Low to moderate sugar-sweetened beverage consumption impairs glucose and lipid metabolism and promotes inflammation in healthy young men: a randomized controlled trial¹–⁴

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ABSTRACT

Background: Sugar-sweetened beverages (SSBs) have unfavorable effects on glucose and lipid metabolism if consumed in high quantities by obese subjects, but the effect of lower doses in normal-weight subjects is less clear.

Objective: The aim was to investigate the effects of SSBs consumed in small to moderate quantities for 3 wk on LDL particle distribution and on other parameters of glucose and lipid metabolism as well as on inflammatory markers in healthy young men.

Design: Twenty-nine subjects were studied in a prospective, randomized, controlled crossover trial. Six 3-wk interventions were assigned in random order as follows: 600 mL SSBs containing 1) 40 g fructose/d [medium fructose (MF)], 2) 80 g fructose/d [high fructose (HF)], 3) 40 g glucose/d [medium glucose (MG)], 4) 80 g glucose/d [high glucose (HG)], 5) 80 g sucrose/d [high sucrose (HS)], or 6) dietary advice to consume low amounts of fructose. Outcome parameters were measured at baseline and after each intervention.

Results: LDL particle size was reduced after HF by −0.51 nm (95% CI: −0.19, −0.82 nm) and after HS by −0.43 nm (95% CI: −0.12, −0.74; P < 0.05 for both). Similarly, a more atherogenic LDL subclass distribution was seen when fructose-containing SSBs were consumed (MF, HF, and HS: P < 0.05). Fasting glucose and high-sensitivity C-reactive protein (hs-CRP) increased significantly after all interventions (by 4–9% and 60–109%, respectively; P < 0.05); leptin increased during interventions with SSBs containing glucose only (MG and HG: P < 0.05).

Conclusion: The present data show potentially harmful effects of low to moderate consumption of SSBs on markers of cardiovascular risk such as LDL particles, fasting glucose, and hs-CRP within just 3 wk in healthy young men, which is of particular significance for young consumers. This trial was registered at clinicaltrials.gov as NCT01021969.


INTRODUCTION

Sugar-sweetened beverages (SSBs) are the most commonly consumed caloric beverages and the leading source of added sugars in the United States and in many other Western countries (1). The development of the obesity epidemic in the United States runs in parallel to the increase in free fructose consumption as a result of the introduction of high-fructose corn syrup as a beverage sweetener (2). Whether there is a causal relation between the 2 events remains unclear. There is, however, strong epide-
Subjects and methods

Study design

The entire study consisted of a baseline examination followed by 6 different interventions in random sequence. Each of the interventions lasted 3 wk and was directly followed by an examination in our clinic. Thereafter, a washout period of a minimum of 4 wk was implemented before the beginning of the next intervention. The first subject included underwent the baseline examination in July 2007, and the last subject completed the study in May 2010. During 5 of the 6 interventions, subjects were supplied with SSBs containing fructose, glucose, or sucrose, in amounts likely to be consumed in everyday life and over a limited time period, on lipid and glucose metabolism with a particular focus on LDL particle size and inflammatory markers in healthy young men.
the part derived from the disaccharide sucrose (50% fructose and 50% glucose).

Laboratory analysis

Blood glucose was directly measured from whole-blood samples from the finger stick (both fasting and 2-h samples) by using plasma referenced reflection photometry (Reflotron Sprint; Roche, Basel, Switzerland). The venous blood samples were centrifuged, and the serum and plasma were either directly processed (lipid profile) or stored at −20°C for further analysis. Triglycerides, cholesterol, and free fatty acids were measured in fresh serum with a Roche MODULAR by enzymatic reactions (triglyceride GPO-PAP and cholesterol CHOP-PAP; Roche Diagnostics, Mannheim, Germany), with a Roche INTEGRA by a homogenous enzymatic color reaction (HDL cholesterol plus third generation; Roche Diagnostics) and with a Ketolab (Free Fatty Acids; Thermo Scientific, Dreieich, Germany). Also in fresh serum, aspartate aminotransferase and alanine aminotransferase were determined by enzymatic reaction. From frozen serum, C-peptide was measured by using radioimmunoassay (RIA) (IRMA-C-Pep; CIS Bio International, Bagnols-sur-Cèze Cedex, France), leptin was measured by using ELISA (EZLH-80 SK; Linco Research Inc, St Charles, MO), adiponectin and high-sensitivity CRP (hs-CRP) were also measured by using ELISA (DRP300 and DCRP00; R&D Systems, Minneapolis, MN), and ghrelin was measured by using RIA (R90; Mediadost, Reutlingen, Germany). LDL size and subclasses were determined in frozen samples. For analysis of LDL size and subclasses, nonnadenaturing polyacrylamide gradient gel electrophoresis of plasma was performed and analyzed as described elsewhere (20–22). LDL subclass distribution as a percentage of total LDL was calculated as previously described (20).

Insulin resistance was estimated from fasting glucose and C-peptide concentrations by using a computer-based homeostasis model assessment system (HOMA2-IR) provided by the Oxford Center for Diabetes, Endocrinology, and Metabolism (http://www.dtu.ox.ac.uk/homa). This approach has been previously validated for studies with a similar design (23).

Statistical analysis

Statistical analysis was performed by using the statistical package PASW 18.0 for Windows (SPSS Inc, Chicago, IL). All variables were checked for normal distribution before data analysis. Data are expressed as arithmetic means ± SDs for normally distributed variables and as geometric means ± SDs for nonnormally distributed data. Nonnormally distributed data were log-transformed, and further analysis was carried out with the transformed data. According to the intention-to-treat design of the study, all subjects (completers and noncompleters) were included in the final analysis. The effect of the interventions as well as their order on anthropometric and metabolic parameters were examined by using multiple linear regression (as described in reference 24), with baseline parameters and between-patient differences controlled for. Post hoc Bonferroni correction was applied to account for multiple comparisons. For the comparison of the different interventions to baseline, a correction factor of 6 was used (6 interventions), whereas between interventions (HG compared with HF compared with HS), a corrections factor of 2 was used. Considering a P value <0.05 to be significant (α = 0.05) and a P value <0.01 to be highly significant (α = 0.01), the resulting α levels were $z^*$ = 0.0083 and $z^{**}$ = 0.0017 for comparison to baseline and $z' = 0.025$ and $z'' = 0.005$ for comparison between high sugar interventions. All α levels discussed in Results were Bonferroni-corrected if necessary.

RESULTS

A total of 29 subjects were randomly assigned. The mean study duration from baseline measurements until the end of the last intervention was 44 wk (range: 10–90 wk). The mean (±SD) age of the subjects at baseline was 26.3 ± 6.6 y. The important anthropometric and biochemical data are summarized in Table 1. Whereas a significant change in BMI and weight was observed only in the MG intervention, waist-to-hip ratio was significantly higher in all interventions containing fructose (range: 0.92 ± 0.05 to 0.93 ± 0.05) compared with baseline (0.92 ± 0.06) ($P < 0.0083$). When only the interventions with high sugar doses (HG, HF, and HS) were compared, a significantly higher percentage body fat in the HF intervention than in the HG intervention (15.7 ± 3.2% compared with 15.1 ± 3.4%, $P < 0.005$) and a significantly higher waist circumference in the HS intervention than in the HG intervention (82.9 ± 5.5 compared with 82.6 ± 5.6 cm, $P < 0.005$) were observed.

LDL particle size decreased significantly only after the HF intervention (−0.51 ± 0.80 nm) and HS (−0.43 ± 0.81 nm) interventions compared with baseline ($P < 0.0083$). Both fructose interventions (MF and HF) and HS significantly decreased the large LDL I subclass ($P < 0.0083$), whereas there was no significant increase in small, dense particles. When only HG, HS, and HF interventions where compared, there was a significant difference of the LDL I subclass between the HG and the 2 fructose-containing interventions (Figure 1). The traditional lipid profile parameters (total, LDL, and HDL cholesterol and triglycerides) did not change.

hs-CRP concentrations increased significantly after all of the interventions, with the highest value after the HF intervention (430.1 ± 1697.2 ng/mL, $P < 0.0017$) compared with baseline (205.6 ± 430.7 ng/mL). No significant changes were observed in the adipokines analyzed (Table 1), with the exception of leptin, which increased significantly after the 2 interventions containing glucose only: MG (+0.25 ± 1.38 ng/mL, $P < 0.0083$) and HG (+0.63 ± 0.93 ng/mL, $P < 0.0017$). Liver function did not change after any of the interventions.

Fasting glucose increased significantly after all of the interventions (range: 4.64 ± 0.50 to 4.84 ± 0.30 mmol/L) compared with baseline (4.45 ± 0.45 mmol/L) ($P < 0.0083$). With regard to HOMA2 IR and C-peptide, there was an increase after the HF intervention, although it was not significant after Bonferroni correction (Table 1).

Intakes of energy, the different sugars, macronutrients, fibers, and β-carotene at baseline and during each of the 6 interventions are described in Table 2. Dietary intake of the different sugars varied widely according to the specific interventions. Despite those variations, total energy intake did not differ significantly between the baseline and any of the 6 interventions. Mean energy intake during all interventions was 2507 kcal/d. The different interventions thus provided 6.5% (MF and MG) and 13.1% (HF, HG, and HS) of total daily energy in the form of
Table 1
Anthropometric measures, LDL size and subclasses, high-sensitivity C-reactive protein (hs-CRP), adipokines, glucose metabolism, and liver function tests of the 29 subjects at baseline and after the 6 different interventions. 

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>MF</th>
<th>MG</th>
<th>HF</th>
<th>HG</th>
<th>HS</th>
<th>LF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)²</td>
<td>73.7 ± 8.8</td>
<td>73.9 ± 9.1</td>
<td>74.3 ± 9.1*</td>
<td>73.8 ± 8.9</td>
<td>73.6 ± 9.2</td>
<td>74.4 ± 8.6</td>
<td>74.1 ± 8.7</td>
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<tr>
<td>BMI (kg/m²)³</td>
<td>22.4 ± 1.9</td>
<td>22.4 ± 2.0</td>
<td>22.6 ± 2.0*</td>
<td>22.4 ± 1.9</td>
<td>22.4 ± 1.9</td>
<td>22.5 ± 1.8</td>
<td>22.4 ± 1.8</td>
</tr>
<tr>
<td>Body fat (%)³</td>
<td>15.4 ± 3.1</td>
<td>15.2 ± 3.1</td>
<td>15.5 ± 3.2</td>
<td>15.7 ± 3.2*</td>
<td>15.1 ± 3.4</td>
<td>15.2 ± 3.2</td>
<td>15.4 ± 2.8</td>
</tr>
<tr>
<td>Body fat (kg)³</td>
<td>11.6 ± 3.4</td>
<td>11.5 ± 3.4</td>
<td>11.7 ± 3.4</td>
<td>11.8 ± 3.4</td>
<td>11.3 ± 3.6</td>
<td>11.5 ± 3.3</td>
<td>11.6 ± 3.2</td>
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<tr>
<td>Waist circumference (cm)³</td>
<td>82.5 ± 5.7</td>
<td>82.3 ± 5.5</td>
<td>82.7 ± 5.7</td>
<td>82.6 ± 5.8</td>
<td>82.6 ± 5.6</td>
<td>82.9 ± 5.5††</td>
<td>82.5 ± 5.4</td>
</tr>
<tr>
<td>Waist-to-hip ratio³</td>
<td>0.92 ± 0.06</td>
<td>0.93 ± 0.05**</td>
<td>0.92 ± 0.05</td>
<td>0.93 ± 0.05**</td>
<td>0.92 ± 0.05</td>
<td>0.92 ± 0.05**</td>
<td>0.91 ± 0.05</td>
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<tr>
<td>Systolic blood pressure (mm Hg)²</td>
<td>125.9 ± 8.5</td>
<td>125.5 ± 8.6</td>
<td>126.5 ± 8.5</td>
<td>124.9 ± 8.8</td>
<td>123.6 ± 7.6</td>
<td>126.9 ± 8.7</td>
<td>124.2 ± 9.3</td>
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<tr>
<td>Diastolic blood pressure (mm Hg)²</td>
<td>74.1 ± 8.5</td>
<td>72.0 ± 6.3</td>
<td>72.0 ± 6.2</td>
<td>74.2 ± 9.1</td>
<td>71.5 ± 5.6</td>
<td>72.7 ± 7.0</td>
<td>73.0 ± 7.7</td>
</tr>
<tr>
<td>LDL size (nm)²</td>
<td>27.71 ± 0.76</td>
<td>27.62 ± 1.38</td>
<td>27.30 ± 0.85</td>
<td>27.24 ± 0.82*</td>
<td>27.61 ± 1.30</td>
<td>27.27 ± 1.04*</td>
<td>27.51 ± 0.67</td>
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<tr>
<td>LDL subclasses (%)²</td>
<td></td>
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<tr>
<td>I</td>
<td>34.3 ± 8.3</td>
<td>31.7 ± 7.6*</td>
<td>31.8 ± 7.4</td>
<td>30.2 ± 7.3**†</td>
<td>33.0 ± 7.4</td>
<td>30.0 ± 7.4**††</td>
<td>32.7 ± 7.3</td>
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<tr>
<td>IIa</td>
<td>16.4 ± 3.2</td>
<td>16.2 ± 3.7</td>
<td>17.0 ± 3.2</td>
<td>17.2 ± 3.6</td>
<td>16.3 ± 2.9</td>
<td>17.2 ± 3.4</td>
<td>17.7 ± 2.9</td>
</tr>
<tr>
<td>IIb</td>
<td>15.4 ± 2.4</td>
<td>16.5 ± 2.7*</td>
<td>17.0 ± 3.0**</td>
<td>17.6 ± 2.8*</td>
<td>16.1 ± 2.7</td>
<td>17.6 ± 3.2**</td>
<td>16.3 ± 2.6</td>
</tr>
<tr>
<td>IIIa</td>
<td>12.0 ± 2.8</td>
<td>12.9 ± 3.5</td>
<td>12.7 ± 3.8</td>
<td>13.4 ± 4.1*</td>
<td>13.0 ± 3.6</td>
<td>13.6 ± 4.0**</td>
<td>12.3 ± 2.0</td>
</tr>
<tr>
<td>IIIb</td>
<td>5.4 ± 1.1</td>
<td>6.0 ± 1.8</td>
<td>5.6 ± 1.2</td>
<td>5.8 ± 1.2</td>
<td>5.9 ± 1.2</td>
<td>5.9 ± 1.2</td>
<td>5.4 ± 1.1</td>
</tr>
<tr>
<td>IVa</td>
<td>7.7 ± 1.8</td>
<td>8.3 ± 2.2</td>
<td>7.4 ± 1.7</td>
<td>7.6 ± 1.3</td>
<td>7.5 ± 1.6</td>
<td>7.7 ± 1.6</td>
<td>7.5 ± 1.6</td>
</tr>
<tr>
<td>IVb</td>
<td>8.8 ± 2.8</td>
<td>8.5 ± 2.0</td>
<td>8.4 ± 2.3</td>
<td>8.1 ± 1.7</td>
<td>8.1 ± 2.0</td>
<td>8.0 ± 1.9</td>
<td>8.1 ± 2.3</td>
</tr>
<tr>
<td>hs-CRP (ng/mL)²</td>
<td>205.6 ± 430.7</td>
<td>374.6 ± 1182.1***</td>
<td>394.4 ± 1258.4**</td>
<td>430.1 ± 1697.2**</td>
<td>390.1 ± 2336.2**</td>
<td>422.4 ± 1393.4**</td>
<td>329.1 ± 662.0**</td>
</tr>
<tr>
<td>Leptin (ng/mL)²</td>
<td>1.21 ± 1.68</td>
<td>1.31 ± 1.36</td>
<td>1.44 ± 1.29*</td>
<td>1.75 ± 1.83</td>
<td>1.83 ± 1.96**</td>
<td>1.48 ± 1.34</td>
<td>1.24 ± 0.80</td>
</tr>
<tr>
<td>Adiponectin (pg/mL)²</td>
<td>6.44 ± 7.69</td>
<td>7.39 ± 4.39</td>
<td>7.40 ± 2.37</td>
<td>7.64 ± 2.95</td>
<td>7.77 ± 2.76</td>
<td>7.57 ± 10.00</td>
<td>7.61 ± 12.09</td>
</tr>
<tr>
<td>Ghrelin (pg/mL)²</td>
<td>7.18 ± 414</td>
<td>7.28 ± 359</td>
<td>7.80 ± 365</td>
<td>7.89 ± 415</td>
<td>7.34 ± 324</td>
<td>7.50 ± 377</td>
<td>692 ± 320</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)²</td>
<td>4.45 ± 0.45</td>
<td>4.70 ± 0.32**</td>
<td>4.81 ± 0.30**</td>
<td>4.64 ± 0.50*</td>
<td>4.68 ± 0.33**</td>
<td>4.76 ± 0.34**</td>
<td>4.84 ± 0.30**</td>
</tr>
<tr>
<td>Postprandial glucose (2 h) (mmol/L)²</td>
<td>5.09 ± 0.94</td>
<td>4.73 ± 0.58</td>
<td>4.97 ± 0.60</td>
<td>4.84 ± 0.61</td>
<td>4.97 ± 0.59</td>
<td>5.21 ± 0.66</td>
<td>5.38 ± 0.73</td>
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<tr>
<td>C-peptide (pmol/L)²</td>
<td>128 ± 223</td>
<td>115 ± 206</td>
<td>92 ± 363</td>
<td>157 ± 251</td>
<td>103 ± 197</td>
<td>102 ± 189</td>
<td>113 ± 218</td>
</tr>
<tr>
<td>HOMA2 IR²</td>
<td>0.27 ± 0.48</td>
<td>0.25 ± 0.45</td>
<td>0.20 ± 0.78</td>
<td>0.34 ± 0.52</td>
<td>0.22 ± 0.42</td>
<td>0.22 ± 0.41</td>
<td>0.26 ± 0.47</td>
</tr>
<tr>
<td>Free fatty acids (µmol/L)²</td>
<td>319 ± 180.1</td>
<td>306.6 ± 170.1</td>
<td>307.6 ± 217.6</td>
<td>296.9 ± 184.7</td>
<td>327.6 ± 175.9</td>
<td>307.9 ± 164.7</td>
<td>332.1 ± 169.5</td>
</tr>
<tr>
<td>AST (U/L)²</td>
<td>26 ± 6</td>
<td>27 ± 6</td>
<td>28 ± 7</td>
<td>27 ± 8</td>
<td>28 ± 6</td>
<td>29 ± 9</td>
<td>28 ± 7</td>
</tr>
<tr>
<td>ALT (U/L)²</td>
<td>23 ± 7</td>
<td>25 ± 11</td>
<td>26 ± 10</td>
<td>25 ± 9</td>
<td>25 ± 10</td>
<td>25 ± 13</td>
<td>23 ± 8</td>
</tr>
</tbody>
</table>

¹ MF, moderate fructose (40 g fructose/d); MG, moderate glucose (40 g glucose/d); HF, high fructose (80 g fructose/d); HG, high glucose (80 g glucose/d); HS, high sucrose (80 g sucrose/d); LF, low fructose (dietary advice to consume low fructose); AST, aspartate aminotransferase; ALT, alanine aminotransferase; HOMA2 IR, computer-based homeostasis model assessment system (provided by the Oxford Center for Diabetes, Endocrinology, and Metabolism; http://www.dtu.ox.ac.uk/home). 
² Significantly different from baseline on the basis of multiple linear regression with Bonferroni correction for multiple comparisons (P < 0.05; 0.0083, corresponds to P < 0.05 after correction). 
³ Significantly different from baseline on the basis of multiple linear regression with Bonferroni correction for multiple comparisons (P < 0.05; 0.0017, corresponds to P < 0.01 after correction). 
⁴ Significantly different from baseline on the basis of multiple linear regression with Bonferroni correction for multiple comparisons (P < 0.01; 0.005, corresponds to P < 0.01 after correction). 
⁵ Values are arithmetic means ± SDs. 
⁶ Values are geometric means ± SDs.
Protein (% of energy) 15.3
Fat (% of energy) 36.5
Fiber (g/d) 22.1
Carbohydrates (% of energy) 48.4
Carotene (mg/d) 4.6
Free glucose (g/d) 14.0
Total fructose (g/d) 48.4
Total cholesterol (mg/dL) 2329
VLDL cholesterol (mg/dL) 154
LDL cholesterol (mg/dL) 105
HDL cholesterol (mg/dL) 48
Glucose (mg/dL) 80
Insulin (mU/mL) 5.1
BMI (kg/m²) 26
Waist circumference (cm) 88
Hip circumference (cm) 79
Waist-to-hip ratio 1.0
Systolic blood pressure (mm Hg) 120
Diastolic blood pressure (mm Hg) 78

**DISCUSSION**

This is the first study to show adverse effects of low to moderate consumption of fructose-, glucose-, and sucrose-containing beverages over a period of only 3 wk on LDL size and other parameters of lipid and glucose metabolism as well as on inflammatory response in healthy young men. Even with lower doses (40 g sugar/d), which provided just 6.5% of daily energy in the form of SSBs, adverse effects could be observed with regard to LDL particle size and distribution, waist-to-hip ratio, fasting glucose, and inflammatory markers. Previous studies in humans have also shown negative effects of high fructose consumption, mainly with regard to dyslipidemia and insulin resistance, but these studies provided ≥25% of daily energy in the form of fructose, amounts which are rarely consumed in everyday life (15, 16).

In the present study, waist-to-hip ratio increased significantly compared with baseline after the fructose and sucrose but not after the glucose interventions. Although the change in waist-to-hip ratio within 3 wk was small, we think that this finding is still worrisome since it shows the effects of only 3 wk of consumption of SSBs in young healthy men. This is in accordance with the

**TABLE 2**

Dietary intake of the 29 subjects at baseline and after different interventions

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>MF</th>
<th>MG</th>
<th>HF</th>
<th>HG</th>
<th>HS</th>
<th>LF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy (kcal/d)</td>
<td>2329 ± 523</td>
<td>2431 ± 671</td>
<td>2505 ± 382</td>
<td>2468 ± 559</td>
<td>2533 ± 518</td>
<td>2596 ± 576</td>
<td>2340 ± 714</td>
</tr>
<tr>
<td>Free fructose (g/d)</td>
<td>16.1 ± 9.0</td>
<td>54.9 ± 10.1**</td>
<td>16.8 ± 8.8</td>
<td>91.6 ± 8.6**</td>
<td>16.9 ± 9.0</td>
<td>13.4 ± 9.6</td>
<td>7.2 ± 6.8**</td>
</tr>
<tr>
<td>Total fructose (g/d)</td>
<td>48.4 ± 23.0</td>
<td>85.0 ± 26.0**</td>
<td>49.4 ± 22.0</td>
<td>115.9 ± 18.9**</td>
<td>46.6 ± 19.7</td>
<td>78.6 ± 21.3**</td>
<td>33.7 ± 24.1*</td>
</tr>
<tr>
<td>Free glucose (g/d)</td>
<td>14.0 ± 6.8</td>
<td>12.4 ± 6.4</td>
<td>54.3 ± 6.2**</td>
<td>11.4 ± 6.2</td>
<td>92.9 ± 5.8**</td>
<td>14.0 ± 13.6</td>
<td>8.0 ± 7.1</td>
</tr>
<tr>
<td>Total glucose (g/d)</td>
<td>46.3 ± 21.0</td>
<td>42.5 ± 23.6</td>
<td>86.8 ± 19.5**</td>
<td>35.8 ± 16.7</td>
<td>122.7 ± 17.9**</td>
<td>79.2 ± 21.2**</td>
<td>34.5 ± 24.3</td>
</tr>
<tr>
<td>Sucrose (g/d)</td>
<td>64.6 ± 33.9</td>
<td>60.1 ± 39.1</td>
<td>65.1 ± 34.2</td>
<td>48.6 ± 25.5</td>
<td>59.5 ± 28.2</td>
<td>130.4 ± 30.3**</td>
<td>53.1 ± 37.3</td>
</tr>
<tr>
<td>Carbohydrates (% of energy)</td>
<td>48.4 ± 6.7</td>
<td>50.9 ± 6.0</td>
<td>52.5 ± 9.1*</td>
<td>54.9 ± 5.0**</td>
<td>56.5 ± 4.8**</td>
<td>54.8 ± 6.2**</td>
<td>45.8 ± 7.5</td>
</tr>
<tr>
<td>Protein (% of energy)</td>
<td>15.3 ± 2.5</td>
<td>14.4 ± 2.6</td>
<td>13.1 ± 3.1**</td>
<td>13.5 ± 2.2*</td>
<td>12.8 ± 2.5**</td>
<td>13.0 ± 1.8**</td>
<td>16.3 ± 2.6</td>
</tr>
<tr>
<td>Fat (% of energy)</td>
<td>36.5 ± 6.3</td>
<td>34.7 ± 6.6</td>
<td>31.9 ± 5.9**</td>
<td>31.5 ± 4.7**</td>
<td>30.5 ± 4.1**</td>
<td>32.2 ± 5.9</td>
<td>38.0 ± 7.1</td>
</tr>
<tr>
<td>Fiber (g/d)</td>
<td>22.1 ± 7.6</td>
<td>19.9 ± 6.4</td>
<td>22.3 ± 7.4</td>
<td>20.0 ± 6.3</td>
<td>19.9 ± 5.5</td>
<td>21.4 ± 7.6</td>
<td>18.7 ± 5.4</td>
</tr>
<tr>
<td>Carotene (mg/d)</td>
<td>4.6 ± 4.6</td>
<td>2.8 ± 1.9*</td>
<td>3.2 ± 2.0*</td>
<td>2.8 ± 1.9*</td>
<td>2.6 ± 1.2**</td>
<td>2.9 ± 2.1**</td>
<td>2.2 ± 2.3**</td>
</tr>
</tbody>
</table>

*All values are arithmetic means ± SDs. MF, moderate fructose (40 g fructose/d); MG, moderate glucose (40 g glucose/d); HF, high fructose (80 g fructose/d); HG, high glucose (80 g glucose/d); HS, high sucrose (80 g sucrose/d); LF, low fructose (dietary advice to consume low free fructose).

**DISCUSSION**

This is the first study to show adverse effects of low to moderate consumption of fructose-, glucose-, and sucrose-containing beverages over a period of only 3 wk on LDL size and other parameters of lipid and glucose metabolism as well as on inflammatory response in healthy young men. Even with lower doses (40 g sugar/d), which provided just 6.5% of daily energy in the form of SSBs, adverse effects could be observed with regard to LDL particle size and distribution, waist-to-hip ratio, fasting glucose, and inflammatory markers. Previous studies in humans have also shown negative effects of high fructose consumption, mainly with regard to dyslipidemia and insulin resistance, but these studies provided ≥25% of daily energy in the form of fructose, amounts which are rarely consumed in everyday life (15, 16).

In the present study, waist-to-hip ratio increased significantly compared with baseline after the fructose and sucrose but not after the glucose interventions. Although the change in waist-to-hip ratio within 3 wk was small, we think that this finding is still worrisome since it shows the effects of only 3 wk of consumption of SSBs in young healthy men. This is in accordance with the
findings of Stanhope et al (15), whose results suggested that fructose consumption may specifically promote lipid deposition in visceral adipose tissue, particularly in men, whereas glucose consumption appears to favor lipid deposition in subcutaneous adipose tissue. Furthermore, in accordance with this finding, a significant increase in leptin concentrations was seen only in the interventions that did not contain any fructose but only glucose. This is also in agreement with previous studies showing that leptin production is higher in subcutaneous adipocytes compared with omental adipocytes (25, 26).

Even though we found no effect of any of the different diets on the traditional lipid profile, a reduction in large, buoyant LDL particles (LDL 1) was observed during interventions containing fructose (MF, HF, and HS). In addition, when comparing the effects of 80 g glucose, 80 g fructose, and 80 g sucrose, it was shown that large LDL particles decreased significantly after the HF and HS intervention compared with the HG intervention. Interestingly, LDL size decreased during the HF and HS intervention. Those findings are in line with a meta-analysis investigating the effect of fructose interventions (providing \( \geq 100 \) g fructose/d) in which no adverse effect on triglycerides was observed (27). Moreover, we were able to confirm our previous findings in overweight children (3) in normal-weight individuals, namely that fructose intake is inversely associated with LDL particle size. Even though we found the strongest effect on LDL particle size after the HF diet, the sucrose diet also led to a significant reduction, indicating that this sugar may be harmful with regard to lipid metabolism. This is consistent with a recent study that showed that high-fructose and high-glucose diets led to similar increases in VLDL triacylglycerols (28). A study by Stanhope et al (15) found that both LDL and small dense LDL increased with fructose- but not with glucose-sweetened beverages; however, this was in a population of overweight/obese adults and sugar amounts were higher (25%).

Subclinical inflammation has been shown to be a key factor in the development of insulin resistance and cardiovascular disease (29, 30). Fructose can activate inflammatory pathways such as nuclear transcription factor \( \kappa B \) in animal models (31). Sorensen et al (9) found in a 10-wk intervention study that CRP concentrations increased in the sucrose group although they decreased in the sweeteren group. Furthermore, Schulze et al (8) showed a positive association between dietary patterns high in SSBs and markers of inflammation in an observational study. In the present study we were able to show for the first time to our knowledge that SSB consumption markedly increases hs-CRP concentrations in humans.

We found elevated fasting glucose concentrations after all interventions. Stanhope et al (15) observed in a population of overweight/obese adults that fasting glucose increased with fructose- but not with glucose-sweetened beverages. These discrepancies may, as described above, well be due to differences in the study protocol. In the present study, there was an increase albeit not significant in both C-peptide and HOMA2-IR after the fructose interventions. Thus, 3-wk consumption of SSBs seems to be sufficient to induce subtle changes in glucose metabolism that may over the long term lead to insulin resistance. Several previous studies have found effects on fasting glucose or insulin resistance after the ingestion of high-fructose but not high-glucose diets (12, 15, 32, 33), although the results have not been always consistent (28, 33). However, the amounts of sugar used in the studies mentioned above were considerably higher compared with those in our study. In the present study, an increase in fasting glucose was also found after the LF intervention. A potential explanation for this observation is that dietary patterns may have been altered during the LF intervention toward a diet with a high glycemic load, indicated by lower fiber and \( \beta \)-carotene consumption.

We found differential effects between glucose and fructose on waist-to-hip ratio (reflecting visceral fat deposition) and on LDL subfraction distribution, both suggesting a more detrimental effect of fructose compared with glucose. These differences may be due, at least in part, to the fact that although calorically identical to glucose intake, fructose metabolism differs considerably from that of glucose (2, 34). For example, fructose, unlike glucose, has been shown to increase de novo lipogenesis (15). Moreover, the rate of hepatic uptake of fructose from the portal circulation is greater than the rate of glucose uptake; furthermore, fructose metabolism bypasses phosphofructokinase, and thus is not under the regulatory control of insulin (34).

The main limitation of the present study is that the 3-wk intervention period may not have been long enough to observe significant effects in parameters such as lipoprotein concentrations, insulin resistance, adipokines, body weight, and blood pressure, which were previously described by others (15, 35–37). However, it should be pointed out that the studies showing such associations either used very high amounts of SSBs (\( \geq 25\% \) of the total daily energy requirements) or had a nonrandomized design. In addition, the crucial aim of this study was to mimic sugar dosages comparable to those used in commercially available SSBs, thereby allowing us to draw clinically relevant conclusions. Daily consumption of 4–8 dL of SSBs for 3 wk (eg, during vacations) is much more relevant and closer to real life than is a 2- to 3-mo consumption of several liters of SSBs. However, it still has to be clearly pointed out that 4 of the 5 SSB interventions used in the current study had a composition not generally found in commercially available SSBs because they contained either only fructose or only glucose. Thus, even though the amounts of sugar used mimicked a real-life situation, the sugar composition itself did not. However, for the further development of new products, especially with regard to healthier diets, it is of utmost importance to understand the effects of the different sugar components both individually and combined.

Another limitation is the possibility of carryover effects between the different interventions as well as the time difference between measurements at baseline and after the interventions. To limit this possible bias, a randomly assigned order of the interventions was chosen and a washout period of \( \geq 4 \) wk was included in the study protocol. Furthermore, the effects of the interventions themselves were separated from the effects of the order of the interventions by multiple linear regression. This analysis indeed showed differences of 2 parameters—waist-to-hip ratio and fasting glucose—between the first and the last intervention that were independent of the type of the intervention. Although the interventions lasted only 3 wk and the washout periods 4 wk, the adverse changes produced by SSBs seem to have accumulated over the entire study period.

In conclusion, this study clearly shows that consumption of SSBs, even in moderate amounts, has adverse effects on lipid and glucose metabolism as well as on the inflammatory status of healthy young men. It also shows that even though there are differential effects caused by the different sugars, all of them
LOW AMOUNTS OF SSBs IMPAIR GLUCOSE AND LIPID METABOLISM

seem to be detrimental to some extent. Therefore, not only does chronic consumption of high amounts of SSBs in predisposed subjects increase cardiovascular risk markers but it appears that only a few weeks of moderate consumption in healthy young men is sufficient to increase these risk markers.

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The authors’ responsibilities were as follows—KB: designed the research; IA, PAG, MH, and KB: conducted the research; IA, PAG, SRH, IG-B, HKB, and KB: analyzed data or performed statistical analysis; IA, PAG, SK, GAS, and KB: wrote the manuscript; and KB: had primary responsibility for final content of the manuscript. None of the authors had any conflicts of interest with regard to this manuscript.

REFERENCES