Fructose overconsumption causes dyslipidemia and ectopic lipid deposition in healthy subjects with and without a family history of type 2 diabetes1−4

Kim-Anne Lé, Michael Ith, Roland Kreis, David Faeh, Murielle Bortolotti, Christel Tran, Chris Boesch, and Luc Tappy

ABSTRACT

Background: Both nutritional and genetic factors are involved in the pathogenesis of nonalcoholic fatty liver disease and insulin resistance.

Objective: The aim was to assess the effects of fructose, a potent stimulator of hepatic de novo lipogenesis, on intrahepatocellular lipids (IHCLs) and insulin sensitivity in healthy offspring of patients with type 2 diabetes (OffT2D)—a subgroup of individuals prone to metabolic disorders.

Design: Sixteen male OffT2D and 8 control subjects were studied in a crossover design after either a 7-d isocaloric diet or a hypercaloric high-fructose diet (3.5 g·kg FFM−1·d−1, +35% energy intake). Hepatic and whole-body insulin sensitivity were assessed with a 2-step hyperinsulinemic euglycemic clamp (0.3 and 1.0 mU·kg−1·min−1), together with 6,6-[2H2]glucose. IHCLs and intramyocellular lipids (IMCLs) were measured by 1H-magnetic resonance spectroscopy.

Results: The OffT2D group had significantly (P<0.05) higher IHCLs (+94%), total triacylglycerols (+35%), and lower whole-body insulin sensitivity (−27%) than did the control group. The high-fructose diet significantly increased IHCLs (control: +76%; OffT2D: +79%), IMCLs (control: +47%; OffT2D: +24%), VLDL-triacylglycerols (control: +51%; OffT2D: +110%), and fasting hepatic glucose output (control: +4%; OffT2D: +5%). Furthermore, the effects of fructose on VLDL-triacylglycerols were higher in the OffT2D group (group × diet interaction; P<0.05).

Conclusions: A 7-d high-fructose diet increased ectopic lipid deposition in liver and muscle and fasting VLDL-triacylglycerols and decreased hepatic insulin sensitivity. Fructose-induced alterations in VLDL-triacylglycerols appeared to be of greater magnitude in the OffT2D group, which suggests that these individuals may be more prone to developing dyslipidemia when challenged by high fructose intakes. This trial was registered at clinicaltrials.gov as NCT00523562. Am J Clin Nutr 2009;89:1760–5.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) represents the most common liver pathology in industrialized countries and is closely associated with obesity and features of the metabolic syndrome (1). The first step in the pathogenesis of NAFLD is the accumulation of intrahepatocellular lipids (IHCLs). IHCLs may stem from either nonesterified fatty acid (NEFA) reesterification or from hepatic de novo lipogenesis and/or from a decrease in IHCL disposal due to low hepatic fat oxidation or low VLDL-triacylglycerol secretion (2). High-fat diets rapidly increase IHCL in rodents (3) and humans (4), whereas caloric restriction reverses hepatic steatosis in obese patients (5), which indicates that nutritional factors play a prominent role in this process.

Of the nutritional factors, fructose is known to potentiate hepatic de novo lipogenesis. This unique metabolic property of fructose, and the fact that its consumption has increased in parallel with the rising prevalence of obesity, has led several authors to postulate that fructose may play a significant role in the development of metabolic disorders (6, 7). In rodents, a high-fructose or high-sucrose diet increases IHCLs and intramyocellular lipids (IMCLs), together with the development of tissue-specific insulin resistance (8). In humans, accumulation of IHCLs after fructose ingestion has not yet been shown; however, it was shown that fructose stimulates de novo lipogenesis, increases plasma fasting and postprandial VLDL-triacylglycerols (9–12), and decreases lipolysis and whole-body lipid oxidation (13, 14).

Besides dietary factors, genetic susceptibility for metabolic disorders may increase the risk of NAFLD. Indeed, the prevalence of NAFLD is higher in type 2 diabetic patients than in weight-matched obese patients (15). The pathogenesis of type 2 diabetes mellitus includes a strong genetic component, and offspring of type 2 diabetic patients (OffT2D) have a higher risk of developing type 2 diabetes (16). This leads to the hypothesis that fructose may have more harmful effects on liver metabolism in this susceptible population.

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The aim of this study was to assess the effects of a 7-d high-fructose diet (HRfD) on IHCL concentrations and on glucose and lipid metabolism in healthy young men without a family history of diabetes and in a healthy young OffT2D group, who are prone to develop metabolic disorders.

SUJECTS AND METHODS

Subjects

Sixteen healthy nonsmoking male offT2D (mean ± SEM age: 24.7 ± 1.3 y) and 8 control subjects (mean ± SEM age: 24 ± 1 y) of similar age, body mass index (BMI; in kg/m²), and total body fat participated in the study (Table 1). Subjects in the OffT2D group had at least one parent with type 2 diabetes. According to a physical examination and a brief medical history, all subjects were in good health, had a BMI between 19 and 25, and were moderately physically active (<1 h/wk). They were not taking any medications and did not regularly consume alcohol or sugar-sweetened beverages. The initial recruitment started in July 2006. The study was approved by the ethical committee of Lausanne University School of Medicine, and the participants provided written informed consent.

Study design and diet

Each subject consumed, in a crossover randomized order, a 7-d isocaloric diet containing 55% carbohydrate, 30% fat, and 15% protein or the same isocaloric diet supplemented with 3.5 g fructose/kg fat-free mass (FFM) daily (+35% energy requirement). The study was performed on an outpatient basis. During the 3 d preceding the metabolic investigations, the subjects were provided with all the dietary constituents as pre-packed food items with instruction on how and when to consume them. The fructose provided was equally consumed as a 20% solution with the 3 main meals. A 4–5-wk washout period separated the diets. Leisure sports activity was restricted to <1 h/wk throughout the study period. Insulin sensitivity was determined with a 2-step hyperinsulinenic euglycemic clamp, and IHCL and IMCL contents were determined by proton magnetic resonance spectroscopy (1H-MRS).

Metabolic investigation

Subjects reported at 0700 to the metabolic unit of the Lausanne University Hospital after a 10-h fast. On arrival, subjects were asked to void, and body composition was estimated from subcutaneous skinfold-thickness measurements at the biceps, triceps, subscapular, and suprailliac sites (17). While the subjects rested quietly in a bed in a semirecumbent position, an indwelling catheter was inserted into the vein of the right wrist for blood sampling. A second indwelling catheter was inserted into an antecubital vein of the other arm for glucose, insulin, and tracer infusions. Whole-body glucose turnover was assessed in the basal condition after a 2-h 6,6-[2H2]glucose infusion (bolus: 2 mg/kg; continuous: 20 µg · kg⁻¹ · min⁻¹). Blood was collected during baseline for the measurement of plasma concentrations of

TABLE 1

Anthropometric and metabolic variables, substrate oxidation, and insulin sensitivity after the isocaloric and high-fructose diets

<table>
<thead>
<tr>
<th></th>
<th>Control group (n = 8)</th>
<th>OffT2D group (n = 16)</th>
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<tbody>
<tr>
<td></td>
<td>Isocaloric</td>
<td>High fructose</td>
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<tr>
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<td>Isocaloric</td>
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<td>High fructose</td>
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<td>D, G, or G × D effect</td>
</tr>
<tr>
<td>Anthropometric variables</td>
<td></td>
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</tr>
<tr>
<td>Body weight (kg)</td>
<td>71.2 ± 1.9</td>
<td>71.8 ± 2.1</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>14.7 ± 1.2</td>
<td>15.4 ± 1.3</td>
</tr>
<tr>
<td>Metabolic variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.2 ± 0.1</td>
<td>5.2 ± 0.1</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>0.87 ± 0.02</td>
<td>1.10 ± 0.07</td>
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<tr>
<td>Insulin (pmol/L)</td>
<td>49 ± 4</td>
<td>57 ± 3</td>
</tr>
<tr>
<td>Nonesterified fatty acids (µmol/L)</td>
<td>616 ± 36</td>
<td>367 ± 34</td>
</tr>
<tr>
<td>β-Hydroxybutyrate (µmol/L)</td>
<td>85 ± 14</td>
<td>20 ± 9</td>
</tr>
<tr>
<td>Uric acid (µmol/L)</td>
<td>300 ± 8</td>
<td>335 ± 17</td>
</tr>
<tr>
<td>ALAT (U/L)</td>
<td>16.9 ± 1.2</td>
<td>24.9 ± 4.2</td>
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<tr>
<td>Leptin (µg/mL)</td>
<td>1.8 ± 0.4</td>
<td>1.8 ± 0.3</td>
</tr>
<tr>
<td>Adiponectin (µg/mL)</td>
<td>5.9 ± 0.8</td>
<td>6.4 ± 0.8</td>
</tr>
<tr>
<td>Calorimetric variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Energy expenditure (kcal/min)</td>
<td>0.95 ± 0.01</td>
<td>0.95 ± 0.04</td>
</tr>
<tr>
<td>Carbohydrate oxidation (mg · kg⁻¹ · min⁻¹)</td>
<td>1.55 ± 0.05</td>
<td>1.94 ± 0.05</td>
</tr>
<tr>
<td>Lipid oxidation (mg · kg⁻¹ · min⁻¹)</td>
<td>0.54 ± 0.03</td>
<td>0.40 ± 0.05</td>
</tr>
<tr>
<td>Hepatic insulin sensitivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting HGO (mg · kg⁻¹ · min⁻¹)</td>
<td>2.1 ± 0.1</td>
<td>2.2 ± 0.1</td>
</tr>
<tr>
<td>Fasting hepatic IS</td>
<td>6.4 ± 0.6</td>
<td>4.9 ± 0.6</td>
</tr>
<tr>
<td>HGO suppression by low insulin (%)</td>
<td>66 ± 8</td>
<td>59 ± 4</td>
</tr>
<tr>
<td>Whole-body insulin sensitivity (mg · kg⁻¹ · min⁻¹)</td>
<td>3.1 ± 0.2</td>
<td>3.4 ± 0.1</td>
</tr>
<tr>
<td>GDR at low insulin</td>
<td>7.6 ± 0.4</td>
<td>7.7 ± 0.5</td>
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1 All values are means ± SEMs. D, G, or G × D effect, significant (P < 0.05) diet (D), group (G), or group × diet interaction (G × D) effect, respectively; OffT2D, offspring of type 2 diabetic patients; ALAT, alanine aminotransferase; IS, insulin sensitivity; HGO, hepatic glucose output; GDR, glucose disposal rate. All data were analyzed by using 2-factor repeated-measures ANOVA.
glucose, lactate, insulin, NEFAs, \( \beta \)-hydroxybutyric acid, uric acid, total triacylglycerols, alanine aminotransferase, leptin, adiponectin, and VLDL, LDL, and HDL subfractions. Energy expenditure and substrate utilization were continuously measured by indirect calorimetry (ventilated canopy) from 0800 to 1300 (18) by using the equations of Livesey and Elia (19).

Liver, adipose, and whole-body insulin sensitivity were measured for 3 h after the initial 2-h tracer infusion. A 2-step hyperinsulinemic euglycemic clamp (20, 21) (0.3 and 1 mU \( \cdot \) kg\(^{-1} \) \cdot \) min\(^{-1} \)) achieved a glycemia of 5.5 mmol/L, performed in combination with measures of hepatic glucose output (6,6-[\( ^{2} \)H\(_{2} \)]glucose; hot infusion model; 22) and of lipolysis (plasma NEFA concentrations). Blood samples were collected every 5 min during the clamp to monitor plasma glucose concentration and at 30-min intervals for the analysis of tracer, insulin, glucagon, triacylglycerols, and NEFA concentrations. Fasting hepatic insulin sensitivity index was calculated as [100/(hepatic glucose output \( \times \) insulin)] (23) and whole-body insulin sensitivity from the glucose disposal rate at moderate and high insulinemia.

**Analytic procedures**

Plasma was immediately separated from blood by centrifugation at 4°C for 10 min at 3600 rpm and stored at \(-20^\circ\)C. Colorimetric methods were used to assess plasma concentrations of NEFA (kit from Wako Chemicals, Freiburg, Germany) and triacylglycerols (kit from Biomérieux Vetek Inc, Marcy l’Etoile, France). Commercial radioimmunoassay kits were used to measure plasma insulin, leptin, and adiponectin concentrations (LINCO Research, St Charles, MO). Subfractions of lipoproteins were separated by ultracentrifugation. \( \beta \)-Hydroxybutyric acid and lactate concentrations were measured enzymatically by using kits from Bohringer (Mannheim, Germany). During the clamp, plasma glucose concentrations were measured by the glucose oxidase method with a Beckman glucose analyzer II and lactate concentrations were measured enzymatically by the glucose, lactate, insulin, NEFAs, \( \beta \)-hydroxybutyric acid, total triacylglycerols, alanine aminotransferase, leptin, adiponectin, and VLDL, LDL, and HDL subfractions. Energy expenditure and substrate utilization were continuously measured by indirect calorimetry (ventilated canopy) from 0800 to 1300 (18) by using the equations of Livesey and Elia (19).

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To qualitatively evaluate the effect of an HFrD on hepatic de novo lipogenesis, we monitored the ratio of linoleate (18:2\( \cdot \)6) to palmitate (16:0) in VLDL-triacylglycerols. Because palmitate, but not linoleate, is produced by de novo lipogenesis, a decrease in this ratio indicates a stimulation of hepatic de novo lipogenesis. However, no significant effect of group and no significant interaction group \( \times \) diet were observed.

After the HFrD, fasting plasma concentrations of lactate, insulin, and alanine aminotransferase increased, with no effect of group. There was a significant effect of group on and a group \( \times \) diet interaction for fasting glucose concentrations, but no effect of diet alone. After the HFrD, NEFAs and \( \beta \)-hydroxybutyrate decreased similarly in both groups. There was a significant group \( \times \) diet interaction on leptin. Adiponectin concentrations were not different between groups and were not significantly altered by the HFrD. Fasting hepatic glucose output was significantly increased by fructose, with no significant effect of group and no significant group \( \times \) diet interaction.

**Ectopic lipid deposition**

IHCLs were significantly higher in the OffT2D than in the control group and were higher after the HFrD (Figure 1). This IHCL response to fructose tended to be higher in the OffT2D than in the control group (\( P < 0.07 \) for the group \( \times \) diet interaction). IHCLs were positively correlated with fasting plasma VLDL-triacylglycerols after both diets (isocaloric: \( \rho = 0.59, P < 0.005 \); HFrD: \( \rho = 0.78, P < 0.005 \)) (Figure 2), as were the changes in IHCLs with change in VLDL-triacylglycerols after the HFrD (\( \rho = 0.55, P < 0.005 \)). There was also a significant effect of diet on IMCLs and a trend for an effect of group (\( P = 0.08 \)).

**Insulin sensitivity and substrate oxidation**

The hepatic insulin sensitivity index decreased after the HFrD (Table 1), with no significant effect of group or significant interaction. The glucose disposal rate at high insulinemia was

**Statistical analysis**

Throughout the manuscript, the data are expressed as means \( \pm \) SEMs. Statistical analyses were performed with STATA version 8.2 (Stata Corp, College Station, TX), and \( P < 0.05 \) was considered statistically significant. All data were analyzed by using 2-factor repeated-measures analysis of variance. The following factors were included in the model: group, diet, and the interaction between group and diet (group \( \times \) diet). All correlations were assessed by using Spearman’s correlation test.

**RESULTS**

**Anthropometric and fasting metabolic variables**

As shown in Table 1, most anthropometric and metabolic variables of the subjects were similar between groups. After the HFrD, body weight increased in both groups. HFrD significantly (\( P < 0.05 \)) increased fasting plasma total triacylglycerols (control: +35%; OffT2D: +73%) and VLDL-triacylglycerols (control: +51%; OffT2D: +110%) (Figure 1). Furthermore, the VLDL-triacylglycerol response to the HFrD was significantly different between the OffT2D and control groups (\( P = 0.04 \) for the group \( \times \) diet interaction). The ratio of 18:2 to 16:0 fatty acids in VLDL-triacylglycerols significantly (\( P < 0.001 \)) decreased after the HFrD from 0.36 to 0.31 in the control group and from 0.35 to 0.27 in the OffT2D group, which indicated the stimulation of hepatic de novo lipogenesis by the HFrD. However, no significant effect of group and no significant interaction group \( \times \) diet were observed.

To qualitatively evaluate the effect of an HFrD on hepatic de novo lipogenesis, we monitored the ratio of linoleate (18:2\( \cdot \)6) to palmitate (16:0) in VLDL-triacylglycerols. Because palmitate, but not linoleate, is produced by de novo lipogenesis, a decrease in this ratio indicates a stimulation of hepatic de novo lipogenesis when dietary fat intake is controlled (as was the case in this study) (25). Fatty acid methyl esters were obtained from transmethylation of VLDL-triacylglycerols, and the ratio of linoleate to palmitate was measured by gas chromatography–mass spectrometry.

**\( ^{1} \)H-Magnetic resonance spectroscopy**

All \( ^{1} \)H-MRS examinations were performed on a clinical 1.5T MR scanner with data acquisition (single-voxel localization with 20 ms echo time) and processing similar to a protocol described earlier (11), except that liver spectra were recorded from a large volume (55 cm\(^{3} \)) in brief respiratory arrests in expiration instead of by a double triggering method. Liver fat content was expressed in units of volume percentage.
lower in the OffTD2 group, with no effect of diet or interaction. No differences in carbohydrate and lipid oxidation, energy expenditure, and respiratory quotient were observed between groups. After the HFrD, carbohydrate oxidation significantly increased, with a concomitant decrease in lipid oxidation in both groups.

**DISCUSSION**

It is known that fructose can increase VLDL-triaclylglycerols and impair hepatic insulin sensitivity in healthy humans (9, 11, 26). In addition to these features, this study showed that fructose also increased IHCL and IMCL concentrations in healthy individuals. We also found that the effects exerted by fructose on plasma VLDL-triaclylglycerols were more severe in the OffTD2 group than in the control group, which suggests that they were at increased risk when exposed to fructose.

Dietary fructose intake has been known for many years to increase fasting plasma triacylglycerols in both healthy subjects and in type 2 diabetic patients (26). In the present study, very large amounts of fructose, exceeding by 2- to 3-fold the average daily intake reported in the US third National Health and Examination Survey (NHANES) (27), were administered. This amount was chosen to metabolically challenge the organism and investigate mechanisms involved in fructose-induced alterations. Consistent with previous studies, we observed that the HFrD increased fasting VLDL-triaclylglycerols in control subjects (11, 28). In addition to these higher VLDL-triaclylglycerol concentrations, IHCL concentrations increased by 76% after the HFrD. Because plasma NEFAs decreased as a result of the antilipolytic effect of HFrD (13), the increase in IHCLs cannot be attributed to NEFA reesterification in the liver and is best explained by the stimulation of de novo lipogenesis by the HFrD. Fructose uptake essentially occurs in the liver, where it is rapidly converted into triose-phosphates, which are potent fatty acid precursors. In addition, the transcription factors sterol regulatory element binding protein-1c and carbohydrate-responsive element binding protein can be activated by dietary fructose (29, 30) and enhance the expression of key lipogenic enzymes, such as acetyl-CoA carboxylase and fatty acid synthase. The initial step of de novo lipogenesis is the synthesis of malonyl-CoA, which acts as a potent inhibitor of carnitine palmitoyl transferase-I. Therefore, de novo lipogenesis and lipid oxidation are simultaneously and inversely regulated by fructose in liver cells. Accordingly, an HFrD has been shown to stimulate de novo lipogenesis in humans, while reducing whole-body lipid oxidation (9, 13, 14). The decrease in the ratio of 18:2 to 16:0 fatty acids in VLDL-triaclylglycerols observed in both groups corroborates that fructose increased hepatic de novo lipogenesis in both the

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**FIGURE 1.** Means (±SEM) changes in (A) plasma total triacylglycerol (TG), (B) plasma VLDL-TG, (C) intrahepatocellular lipids (IHCL), and (D) intramyocellular lipids (IMCL) in control subjects (n = 8) and offspring of type 2 diabetic patients (offspring T2D; n = 16) after the isocaloric and high-fructose diets. All data were analyzed by using 2-factor repeated-measures ANOVA. The group × diet interaction was significant (P < 0.05) for both total- and VLDL-TG and showed a trend for IHCL (P = 0.07). The effect of fructose was significant (P < 0.05) for all variables. The group effect was significant for IHCL (P < 0.05) and showed a trend for IMCL (P = 0.08).

**FIGURE 2.** Correlation between intrahepatocellular lipids (IHCL) and VLDL-triaclylglycerol (TG) concentrations after the isocaloric (A) and the high-fructose diet (B) in the control group (□; n = 8) and in the offspring of type 2 diabetic patients (●; n = 16). Correlations were assessed by using Spearman’s correlation test.
OffT2D and control groups. This measurement, however, does not allow a quantitative comparison between the 2 groups. The decreased concentration of plasma β-hydroxybutyrate observed in the present study further indicates that hepatic β-oxidation and ketogenesis were indeed reduced after HFrD. It is therefore likely that the stimulation of de novo lipogenesis and the concomitant inhibition of intrahepatic lipid oxidation and ketogenesis both contributed to increased intrahepatic triacylglycerol synthesis and finally to IHCL accumulation and increased VLDL-triacylglycerol secretion. The strong positive correlation between these 2 variables further supports this assumption.

Besides increasing hepatic fat deposition, the HFrD also caused deposition of fat as IMCLs in the skeletal muscle. Mechanisms remain speculative at this point, but may include enhanced VLDL-triacylglycerol secretion by the liver together with suppressed whole-body lipid oxidation. Although this effect was not associated with reduced whole-body insulin sensitivity, an increase in IMCLs suggests that longer exposure to such an HFrD may cause further muscle lipotoxicity and eventually insulin resistance.

One major limitation of our study was that fructose was administered as part of a hypercaloric diet. Therefore, it was not possible, based on the present data, to determine whether the increase in IHCLs was due to energy overconsumption or to the specific effects of fructose. It has indeed been shown that short-term fat overconsumption also increases IHCLs to a similar extent (4, 31). No data are available regarding the effects of fructose compared with those of glucose or starch on IHCLs in humans, but it has been reported in rodents that 2 wk of overconsumption of fructose, but not glucose, markedly increased IHCLs and plasma triacylglycerols (32). Of the postulated mechanisms, the authors suggested that fructose decreased peroxisome proliferator-activated receptor–mediated hepatic lipid oxidation. In humans, acute fructose administration increased hepatic de novo lipogenesis and postprandial triacylglycerols to a greater extent than comparable glucose loads (33, 34). Similarly, fructose, but not glucose, administered over a 6-wk period increased fasting and postprandial triacylglycerols in insulin-resistant male subjects (26). Additional human studies comparing the chronic effects of fructose and glucose overconsumption will be required to better delineate the various pathways involved in lipid metabolism.

The effects of fructose on hepatic metabolism may be modulated by genetic factors. We therefore compared the effects of an HFrD in a group of 16 healthy offspring of patients with type 2 diabetes, who have an increased risk of diabetes and related disorders (16), and in control subjects with no family history of diabetes. Although the OffT2D subjects had only one parent with type 2 diabetes mellitus, they had lower whole-body insulin sensitivity and higher IMCL concentrations. These 2 features have been repeatedly reported in similar groups and are considered indicators of genetically determined metabolic alterations (16). One of the novel findings of this study was that offspring of patients with type 2 diabetes also have higher IHCL concentrations, which further indicates that they may have some latent hepatic metabolic dysfunction. The HFrD increased VLDL-triacylglycerols to a greater extent in the OffT2D group than in the control group. The same trend was observed for IHCLs; however, it was not significant.

On the basis of their greater plasma VLDL-triacylglycerol concentrations in response to fructose, the OffT2D group appeared to be more susceptible to the adverse effects of an HFrD on lipid homeostasis. The underlying mechanisms remain undetermined; however, several hypotheses can be raised. First, the OffT2D group had higher IHCL concentrations, even under isocaloric conditions; given the strong positive correlation between IHCLs and VLDL-triacylglycerols, it is tempting to speculate that both variables are regulated by a common mechanism and that their increase may be a consequence of a higher stimulation of hepatic de novo lipogenesis. In obese subjects, fasting de novo lipogenesis is greater than in lean subjects (35). Whether the same is true in nonobese offspring of patients with type 2 diabetes remains unknown. Second, IHCL concentrations may be increased as a consequence of lower insulin sensitivity in offspring of patients with type 2 diabetes, which may affect the daylong lipid profile. Although plasma NEFAs and their suppression by insulin were similar in the control and OffT2D groups, plasma NEFA turnover was not directly measured. We therefore cannot definitively discard the hypothesis that offspring of patients with type 2 diabetes are resistant to the antilipolytic effects of insulin and lead, over 24 h, to an enhanced NEFA flux to the liver with subsequent enhanced intrahepatic reesterification of NEFAs to triacylglycerols. Moreover, it is likely that, because of their insulin-resistant state, the OffT2D group may have daylong hyperinsulinemia, which may continuously activate lipogenic enzymes, such as sterol regulatory element binding protein–1c. Third, it is now recognized that a low capacity for fat oxidation may play an important role in several conditions associated with insulin resistance (16). It can therefore be hypothesized that offspring of patients with type 2 diabetes have a low capacity for fat oxidation, which may favor lipid synthesis and secretion as VLDL-triacylglycerols in response to the administration of a lipogenic substrate such as fructose. Additional studies using tracer methods to better delineate the various pathways involved in lipid metabolism will be needed to further address these issues.

In summary, the results of this study showed that 1) an HFrD increases VLDL-triacylglycerols, IHCLs, and IMCLs in healthy individuals, most likely because of the stimulation of hepatic de novo lipogenesis and a concomitant inhibition of tissue lipid oxidation; 2) healthy normal-weight offspring of patients with type 2 diabetes have higher IHCL concentrations; and 3) a high-fructose diet in healthy normal-weight offspring of patients with type 2 diabetes leads to more important increases in VLDL-triacylglycerols. Consequently, they may be more susceptible to the development of dyslipidemia and related metabolic disorders when consuming significant amounts of lipogenic nutrients, such as fructose.

We thank the staff of the Département de Physiologie de Lausanne and of the Magnetic Resonance Spectroscopy Unit of Bern for their excellent assistance and all of the volunteers for their participation. The authors’ responsibilities were as follows—K-AL, DF, and LT: designed the study and performed the clamp experiments; MI, RK, and CB: performed the MR measurements; K-AL, MB, CT, and LT: analyzed the data; K-AL: wrote the draft of the manuscript; and DF, MI, RK, MB, CT, CB, and LT: reviewed and edited the manuscript. None of the authors had a conflict of interest.

REFERENCES
FRUCTOSE INCREASES ECTOPIC LIPIDS IN HUMANS


