Coffee consumption attenuates short-term fructose-induced liver insulin resistance in healthy men


ABSTRACT
Background: Epidemiologic and experimental data have suggested that chlorogenic acid, which is a polyphenol contained in green coffee beans, prevents diet-induced hepatic steatosis and insulin resistance.

Objective: We assessed whether the consumption of chlorogenic acid–rich coffee attenuates the effects of short-term fructose overfeeding, dietary conditions known to increase intrahepatocellular lipids (IHCLs), and blood triglyceride concentrations and to decrease hepatic insulin sensitivity in healthy humans.

Design: Effects of 3 different coffees were assessed in 10 healthy volunteers in a randomized, controlled, crossover trial. IHCLs, hepatic glucose production (HGP) (by 6,6-d2 glucose dilution), and fasting lipid oxidation were measured after 14 d of consumption of caffeinated coffee high in chlorogenic acid (C-HCA), decaffeinated coffee high in chlorogenic acid, or decaffeinated coffee with regular amounts of chlorogenic acid (D-RCA); during the last 6 d of the study, the weight-maintenance diet of subjects was supplemented with 4 g fructose · kg−1 · d−1 (total energy intake ± SD: 143 ± 1% of weight-maintenance requirements). All participants were also studied without coffee supplementation, either with 4 g fructose · kg−1 · d−1 (high fructose only) or without high fructose (control).

Results: Compared with the control diet, the high-fructose diet significantly increased IHCLs by 102% (all P < 0.05). All 3 coffees significantly decreased HGP. Fasting lipid oxidation increased with C-HCA and D-RCA (P < 0.05). None of the 3 coffees significantly altered IHCLs.

Conclusions: Coffee consumption attenuates hepatic insulin resistance but not the increase of IHCLs induced by fructose overfeeding. This effect does not appear to be mediated by differences in the caffeine or chlorogenic acid content. This trial was registered at clinicaltrials.gov as NCT00827450.

INTRODUCTION
Obesity is associated with ectopic lipid deposition in hepatic and skeletal muscle cells. These ectopic lipid stores may result, at least in part, from excessive intakes of dietary fats and sugars (1) and are thought to play a role in the pathogenesis of insulin resistance by generating intracellular lipid metabolites that interfere with insulin’s actions (2, 3). Epidemiologic surveys have shown that high coffee consumption is associated with lower incidences of obesity (4) and type 2 diabetes (5–10). These beneficial effects of coffee are also observed with decaffeinated coffee (7, 9, 11, 12), indicating that components in coffee, other than caffeine, play a role in these effects. Of the known active compounds in coffee, polyphenols have been shown to protect against oxidative stress (13) and reduce risks for cardiovascular disorders and diabetes (14–16). Coffee consumption is also associated with lower incidences of nonalcoholic fatty liver disease and the progression of nonalcoholic fatty liver disease to nonalcoholic steatohepatitis or hepatocellular carcinoma (17–19). Furthermore, it has been observed that coffee polyphenols could downregulate lipogenic pathways and reduce liver fat accumulation in high-fat fed mice (13, 20, 21). These findings have suggested that coffee polyphenols may specifically prevent tissue induced ectopic lipid deposition and insulin resistance.

Chlorogenic acid, which is a polyphenol present in larger amounts in green coffee beans than in roasted coffee (22), has been reported to improve glucose homeostasis (23–25), prevent ectopic fat accumulation in high-fat fed rodents (20, 26), and may be responsible for some of the metabolic effects of coffee. In the current study, we used a short term hypercaloric fructose overfeeding protocol, which has been shown to increase intrahepatocellular lipids (IHCLs)5 and reduce insulin sensitivity in healthy subjects (27, 28), to assess whether the consumption of

1From the Department of Physiology, University of Lausanne, Lausanne, Switzerland (VL, GC, LE, C Binnert, and LT); the Service of Internal Medicine (GC) and the Service of Endocrinology, Diabetes and Metabolism (LT); Lausanne University Hospital, Lausanne; the Department of Clinical Research and Institute of Diagnostic, Interventional, and Pediatric Radiology, University Bern, Bern, Switzerland; the Department of Clinical Research and Institute of Diagnostic, Interventional, and Pediatric Radiology, University Bern, Bern, Switzerland (AB, ELM, RK, and C Boesch); and Nutrition & Health Research, Nestlé Research Center, Nestec SA, Lausanne, Switzerland (C Binnert and CD).
2VL, GC, and LE contributed equally to this work.
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4Address reprint requests and correspondence to L Tappy, Department of Physiology, University of Lausanne, 7 Bugnon Street, 1005 Lausanne, Switzerland. E-mail: luc.tappy@unil.ch.
5Abbreviations used: C, control diet; C-HCA, caffeinated coffee high in chlorogenic acid; CRC, clinical research center; D-HCA, decaffeinated coffee high in chlorogenic acid; D-RCA, decaffeinated coffee with regular amounts of chlorogenic acid; HFr, high-fructose diet; HGP, hepatic glucose production; IHCL, intrahepatocellular lipid; IMCL, intramyocellular lipid; MR, magnetic resonance; MRS, magnetic resonance spectroscopy; NEFA, nonesterified fatty acid.

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chlorogenic-rich coffees, independent of their caffeine content, would prevent IHCL accumulation and hepatic insulin resistance. We further postulated that chlorogenic-rich coffees may exert such beneficial effects by enhancing whole-body energy expenditure and lipid oxidation.

SUBJECTS AND METHODS

Participants

Thirteen healthy men participated in the study; 10 subjects completed the study protocol. Subjects dropped out for personal reasons or minor adverse events related to fructose intake. Baseline variables of the 10 participants who completed the study are shown in Table 1. Participants were light to moderate coffee consumers (≤4 cups coffee/d) and had low to moderate physical activity levels (~30 min walking/d and ≤3 structured physical activities/wk). All subjects were in good physical health, were nonsmokers, and were not taking any drugs or medication at the time of the study. The experimental protocol (version dated 20 June 2008) was approved by the Ethical Committee of Lausanne University School of Medicine (protocol 144/08; accepted 4 August 2008). All participants provided informed, written consent. This trial was registered at clinicaltrials.gov as NCT00827450.

Study design

Volunteers were recruited by means of advertisements placed in the campus and university hospital. Volunteers were studied on 5 different occasions, each time with 1 of 5 different dietary conditions over a 28-d period (days 1–28), with a washout period ≤4 wk between each condition. The study design and conditions are summarized in Figure 1. At the beginning of each sequence, participants received oral and written instructions to consume a balanced (55% carbohydrate, 30% fat, and 15% protein) weight-maintenance diet and avoid consuming foods rich in chlorogenic acid (eg, apples and artichokes) and caffeine. Participants consumed the prescribed diet on the basis of received instructions from days 1 to 25. From days 26 to 28, subjects received a controlled, balanced weight-maintenance diet (calculated to provide a total energy intake equal to basal energy

![Figure 1](https://example.com/figure1.png)

**FIGURE 1.** Experimental design. In each of the 5 experimental conditions, volunteers received instructions (dietary instructions) to consume a balanced diet and to avoid foods rich in chlorogenic acid for the first 25 d of the study period (28 d). After 14 d, body weight was assessed (thin vertical arrows). Thereafter, in the C condition, participants followed the same dietary instructions for 11 d, received an isocaloric, balanced diet for 3 d (controlled diet), after which intrahepatocellular lipids and intramyocellular lipid concentrations were measured by using proton MRS (bold vertical arrows), body weight was measured (thin vertical arrows), and FM (energy expenditure, substrate oxidation, hepatic glucose production, and lipolysis) was assessed (filled boxes). In the HFr condition, participants ingested 4 g fructose kg⁻¹ d⁻¹ added to their weight-maintenance diet (fructose overfeeding) for 6 d before the assessment of intrahepatocellular lipid concentrations, body weight, and fasting glucose and lipid metabolism. Participants received coffees with varying amounts of chlorogenic acid and caffeine for 14 d and 4 g fructose kg⁻¹ d⁻¹ for 6 d before metabolic assessments in the C-HCA, D-HCA, and D-RCA conditions. C, control diet; C-HCA, caffeinated coffee high in chlorogenic acid; D-HCA, decaffeinated coffee high in chlorogenic acid; D-RCA, decaffeinated coffee with regular amounts of chlorogenic acid; FM, fasting metabolism; HFr, high-fructose diet; MRS, magnetic resonance spectroscopy.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Participant characteristics at inclusion¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Values</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>23 ± 2</td>
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<tr>
<td>Weight (kg)</td>
<td>73.2 ± 2.2</td>
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<tr>
<td>Height (cm)</td>
<td>180 ± 2</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>22.6 ± 0.6</td>
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<tr>
<td>Fat mass (%)</td>
<td>17.6 ± 1.2</td>
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<tr>
<td>Fat mass (kg)</td>
<td>12.9 ± 0.9</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>60.3 ± 1.9</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>140 ± 3</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>78 ± 3</td>
</tr>
<tr>
<td>Resting heart rate (beats/min)</td>
<td>75.4 ± 3.5</td>
</tr>
</tbody>
</table>

¹All values are means ± SEMs. n = 10 subjects.
requirements predicted from the Harris Benedict equation (29) multiplied by 1.4 to account for a low-to-moderate level of physical activity). During this period, subjects received their whole diets as prepacked food items, with specific instructions regarding the time at which each item was to be consumed and instructions for preparation when needed. Participants were carefully instructed not to consume any other foods or beverages in excess of the distributed items, with the exception of water.

On day 14, participants reported to the clinical research center (CRC) at Lausanne University Hospital to have their body weights measured. On day 28, subjects went to University Bern, where their IHCL and intramyocellular lipid (IMCL) concentrations were measured by using proton magnetic resonance spectroscopy (MRS) as previously described (30). On day 29, participants reported to the CRC where their body weights, blood metabolic profiles, hepatic glucose production (HGP), and net substrate oxidation rates were measured after an overnight fast.

Each subject was studied on 5 different occasions as follows:

1. High-fructose diet (HFr): participants consumed, in addition to their weight-maintenance diet, 4 g fructose · kg body weight⁻¹ · d⁻¹ as lemon-flavored drinks taken during meals from days 23 to 28.

2. Subjects consumed 4 cups coffee/d prepared each with 3.4 g soluble, partially roasted caffeinated coffee high in chlorogenic acid (C-HCA) (containing 3.0% caffeine and 9% chlorogenic acid; NESCAFE GreenBlend; Nestlé) from days 15 to 28 as well as 4 g fructose · kg body weight⁻¹ · d⁻¹ from days 23 to 28.

3. Subjects consumed the same diet with 4 cups decaffeinated coffee prepared with partially roasted coffee with a high chlorogenic acid content [decaffeinated coffee high in chlorogenic acid (D-HCA)] (containing 0.3% caffeine and 9% chlorogenic acid; Decaffeinated NESCAFE GreenBlend; Nestlé).

4. Subjects consumed the same diet with 4 cups of coffee prepared with roasted decaffeinated coffee with regular amounts of chlorogenic acid (D-RCA) (containing 0.3% caffeine and 3% chlorogenic acid; Decaffeinated NESCAFE Gold; Nestlé).

5. Subjects consumed, during 14 d, an energy-balanced diet without fructose supplementation (control condition).

In all conditions, except the control condition, fructose was added to the weight-maintenance diet during the last 6 d, which resulted in a total energy intake that corresponded to 143 ± 1% of energy requirements. Participants were randomly allocated 1 of 5 study sequences with a balanced order of treatment: 1: control diet (C), HFr, C-HCA, D-HCA, and D-RCA; 2: HFr, C-HCA, D-HCA, D-RCA, and C; 3: C-HCA, D-HCA, D-RCA, C, and HFr; 4: D-HCA, D-RCA, C, HFr, and C-HCA; and 5: D-RCA, C, HFr, C-HCA, and D-HCA. Sequences were generated at the sponsor site, and a list of the sequences was kept in a sealed envelope. The treatment order was balanced. Participants and investigators were blinded to the type of coffee consumed, but not to the C or HFr because there was no suitable placebo to coffee or fructose. Compliance was checked by asking volunteers to return empty coffee bags to the laboratory at each visit.

**Assessment of ectopic lipid deposition**

Measurements of IHCL and IMCL concentrations were obtained by proton MRS. Measurements were performed on a clinical 3T magnetic resonance (MR) system (TIM Trio; Siemens Medical) as previously described (30). In short, to quantify IHCLs, a volume of interest of 19 mL was localized in the liver and evading large vessels and the proximity to extrahepatic fat by using a double-echo localization sequence combined with Siemens’ prospective acquisition correction scheme (MRS echo time: 30 ms; repetition time: between 2.5 and 6 s depending on the breathing rate). MRS was preceded by fast-spin echo MR imaging in 3 planes by using the same prospective acquisition-correction triggering to visualize the liver and to reliably reproduce the placement of the region of interest in follow-up examinations. Automatic fitting of the MR spectra was performed with the home-written software Fitting Tool for Arrays of Interrelated Datasets (31) by using previous knowledge restraints. The lipid spectrum was modeled with 9 Voigt lines. MR spectra were recorded with water suppression to determine lipid and metabolite spectra (32 scans, with the center frequency at 3 ppm) and without water suppression to acquire the water signal as an internal standard (16 scans with a center frequency at 4.7 ppm). IMCLs were measured in a volume of 2.4 cm³ in the tibialis anterior of the right leg according to Boesch et al (32) but at 3 T and by using an echo time of 30 ms and repetition time of 3s.

**Measurement of fasting metabolism**

On the morning of day 29, participants reported at 0700 to the CRC, Lausanne University Hospital, in the fasting state. On arrival, participants were requested to void and were weighed. Thereafter, they were transferred to a bed where they remained in a semirecumbent position for the next 2.5 h. Two venous catheters were inserted, one catheter into a vein of the left forearm, through which infusions of 6,6-²H₂ glucose (prime dose: 2 mg/kg over 10 min followed by a continuous infusion of 20 µg · kg⁻¹ · min⁻¹) and 1,1,2,3,3-³H₂ glycerol (prime dose: 90 µg/kg over 5 min followed by a continuous infusion of 9 µg · kg⁻¹ · min⁻¹) were infused for 2.5 h. The second catheter was inserted into a wrist vein on the right side to allow for the periodic withdrawal of blood samples. This hand was placed in a heated hand pad to ensure partial arterialization of venous blood. Blood samples were obtained before tracer infusion (baseline) and at 120, 135, and 150 min after the start of tracer infusions for the measurement of tracer, hormones, and substrate concentrations. Respiratory gas exchange was measured throughout the 150-min period with the use of an open circuit indirect calorimeter, Deltrac II (Datex Instruments).

**Body composition**

At baseline, body composition was assessed by using dual x-ray absorptiometry (iDXA; GE Healthcare), and body weight was measured. On days 15 and 29, body weight was recorded to the nearest 0.1 kg (Seca 708, Seca).
Blood analysis

Plasma was immediately separated from blood by centrifugation for 10 min at 4°C and 3600 × g. Samples were stored at −20°C until analysis. Plasma glucose (Glucose Analyzer II; Beckman Instruments), triglycerides (Randox Laboratories), nonesterified fatty acids (NEFAs; Wako Chemicals), and urinary nitrogen (Random Laboratories) were measured by using enzymatic methods; insulin was assessed by using a radioimmunoassay (Millipore).

After plasma deproteinization and partial purification over anion- and cation-exchange resins, plasma $^2$H$_2$-glucose and $^2$H$_5$-glycerol were acetylated in the presence of acetic anhydride and pyridine, and glycerol concentrations and $^2$H$_2$-glucose and $^2$H$_5$-glycerol enrichments were measured by using gas chromatography–mass spectrometry (Agilent Technologies).

Calculations

Basal metabolic and net substrate oxidation rates were calculated from respiratory gas exchange and the urinary nitrogen excretion rate by using the equations of Tappy and Schneiter (33). HGP and glycerol rates of appearance were calculated from plasma $^2$H$_2$-glucose and $^2$H$_5$-glycerol enrichment by using Steele’s equations for steady state conditions.

Statistical analysis

A statistical analysis was performed on data obtained from the 10 participants who completed all 5 experimental conditions. Two distinct hypotheses were tested. The first hypothesis was that the HFr would significantly alter the variables measured compared with the effect of the C (HFr compared with C; hypothesis 1); the second hypothesis was that all 3 tested coffees modulated the effects of the HFr (C-HCA, D-HCA, and D-RCA compared with HFr; hypothesis 2). Both hypotheses were tested by using mixed-model analysis and post hoc comparisons. Mixed models were fitted with the treatment as a fixed effect and the subject as a random effect. BMI at inclusion was added as a fixed covariate ( correlation structure. A single mixed model was used to test hypotheses 1 and 2 by treating the control condition as the reference group for testing the HFr and by using one-sided, Hommel-adjusted contrasts to compare each coffee with the HFr. This statistical analysis was chosen on the basis of the hypothesis that coffee would lower IHCL concentrations, fasting HGP, and plasma triglyceride concentrations through mechanisms related to an increased energy expenditure and enhanced lipid oxidation. This hypothesis has been well supported by several reports that showed that coffee or the potentially active compounds of coffee and tea increase lipolysis and lipid oxidation in humans (34, 35) or increase hepatic insulin sensitivity (21, 36). Therefore, we assumed that any alteration of these variables in a direction other than expected would reflect the effects of unaccounted confounding factors, such as noncompliance to the prescribed diet or changes in physical activity. Before the statistical analysis, data distributions and equality of variance were checked by using Shapiro’s and Bartlett’s tests. IHCL and plasma triglyceride concentrations were nonnormally distributed and were log transformed before the statistical analysis.

The sample size was calculated on the basis of previous data from our laboratory (37) that reported that IHCL accumulation was blunted by a mean (±2SD) of 4.3 ± 3.5 mmol/kg after 4 d high-fat, high-protein consumption compared with that with a high-fat diet (ie, an effect size (as defined by the ratio between the mean and SD of the difference) of 1.228). The hypothesis was that, in ≥1 of the 3 experimental conditions (α = 0.016), the consumption of coffee for 14 d would decrease intrahepatic lipid accumulation (primary outcome) to the same extent as would a high-protein diet (37). With the assumption of a power of 80%, dropout rate of 20%, and Pitman asymptotic relative efficiency of 0.864, the sample size was calculated to be 13 participants (PASS 6.0; NCSS). The statistical analysis was performed with R software (version 2.15.3) (38).

RESULTS

Body weight

Overall, body weight changes ± SDs between days 14 and 29 were $–0.96 ± 0.47, 0.28 ± 0.23, −0.67 ± 0.32, 0.34 ± 0.4, and −0.1 ± 0.38 kg in control, HFr, C-HCA, D-HCA, and D-RCA conditions, respectively (P = NS).

Intrahepatic, intramuscular, and blood lipid concentrations

Compared with the C, the HFr increased IHCL concentrations (P < 0.001; Figure 2A) and total plasma triglycerides (P = 0.018) significantly, whereas it decreased plasma NEFA (P < 0.001) and glycerol (P = 0.033) concentrations (Table 2). Endogenous glycerol production tended to decrease (P = 0.051; Table 2). None of the 3 tested coffees significantly altered these variables (Table 2). Intramyocellular lipid concentrations were unchanged after the HFr and were not altered by the different coffees (Table 2).

Basal metabolic rate and net substrate oxidation

The basal metabolic rate was $0.96 ± 0.04, 0.99 ± 0.03, 1.03 ± 0.05, 0.94 ± 0.03, and 1.04 ± 0.03 kcal/min with the C, HFr, C-HCA, D-HCA, and D-RCA respectively (P = NS). Compared with the C, the HFr decreased the net lipid oxidation (Figure 2B) and increased carbohydrate oxidation (Figure 2C) significantly (P = 0.011 and P = 0.0012, respectively). C-HCA and D-RCA increased lipid oxidation compared with the HFr significantly (P < 0.001 and P = 0.025, respectively; Figure 2B). Compared with the HFr, both C-HCA and D-RCA significantly decreased the net carbohydrate oxidation (P = 0.0014 and P = 0.006, respectively), whereas this decrease showed a trend with D-HCA (P = 0.074) (Figure 2C).

HGP

The HFr significantly increased HGP (P = 0.0016, Figure 2D), but basal fasting plasma glucose and insulin concentrations did not change significantly (Table 2). Compared with the HFr, D-HCA and D-RCA significantly decreased HGP (P = 0.031 and P = 0.016, respectively, Figure 2D), whereas there was only a trend with C-HCA (P = 0.057; Figure 2D). Fasting insulin and glucose concentrations remained unchanged compared with those with the HFr (Table 2).
DISCUSSION

A number of epidemiologic studies indicated that coffee consumption is associated with lower risk of diabetes and metabolic disorders independently of caffeine intake (7, 9, 11, 12). Furthermore, human and animal studies have also suggested that some, as yet unidentified, coffee polyphenols protect against oxidative stress, hepatic steatosis, and insulin resistance induced by hypercaloric diets (13, 25, 39, 40). The purpose of this study was to evaluate whether chlorogenic acid, which is a coffee polyphenol present in a high amount in green coffee bean (41), may prevent the development of hepatic steatosis and hepatic insulin resistance induced by short-term fructose overfeeding in humans. To test this hypothesis, we observed the effects of 3 different coffees, 2 coffees of which had a high chlorogenic acid content with or without caffeine, and one coffee that had with a regular chlorogenic acid content, in healthy, young men overfed for 6 d with fructose. Such fructose overfeeding is known to cause a substantial increase in intrahepatic lipid concentrations within a few days, together with an increase in fasting plasma triglycerides and HGP (27, 28). However, the relative roles of excess energy intake and dietary fructose remain unknown. It was recently observed that the consumption of hypercaloric high-glucose or high-fructose diets increased IHCLs and impaired hepatic insulin sensitivity (42, 43), whereas isocaloric high-glucose or high-fructose diets did not change IHCLs (43), and an hypercaloric high-fat diet did not impair hepatic insulin

![FIGURE 2. Mean (±SEM) effects of short-term fructose overfeeding (HFr) and coffees with varying amounts of chlorogenic acid and caffeine on IHCL (A), fasting lipid oxidation rates (B), fasting glucose oxidation rates (C), and fasting glucose Ra (D). n = 10 participants. ***, Compared with the C condition, ***, P < 0.01 and ****P < 0.001; Compared with the HFr for C-HCA, D-HCA, and D-RCA conditions, **P < 0.1, ***P < 0.05, ****P < 0.01, and *****P < 0.001, P values were obtained by using a single mixed model to test hypotheses 1 and 2 by treating the C condition as the reference group for testing the HFr and by using 1-sided, Hommel-adjusted contrasts to compare each coffee with the HFr. C, control diet; C-HCA, caffeinated coffee high in chlorogenic acid; D-HCA, decaffeinated coffee high in chlorogenic acid; D-RCA, decaffeinated coffee with regular amounts of chlorogenic acid; HFr, high-fructose diet; IHCL, intrahepatic cellular lipids; Ra, rate of appearance.]

<p>| TABLE 2 | Effect of short-term fructose overfeeding and coffee intake on fasting concentrations of metabolites related to glucose and lipid metabolism and on skeletal muscle lipid accumulation |</p>
<table>
<thead>
<tr>
<th>Control</th>
<th>HFr</th>
<th>C-HCA</th>
<th>D-HCA</th>
<th>D-RCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>0.94 ± 0.15</td>
<td>1.45 ± 0.21</td>
<td>1.31 ± 0.29</td>
<td>1.6 ± 0.23</td>
</tr>
<tr>
<td>NEFA (mmol/L)</td>
<td>0.53 ± 0.06</td>
<td>0.31 ± 0.06</td>
<td>0.37 ± 0.04</td>
<td>0.33 ± 0.05</td>
</tr>
<tr>
<td>Glycerol (µmol/L)</td>
<td>51 ± 7.2</td>
<td>37.1 ± 4.9</td>
<td>41.2 ± 29.2</td>
<td>35.6 ± 2.8</td>
</tr>
<tr>
<td>Glycerol Ra (µmol · kg⁻¹ · min⁻¹)</td>
<td>2.02 ± 0.3</td>
<td>1.76 ± 0.28</td>
<td>1.87 ± 0.35</td>
<td>1.77 ± 0.22</td>
</tr>
<tr>
<td>IMCLs (mmol/kg ww)</td>
<td>2.84 ± 0.46</td>
<td>2.86 ± 0.3</td>
<td>2.66 ± 0.51</td>
<td>2.9 ± 0.52</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.2 ± 0.1</td>
<td>5.2 ± 0.1</td>
<td>5.3 ± 0.2</td>
<td>5.4 ± 0.3</td>
</tr>
<tr>
<td>Insulin (mU/mL)</td>
<td>10.7 ± 0.9</td>
<td>11.6 ± 1</td>
<td>12.5 ± 1.4</td>
<td>12.3 ± 1.7</td>
</tr>
</tbody>
</table>

*Values are means ± SEMs. n = 10 participants. † † † † Compared with the control condition, † † † † P < 0.05 and † † † † † P < 0.01. P values were obtained by using a single mixed model to test hypotheses 1 and 2 by treating the control condition as the reference group for testing the HFr and by using 1-sided, Hommel-adjusted contrasts to compare each coffee with the HFr (C-HCA, D-HCA, and D-RCA, respectively, compared with the HFr). C-HCA, caffeinated coffee high in chlorogenic acid; D-HCA, decaffeinated coffee high in chlorogenic acid; D-RCA, decaffeinated coffee with regular amounts of chlorogenic acid; HFr, high-fructose diet; IMCL, intramyocellular lipid; NEFA, nonesterified fatty acid; Ra, rate of appearance; ww, wet weight.
sensitivity (42). Therefore, it is likely that these effects are more broadly related to carbohydrate overfeeding rather than to specific effects of fructose.

Contrary to our expectation, none of the 3 coffees significantly prevented the increase in IHCL concentration or development of hypertriglyceridemia. The coffees also failed to increase endogenous glycerol production or glycerol and NEFA concentrations, which indicated that the coffees did not overcome the fructose-induced inhibition of lipolysis. This result was in contrast with the observation that coffee consumption significantly reduced hepatic steatosis and improved glucose tolerance in high-fructose, high-fat fed rats independently of changes in body composition (40). The very high doses of coffee extract and simultaneous increase in dietary fat and fructose used in this study may have accounted for the difference. The failure of coffee to prevent the increase in IHCLs induced by short-term fructose overfeeding was also in contrast with epidemiologic studies that showed an inverse correlation between coffee intake and the prevalence of hepatic steatosis in humans (17, 44). Epidemiologic studies provide information on long-term effects of coffee and may reflect, in part, effects of coffee on body composition. In contrast, our 6-d overfeeding period was too short to induce clinically relevant changes in body fat mass and essentially reflected metabolic changes directly induced by excess fructose and energy consumption.

Although the coffees did not prevent an increase in IHCLs, all 3 coffees significantly attenuated the increase in fasting HGP induced by short-term fructose overfeeding. In addition, lipid oxidation was significantly increased with the coffee that contained caffeine and normal chlorogenic acid content and with the decaffeinated, high–chlorogenic acid coffee (Figure 2B). We can only speculate on the mechanisms by which coffee improved hepatic insulin sensitivity at this stage. First, 2 of the 3 tested coffees induced the stimulation of lipid oxidation and, hence, may have decreased intraplatelet concentrations of toxic lipid metabolites, even in the absence of a decrease in IHCLs; this effect would bear some similitude with exercise increasing muscle insulin sensitivity independently of changes in intramuscular lipid concentrations, which is a phenomenon referred to as “the athlete paradox” (45). Second, we did not observe significant changes in fasting energy expenditure on the day after exposure to the different coffees but hypothesized that the 24-h energy expenditure and substrate utilization may have increased during the initial days of coffee exposure (35); this effect may possibly have attenuated hepatic glycogen storage induced by fructose overfeeding. Consistent with this hypothesis, an association between glycogen storage and an increase in fasting HGP has been reported in healthy subjects after short-term carbohydrate overfeeding (46). Third, a decrease in fasting HGP may possibly be attributable to chlorogenic acid, which has been reported to inhibit glucose-6-phosphatase (47, 48). Although the statistical design of this exploratory study did not include direct comparisons of the 3 coffees tested, our results did not suggest that chlorogenic acid was primarily involved because this effect was observed with the partially roasted coffees (C-HCA and D-HCA) and fully roasted coffee (D-RCA) despite a 3:1 difference in the concentration of chlorogenic acid. Coffee extracts (39, 40, 49), single constituents of coffee such as caffeine (49), coffee polyphenols (13, 20, 21, 25, 50), and coffee melanoids (13) have all been reported to prevent the impact of dietary interventions on liver function, although sometimes at doses considerably higher than those in the current study. Therefore, it is possible that the reduction of endogenous glucose production was the result of the combination of several coffee bioactives. This issue may be even more complex because there may be genetically determined interindividual variations regarding the health effects of coffee (51). However, additional human studies, including measurements of energy expenditure and substrate oxidation throughout the period of coffee exposure, as well as animal studies that allow intrahepatic concentrations of substrate and lipid intermediates to be assessed, will be required to identify the mechanisms and bioactive compounds actually involved in these effects of coffee (34, 52, 53).

This study has several limitations that have to be kept in mind when evaluating the results. First, we studied the effects of caffeinated and decaffeinated, partially roasted coffees and decaffeinated, roasted coffee but not those of roasted, caffeinated coffee. Furthermore, we limited our statistical analysis to the comparison of each coffee with the HFr condition. Therefore, our statistical analysis did not include the direct comparison of the different coffees and respective roles of chlorogenic acid and caffeine present in the 3 coffees tested. These roles were only indirectly evaluated by assessing which coffee had, or had not, a significant effect. With this exploratory approach, we were able to document a robust, significant effect of the coffees on hepatic insulin resistance and lipid oxidation. However, additional, specifically designed studies will be needed to directly evaluate the effects of coffee compounds of interest. Second, we evaluated effects of coffees with an experimental, short-term, hypercaloric, high-fructose diet. This protocol was convenient because it is known to induce highly reproducible metabolic alterations that mimic some features of the metabolic syndrome. However, the metabolic alterations induced by an HFr differ markedly from those observed in subjects with the metabolic syndrome in whom high fatty acid fluxes secondary to increased fat mass may play a prominent role in ectopic lipid deposition (54). Finally, we were unable to provide study participants with any satisfactory placebo in the C and HFr conditions, and therefore, participants were blinded to the type of coffee they consumed but not to the fact that they consumed coffee.

In conclusion, our current results indicate that the consumption of several coffees with varying chlorogenic acid contents did not prevent intrahepatic lipid accumulation but significantly attenuated the hepatic insulin resistance induced by short-term fructose overfeeding. These effects could not be specifically attributed to chlorogenic acid or caffeine and may possibly be caused by other, as yet unidentified, active compounds.

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The authors’ responsibilities were as follows—LT, RK, C Boesch, and CD: designed the study; C Binnert, GC, LE, and PS: recruited participants; C Binnert, GC, and LE: performed tests and the laboratory analysis; AB and RK: performed MR measurements; C Boesch, RK, and ELM: performed the MRS analysis; VL and LE: performed the statistical analysis; LT and VL: drafted the manuscript; and all authors: revised the manuscript, read and
approved the final manuscript, and had access to the full text. CD had no conflicts of interest.

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