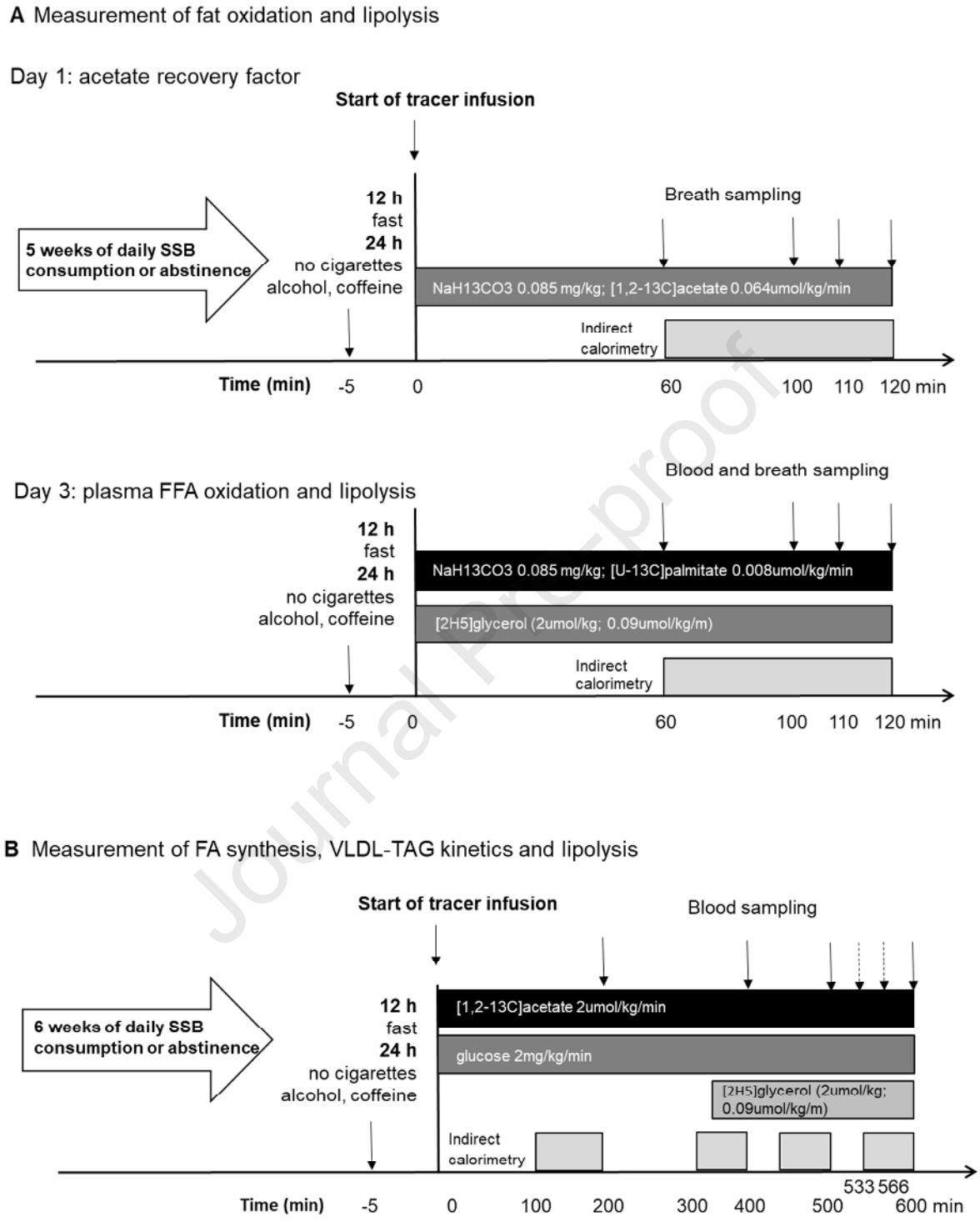


Figure 2

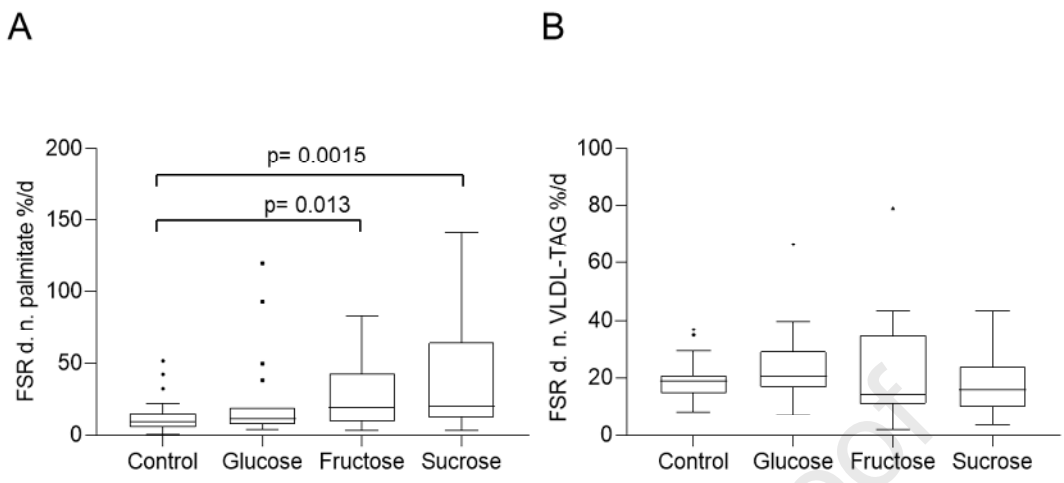
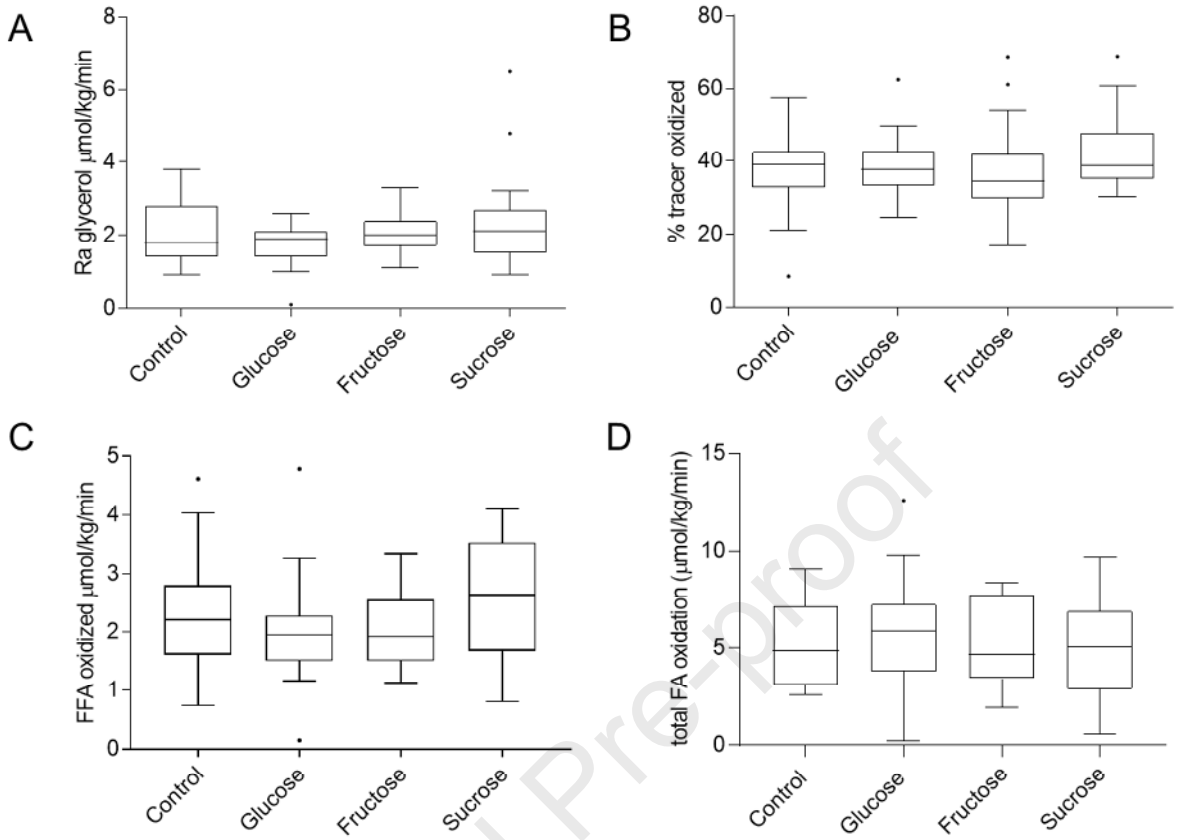


Figure 3



Highlights

- It is debated whether fructose drives the metabolic syndrome or non-alcoholic fatty liver disease
- Fructose in a liquid form as sugar sweetened beverages may impact liver metabolism
- Result: consumption of beverages containing fructose or sucrose increase hepatic lipogenesis
- Increased hepatic lipogenic activity may promote long term metabolic perturbations