Diurnal metabolic profiles after 14 d of an ad libitum high-starch, high-sucrose, or high-fat diet in normal-weight never-obese and postobese women1–3

Anne Raben, Jens J Holst, Joop Madsen, and Arne Astrup

ABSTRACT
Background: The influence of the amount and type of carbohydrates in the diet on risk factors for obesity, diabetes, and cardiovascular disease remains unclear.
Objective: We investigated the effects of 2 low-fat diets (high-sucrose and high-starch) and a high-fat diet on glycemria, lipidemia, and hormonal responses in never-obese and postobese women.
Design: Eighteen normal-weight women (8 postobese and 10 never-obese) consumed 3 ad libitum diets (high-fat, high-starch, and high-sucrose) for 14 d each. On day 15, we measured fasting and postprandial glucose, lactate, insulin, triacylglycerol, nonesterified fatty acids (NEFA), glycerol, glucagon, glucose-dependent insulinotropic polypeptide, and glucagon-like peptide 1.
Results: The high-sucrose diet induced significantly lower total areas under the curve (AUCs) for glucose and NEFA and a significantly higher lactate AUC than did the high-fat and high-starch diets; there were no significant differences in the insulin AUCs. The triacylglycerol AUC was greater with the high-fat and high-sucrose diets than with the high-starch diet. Gastrointestinal hormone concentrations differed between diets, but not between the 2 subject groups. Comparisons between subject groups for all diets combined showed lower relative insulin resistance and lower AUCs for glucose, insulin, and triacylglycerol in the postobese group.
Conclusions: High-starch and high-sucrose diets had no adverse effects on postprandial glycemria, lipidemia, or lipemia compared with a high-fat diet. A sucrose-rich diet may improve glucose metabolism, but may have an adverse effect on lipemia, compared with a starch-rich diet. Postobese women seemed to be more insulin-sensitive and more efficient at storing triacylglycerol than were never-obese women, regardless of dietary composition.

KEY WORDS Obesity, homeostasis model assessment resistance, insulin resistance, women, carbohydrate metabolism, diabetes, cardiovascular disease, glycemria, lipidemia

INTRODUCTION
Current dietary recommendations suggest maintaining a fat intake <30% of energy, a carbohydrate intake between 55% and 60% of energy, and a sucrose intake <10% of energy (1). However, in the latest revision of the Nordic nutrition recommendations, this recommended sucrose intake applies only to those who consume <8 MJ/d and to children (2). The rationale for these recommendations is the supposedly beneficial effects of such a diet in the prevention of diabetes, obesity, and cardiovascular disease. In practice, however, a restricted sucrose intake may be difficult to achieve if a low-fat diet is followed; this is because sucrose consumption may actually help to achieve the goal of following the recommended low-fat, high-carbohydrate diet (3, 4).

It was believed previously that sucrose consumption resulted in rapid, large increases in plasma glucose and insulin concentrations; therefore, restrictions were recommended for diabetic individuals. However, studies conducted in the 1980s and 1990s showed that sucrose produces lower postprandial glycemic and insulinemic responses than do many types of starch (5, 6). Although recommendations about sucrose intake are therefore less restrictive now, uncertainties persist among both scientists and laypersons as to whether sucrose has detrimental effects on glucose control and insulin sensitivity in healthy and diabetic individuals when sucrose is consumed for longer periods.

Another issue that has been of major concern for >30 y is the possible adverse effect of sucrose (and fructose) on blood lipids and other risk factors for coronary heart disease (7). Some believe that a high-starch, high-fiber diet, which was recommended previously, also has these adverse effects. It was therefore suggested that the dietary recommendations be revised.

1From the Research Department of Human Nutrition, Center for Food Research, The Royal Veterinary and Agricultural University, Frederiksberg, Denmark, and the Department of Medical Physiology, The Panum Institute, the University of Copenhagen.
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3Address reprint requests to A Raben, Research Department of Human Nutrition, Center for Food Research, The Royal Veterinary and Agricultural University, 30 Rolighedsvej, DK-1958 Frederiksberg, Copenhagen, Denmark. E-mail: ar@kvl.dk.
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accordingly to recommend less carbohydrate in the diet (8, 9). This is, however, still controversial (10, 11).

Obesity is a growing health problem all over the world. The increased prevalence is probably a result of both a sedentary lifestyle and consumption of high-fat, energy-dense foods (12). Studies on subjects with genetic susceptibility to obesity showed that their lipid metabolism in particular was abnormal compared with subjects who were not predisposed to obesity (13–17). However, these results were obtained after only 0–3 d of dietary intervention and the subjects’ habitual diets—typically more carbohydrate-rich in successful postobese subjects (18)—may have influenced the results. To our knowledge, the metabolic profiles of postobese subjects have not been studied after more prolonged dietary interventions.

The purpose of the present study was 2-fold. The first objective was to compare the effects of 3 diets (a low-fat, high-sucrose diet; and a high-fat diet) on fasting and postprandial glycemia, lipidemia, and hormonal changes when the diets were consumed for 14 d ad libitum. The second objective was to compare the responses to the diets of normal-weight never-obese women with those of normal-weight postobese women.

**SUBJECTS AND METHODS**

**Subjects**

A total of 18 healthy, normal-weight women were included. Ten were never-obese and 8 were postobese. The 2 groups were closely matched for age, weight, height, fat mass, and fat-free mass (Table 1). The postobese women had a family history of obesity (at least one obese parent or sibling), had been >10% overweight (x ± SEM: 38 ± 9%) (19), and had been weight-stable for ≥2 mo. None had undergone surgical procedures to reach their normal weight. The study was approved by the Municipal Ethical Committee of Copenhagen and Frederiksberg and was found to be in accordance with the Helsinki II Declaration. All subjects gave their written consent after the experimental procedure was explained to them.

**Experimental design**

The study used a crossover design, which was described previously in detail (18). In brief, each subject completed three 14-d ad libitum dietary intervention periods: high-sucrose, high-starch, and high-fat. Ad libitum diets were used to investigate the effects of diets comparable with diets routinely consumed in everyday life, thereby creating a more realistic situation than if energy-fixed diets were used. Subjects in the never-obese and postobese groups were paired (except for 2 never-obese subjects) so that the sequence of diets was similar in the 2 groups. For each subject, all the dietary periods took place at the same time in her menstrual cycle. Before each experimental period, subjects were given a standardized weight-maintenance diet for 3 d (days −2, −1, and 0). After the standardized diet, the experimental diets were supplied in ad libitum amounts for 3–4 d at a time, to be consumed at home. Days 0 and 14 were spent in our respiration chambers (18). On day 15, we obtained fasting and postprandial blood samples. Body weight and body composition were measured in the fasting state on days 1 and 15. The dietary intervention periods were separated by ≥2 wk but ≤6 wk. The subjects were instructed to make no changes in their physical activity pattern during or between the 3 experimental diets.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Subject characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Never-obese (n = 10)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>38 ± 3 (27–52)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.65 ± 1.3 (1.59–1.71)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>62.1 ± 1.3 (56.0–70.2)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.9 ± 0.3 (21.7–24.6)</td>
</tr>
<tr>
<td>Maximal weight (kg)</td>
<td>63 ± 1 (59–71)</td>
</tr>
<tr>
<td>Previous overweight (%)</td>
<td>2 ± 6 (0–5)</td>
</tr>
</tbody>
</table>

Fat mass (kg) | 18.2 ± 0.6 (16.1–21.1) | 18.8 ± 0.9 (13.2–21.4) |

Fat-free mass (kg) | 43.9 ± 0.9 (39.9–49.1) | 46.5 ± 0.8 (43.3–50.2) |

Data on ad libitum macronutrient and energy intakes, body weight and composition, 24-h energy expenditure, substrate oxidation, appetite sensations, habitual food intake, plasma catecholamines, blood cholesterol, and coagulation and fibrinolysis factors were published previously (18, 20).

**Diets**

The standardized weight-maintenance diet provided to subjects before each dietary period contained 13% of energy as protein, 37% as fat, 50% as carbohydrate (9% as sucrose), and 2.9 g dietary fiber/MJ and had a polyunsaturated-to-saturated fatty acid ratio (P:S) 0.4. The diet was prepared according to each subject’s individual energy needs, adjusted to the nearest 0.5 MJ (21). The average macronutrient intakes (as percentages of energy intake) were as planned: 59% carbohydrate (23% sucrose), 28% fat, and 13% protein with the high-sucrose diet; 46% fat, 41% carbohydrate (2% sucrose), and 13% protein with the high-fat diet; and 59% carbohydrate (2% sucrose), 28% fat, and 13% protein with the high-starch diet. Dietary fiber amounted to 22, 32, and 20 g/d with the high-fat, high-starch, and high-sucrose diets, respectively. The P:S was 0.4 with the high-fat diet and 0.7 with both the high-sucrose and high-starch diets. The amounts of saturated, monounsaturated, and polyunsaturated fatty acids, respectively, as percentages of total fat were as follows: 45%, 37%, and 18% with the high-fat diet; 38%, 37%, and 26% with the high-sucrose diet; and 35%, 40%, and 25% with the high-starch diet. The distribution of macronutrients was similar in all meals during the day (breakfast, lunch, dinner, and snack). The 14-d ad libitum energy intake was significantly lower during the high-starch diet (9.1 ± 0.4 MJ/d) than during both the high-sucrose (10.3 ± 0.5 MJ/d) and high-fat (10.3 ± 0.4 MJ/d) diets (P < 0.05). Postobese subjects consumed significantly more energy than never-obese subjects during the high-fat diet (11.0 ± 0.7 and 9.7 ± 0.4 MJ/d, respectively; P < 0.001) and during the high-sucrose diet (11.4 ± 0.7 and 9.5 ± 0.5 MJ/d, respectively; P < 0.0001).

The types and amounts of foods provided to subjects for breakfast and lunch on day 15 were similar to the ad libitum amounts consumed on day 14 in the chamber (Tables 2 and 3). Coffee, tea, and water consumption and smoking (by 2 postobese subjects and 1 never-obese subject) were allowed, but the...
amounts and times were duplicated from the first dietary period. On average, both groups consumed more energy during the high-fat and high-sucrose diets at breakfast, whereas there were no significant differences at lunch (Table 3). Total energy intake at both breakfast and lunch was significantly lower during the high-starch diet than during the high-fat and high-sucrose diets ($P < 0.01$). There were no group differences in energy intake over the day (Table 3). The computer database of foods from the National Food Agency of Denmark (DANKOST version 2.0) was used to calculate the energy and nutrient intakes (22).

**Body weight**

Body weight was measured in the morning on days 1 and 15 after subjects fasted for 10 h and voided. The same digital scale was used each time (model 707; Seca, Copenhagen) and subjects were blinded to their weight results.

**Blood sampling**

On day 15, the subjects left the respiration chamber at 0900. After voiding and being weighed, each subject lay down on a bed in the supine position and a Venflon catheter (Viggo, Gothenburg, Sweden) was inserted into an antecubital arm vein. After 10 min, a fasting blood sample was obtained. Subjects ate breakfast at 0900 and lunch at 1400. Blood samples were obtained 15, 30, 60, 120, and 240 min after the beginning of both breakfast and lunch, ie, blood was sampled over an 8-h time span. Subjects rested in the supine position for 10 min before each blood sample was obtained. During the day, they could sit, walk quietly, or go to the toilet. The type of activity each subject engaged in during day 15 of the first dietary period was noted and repeated on day 15 in the remaining 2 dietary periods.

**Laboratory analyses**

Blood was sampled without stasis through an indwelling antecubital cannula and was centrifuged at 3000 $\times$ $g$ for 10 min at 4$^\circ$C. Iced syringes were used to store samples for glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide-1 (GLP-1), and glucagon analyses.

Blood for glucose and lactate analyses was sampled in tubes containing fluoride and EDTA. Glucose concentrations were determined with a Cobas Mira blood sample analyzer (Roche Diagnostic System, Basel, Switzerland) by using an endpoint analysis with MPR3 Gluco-quant R glucose/HK kinetic 1442457 (Boehringer Mannheim GmbH Diagnostica, Mannheim, Germany) and the hexokinase-glucose-6-phosphate 1-dehydrogenase method (23). Lactate concentrations were determined by using a Cobas Mira analyzer with an MPR3 lactate 256773 kit (Boehringer Mannheim GmbH Diagnostica) according to a method modified by Noll (24). Blood for insulin analysis was sampled in dry tubes. Serum insulin was determined with an enzyme-linked immunosorbent assay; we used a noncompetitive sandwich assay with a DAKO RIA insulin kit (code no. K6219; DAKO A/S, Glostrup, Denmark). An index of insulin resistance was obtained by using the homeostasis model assessment (HOMA; 25):

$$\text{HOMA-R (relative insulin resistance)} = \frac{\text{glucose (mmol/L)}}{\text{insulin (mU/L)}}$$

where glucose is in mmol/L and insulin is in mU/L.

**TABLE 3**

<table>
<thead>
<tr>
<th>Diets</th>
<th>High-fat</th>
<th>High-starch</th>
<th>High-sucrose</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>$kJ$</td>
<td>$kJ$</td>
<td>$kJ$</td>
</tr>
<tr>
<td>Breakfast</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never-obese</td>
<td>2371 ± 192</td>
<td>2307 ± 206</td>
<td>2636 ± 265</td>
</tr>
<tr>
<td>Postobese</td>
<td>2816 ± 324</td>
<td>2141 ± 223</td>
<td>3006 ± 370</td>
</tr>
<tr>
<td>All subjects</td>
<td>2569 ± 182$^b$</td>
<td>2233 ± 148$^a$</td>
<td>2800 ± 218$^b$</td>
</tr>
<tr>
<td>Lunch</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never-obese</td>
<td>3544 ± 310</td>
<td>3149 ± 278</td>
<td>3188 ± 176</td>
</tr>
<tr>
<td>Postobese</td>
<td>3948 ± 478</td>
<td>3022 ± 356</td>
<td>4216 ± 400</td>
</tr>
<tr>
<td>All subjects</td>
<td>3723 ± 269</td>
<td>3092 ± 215</td>
<td>3644 ± 232</td>
</tr>
<tr>
<td>Breakfast + lunch</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never-obese</td>
<td>5915 ± 294</td>
<td>5456 ± 326</td>
<td>5823 ± 364</td>
</tr>
<tr>
<td>Postobese</td>
<td>6764 ± 730</td>
<td>5163 ± 519</td>
<td>7222 ± 658</td>
</tr>
<tr>
<td>All subjects</td>
<td>6292 ± 365$^a$</td>
<td>5326 ± 286$^b$</td>
<td>6445 ± 383$^a$</td>
</tr>
</tbody>
</table>

$^a$SEM; $n = 10$ for never-obese, 8 for postobese, 18 for all subjects. Values in the same row with different superscript letters are significantly different, $P < 0.05$ (ANOVA for diet effect). There was no significant group $\times$ diet interaction.
Plasma glycerol was determined enzymatically after protein precipitation in blood collected in heparin-prepared tubes (26). Blood for analysis of serum triacylglycerol was collected in dry tubes. Triacylglycerol was determined by enzymatic hydrolysis and subsequent determination of liberated glycerol by colorimetry (27). An MPR2 triacylglycerol GPO-PAP 701912 kit (Boeringer Mannheim GmbH Diagnostica) and a Cobas Mira analyzer (Roche Diagnostic System) were used. Blood for determination of serum nonesterified fatty acid (NEFA) concentrations was sampled in dry tubes and was immediately centrifuged, extracted, and stored at −20°C. NEFA concentrations were determined by an enzymatic colorimetric method (ACS-ACOD method, NEFA C code no. 994–75409E; Wako Chemicals Inc, Richmond, VA) by using a Cobas Mira Plus analyzer (Roche Diagnostic System).

GIP, glucagon, and GLP-1 concentrations in plasma were all measured after extraction of plasma with 70% ethanol (vol:vol, final concentration). For the GIP radioimmunoassay (28), we used the C-terminally directed antisera R65, which cross-reacts fully with human GIP but not with the so-called GIP 8000, whose chemical nature and relation to GIP secretion is uncertain. Human GIP and 125I human GIP (70 MBq/ml) were used for standards and tracer. The glucagon radioimmunoassay was directed against the C-terminus of the glucagon molecule (antibody code no. 4305) and therefore mainly measured glucagon of pancreatic origin (29). The plasma concentrations of GLP-1 were measured against standards of synthetic GLP-1 7–36 amide by using antisera code no. 89390, which is specific for the amidated C-terminus of GLP-1 and therefore mainly reacts with GLP-1 of intestinal origin (30). For these 3 assays, sensitivity was <1 pmol/L, the intraassay CV was <6% at 20 pmol/L, and the recovery of standard (added to plasma before extraction) was =100% when corrected for losses inherent in the plasma extraction procedure.

Statistical analyses

All results are given as means ± SEMs. Initial group characteristics were compared by using unpaired t tests (Table 1). The areas under the curves (AUCs) were calculated separately for each subject as the difference between the integrated area of the response curve and the rectangular area determined by the basal values. For ∆AUC, ie, the change from fasting concentrations, negative areas were included. The normal distributions of all data were verified by residual plots before further data analysis. Differences in fasting concentrations and AUCs among the 3 diets and 2 subject groups were tested by parametric analysis of variance (ANOVA) with the general linear model (GLM) procedure in SAS (SAS Institute Inc, Cary, NC). The factors were group × diet, group, and diet using subject(group) as an error term for group effects. For significant values, a t test on least-squares means (for unbalanced designs) was used to test for differences between groups or diets. Differences in postprandial responses were tested with ANOVA by using GLM in SAS and with diet × time × group, diet × group, time × group, diet × time, time, diet, and group as factors and subject(group) as the error term for all group effects.

To explain observed differences between diets and groups, we performed simple linear regression analyses by using the means of groups and diets (n = 6). A plot was used to determine whether a significant correlation was valid. To investigate whether observed differences in AUCs were the result of differences in ad libitum energy intake on day 15, the latter was included as a covariate in the ANOVA. Changes in fasting blood concentrations were also reanalyzed with the following as covariates: 14-d changes in body weight and 14-d average energy, carbohydrate, fat, and sucrose intakes.

The significance level was set at P < 0.05. STATGRAPHICS software (version 4.2; Graphic Software Systems Inc, Rockville, MD) and the STATISTICAL ANALYSIS PACKAGE (version 6.12 for WINDOWS; SAS Institute) were used to perform the statistical calculations.

RESULTS

Plasma glucose

No significant differences among groups were observed for fasting glucose concentrations on day 1 (for all groups combined: 4.77 ± 0.05 mmol/L) or day 15 of the 3 dietary periods (Table 4). After the meals, however, there were significant differences in the glucose responses between diets and between groups (Figure 1). During the high-sucrose diet in both subject groups, there was a slightly faster, although lower, peak after lunch than there was during the high-starch or high-fat diets. Lower total and incremental AUCs were seen during the high-sucrose diet than during the high-starch and high-fat diets. Plasma glucose concentrations only fell below fasting concentrations in postobese subjects consuming the high-sucrose diet 1 h after breakfast. During all 3 diets, postobese subjects had lower AUCs and ∆AUCs than did never-obese subjects. The above findings were not altered by adjustment analyses.

Plasma lactate

Fasting lactate concentrations were not significantly different among groups on day 1 (for all groups combined: 0.61 ± 0.03 mmol/L), but on day 15, concentrations were higher after the high-sucrose diet than after the high-starch diet for all subjects combined (diet effect: P < 0.01; Table 4). After the meals, the increases in lactate concentration differed among the diet groups (high-sucrose diet > high-starch diet > high-fat diet; Figure 2). The postobese subjects had a lower lactate response than did the never-obese subjects to the high-sucrose diet (diet × group interaction, P < 0.05). Adjustment for differences in energy intake did not change these results.

Serum insulin

Fasting insulin concentrations on day 1 (for all groups combined: 33 ± 3 pmol/L) and day 15 and changes from days 1 to 15 were not significantly different between diets or groups (Table 4). After the meals, there was a significant time × diet interaction in insulin responses, with a steeper initial rise in insulin after the high-sucrose diet (Figure 3). The AUCs did not differ significantly among the diets, however. A main effect of subject group was found, with a lower AUC and ∆AUC in postobese than in never-obese subjects. Adjusting for differences in energy intake on day 15 did not alter these findings. HOMA-R did not differ significantly between diets, but was significantly lower in postobese than in never-obese subjects for all diets, whether we used fasting values (day 15) or AUC values (Table 5).

Serum triacylglycerol

On day 1, fasting triacylglycerol concentrations were not significantly different between diets, but were lower in postobese than in never-obese subjects (0.68 ± 0.04 compared with 0.94 ± 0.04 mmol/L; P < 0.01 for group effect). Fasting tria-
Lactate (mmol/L) However, when we adjusted for differences in energy intake because the subjects had lower total AUCs than did never-obese subjects and high-starch diets (Figure 4). During all 3 diets, postobese subjects had larger after the high-fat diet than after the high-sucrose diet, whereas the incremental AUCs then decreased, reaching fasting concentrations 4 h after lunch. During the high-sucrose diet, a slow, prolonged increase was observed over the day. During the high-starch diet, these differences among diets, however. The postprandial triacylglycerol response differed significantly among diets and among subject groups (diet × time × group interaction, P < 0.05; Figure 4). During the high-fat diet, a large increase was seen 1 h after lunch. During the high-sucrose diet, a slow, prolonged increase was observed over the day. During the high-starch diet, these differences among diets, however. The postprandial triacylglycerol concentrations increased until 1 h after lunch and then decreased, reaching fasting concentrations 4 h after lunch. Total AUCs were larger after the high-fat and high-sucrose diets than after the high-starch diet, whereas the incremental AUCs were larger after the high-fat diet than after the high-sucrose and high-starch diets (Figure 4). During all 3 diets, postobese subjects had lower total AUCs than did never-obese subjects (Figure 4). This could have been a result of the lower fasting triacylglycerol concentrations in postobese subjects (Table 4) because the ΔAUCs did not differ significantly between groups (Figure 4). However, when we adjusted for differences in energy intake on day 15, the ΔAUCs became lower in postobese subjects for all 3 diets.

**Serum nonesterified fatty acids**

Fasting serum NEFA concentrations were lower in postobese than in never-obese subjects (503 ± 26 compared with 656 ± 39 µmol/L; P < 0.05 for group effect) before the 3 diets. After the dietary periods, a larger decrease in fasting NEFA concentration was found after the high-sucrose diet than after the high-fat or high-starch diets (Table 4). After the meals on day 15, NEFA concentrations were suppressed with all 3 diets, but this was more pronounced with the high-sucrose diet than with the high-fat and high-starch diets (Figure 5). Total AUCs were also lower after the high-sucrose diet than after the high-fat or high-starch diets, whereas the ΔAUCs were lower after the high-sucrose and high-starch diets than after the high-fat diet (Figure 5). There were no significant differences between postobese and never-obese subjects. Adjustment for energy intake on day 15 changed the results slightly for total AUCs, to high-fat diet > high-starch diet > high-sucrose diet (P < 0.0001 for diet effect); there were still no significant differences between the subject groups.

### Table 4

Fasting plasma or serum concentrations on day 15 and changes from baseline (days 15 – 1) in never-obese and postobese subjects after consuming diets high in fat, starch, or sucrose for 14 d ad libitum

<table>
<thead>
<tr>
<th>Analysis</th>
<th>High fat</th>
<th>High starch</th>
<th>High sucrose</th>
<th>Change (days 15 – 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never-obese</td>
<td>4.76 ± 0.14</td>
<td>4.72 ± 0.10</td>
<td>4.80 ± 0.10</td>
<td>-0.11 ± 0.08</td>
</tr>
<tr>
<td>Postobese</td>
<td>4.64 ± 0.17</td>
<td>4.58 ± 0.12</td>
<td>4.64 ± 0.13</td>
<td>-0.09 ± 0.11</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never-obese</td>
<td>0.69 ± 0.06</td>
<td>0.66 ± 0.07</td>
<td>0.89 ± 0.08</td>
<td>0.00 ± 0.09</td>
</tr>
<tr>
<td>Postobese</td>
<td>0.67 ± 0.07</td>
<td>0.57 ± 0.05</td>
<td>0.61 ± 0.06</td>
<td>0.14 ± 0.07</td>
</tr>
<tr>
<td>All subjects</td>
<td>0.68 ± 0.04</td>
<td>0.62 ± 0.04</td>
<td>0.77 ± 0.06</td>
<td>0.00 ± 0.07</td>
</tr>
<tr>
<td>Insulin (pmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never-obese</td>
<td>51 ± 6</td>
<td>56 ± 5</td>
<td>64 ± 9</td>
<td>17 ± 9</td>
</tr>
<tr>
<td>Postobese</td>
<td>39 ± 7</td>
<td>45 ± 6</td>
<td>42 ± 6</td>
<td>7 ± 6</td>
</tr>
<tr>
<td>Triacylglycerol (mmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never-obese</td>
<td>0.74 ± 0.06</td>
<td>0.89 ± 0.08</td>
<td>1.10 ± 0.11</td>
<td>-0.21 ± 0.07</td>
</tr>
<tr>
<td>Postobese</td>
<td>0.64 ± 0.07</td>
<td>0.71 ± 0.04</td>
<td>0.76 ± 0.04</td>
<td>-0.03 ± 0.05</td>
</tr>
<tr>
<td>All subjects</td>
<td>0.69 ± 0.05</td>
<td>0.81 ± 0.05</td>
<td>0.95 ± 0.07</td>
<td>-0.13 ± 0.05</td>
</tr>
<tr>
<td>NEFA (µmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never-obese</td>
<td>501 ± 44</td>
<td>546 ± 76</td>
<td>502 ± 65</td>
<td>-145 ± 59</td>
</tr>
<tr>
<td>Postobese</td>
<td>436 ± 69</td>
<td>549 ± 81</td>
<td>368 ± 74</td>
<td>18 ± 97</td>
</tr>
<tr>
<td>All subjects</td>
<td>-73 ± 56</td>
<td>-26 ± 48</td>
<td>-26 ± 48</td>
<td>-201 ± 49</td>
</tr>
<tr>
<td>Glycerol (µmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never-obese</td>
<td>63 ± 7</td>
<td>88 ± 10</td>
<td>71 ± 7</td>
<td>-22 ± 12</td>
</tr>
<tr>
<td>Postobese</td>
<td>70 ± 6</td>
<td>78 ± 7</td>
<td>67 ± 8</td>
<td>14 ± 10</td>
</tr>
<tr>
<td>All subjects</td>
<td>66 ± 5</td>
<td>83 ± 6</td>
<td>69 ± 5</td>
<td>-6 ± 9</td>
</tr>
<tr>
<td>Glucagon (pmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never-obese</td>
<td>6 ± 1</td>
<td>6 ± 2</td>
<td>5 ± 1</td>
<td>2 ± 1</td>
</tr>
<tr>
<td>Postobese</td>
<td>6 ± 1</td>
<td>5 ± 1</td>
<td>5 ± 1</td>
<td>2 ± 1</td>
</tr>
<tr>
<td>GIP (pmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never-obese</td>
<td>9 ± 1</td>
<td>6 ± 1</td>
<td>9 ± 2</td>
<td>-2 ± 1</td>
</tr>
<tr>
<td>Postobese</td>
<td>9 ± 2</td>
<td>11 ± 3</td>
<td>8 ± 2</td>
<td>-2 ± 2</td>
</tr>
<tr>
<td>GLP-1 (pmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never-obese</td>
<td>13 ± 2</td>
<td>15 ± 2</td>
<td>15 ± 3</td>
<td>-2 ± 1</td>
</tr>
<tr>
<td>Postobese</td>
<td>14 ± 2</td>
<td>13 ± 2</td>
<td>12 ± 2</td>
<td>0 ± 1</td>
</tr>
</tbody>
</table>

1,2,3 ± SEM; n = 10 for never-obese, 8 for postobese, and 18 for all subjects. GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1; NEFA, nonesterified fatty acids. All analytes were measured in plasma except for triacylglycerol and fatty acids, which were measured in serum. For all subjects, values in the same row and time period with different superscript letters are significantly different, P < 0.05 (ANOVA for diet effect).

1,2,3 Significant group × diet interaction for never-obese compared with postobese: 1 P < 0.05, 2 P < 0.01, 3 P < 0.001.
FIGURE 1. Mean plasma glucose concentrations and mean (±SEM) total areas under the curves (AUCs) and AUCs for the change (Δ) from fasting concentrations in 10 never-obese (NO) and 8 postobese (PO) women after consumption of high-fat (●), high-starch (■), and high-sucrose (▲) diets ad libitum for 14 d each. For the curves, the ANOVA results were significant for group × time (P < 0.01), diet × time (P < 0.0001), group (P < 0.01; PO < NO), diet (P < 0.0001; high-sucrose diet < high-starch and high-fat diets), and time (P < 0.0001). For both the AUCs and ΔAUCs, there was a significant diet effect (P < 0.0001) and group effect (P < 0.01). Diets with different superscript letters are significantly different, P < 0.0001.

FIGURE 2. Mean plasma lactate concentrations and mean (±SEM) total areas under the curves (AUCs) and AUCs for the change (Δ) from fasting concentrations in 10 never-obese (NO) and 8 postobese (PO) women after consumption of high-fat (●), high-starch (■), and high-sucrose (▲) diets ad libitum for 14 d each. For the curves, the ANOVA results were significant for diet × group (P < 0.01), diet × time (P < 0.0001), diet (P < 0.0001; high-sucrose diet > high-starch diet > high-fat diet), and time (P < 0.0001). For the AUCs, there was a significant diet × group effect (P < 0.05) and diet effect (P < 0.0001). For the ΔAUCs, there was a significant diet effect (P < 0.0001). ***Significantly different from NO, P < 0.001. Diets with different superscript letters are significantly different, P < 0.001.
Plasma glycerol

No significant differences in fasting glycerol concentrations were observed before the diets (for all groups combined: 69 ± 5 μmol/L). After the high-starch diet, fasting glycerol increased, whereas it decreased after the high-sucrose and high-fat diets (P < 0.01 for diet effect; Table 4). Postprandial glycerol responses also differed between diets, with the high-starch diet resulting in higher pre-lunch increases than the high-sucrose or high-fat diets (time × diet interaction, P < 0.0001; Figure 6). Total AUCs did not differ significantly among the diets, but the incremental AUCs were lower after the high-starch and high-sucrose diets than after the high-fat diet (Figure 6). After adjustment for energy intake on day 15, only the incremental AUC for the high-sucrose diet remained lower than that for the high-fat diet (P < 0.05).

Plasma glucagon

There were no significant differences in fasting plasma glucagon concentrations on day 1 (for all groups combined: 4.5 ± 0.3 pmol/L) or after the dietary periods (Table 4). After the meals on day 15, different responses to the 3 diets were observed, but no clear patterns emerged (time × diet interaction, P < 0.0001; Figure 7). The AUCs and ΔAUCs did not differ significantly between diets or subject groups, and adjustment for energy intake did not alter these findings.

Plasma glucose-dependent insulinotropic polypeptide

On day 1, the mean fasting GIP concentration was slightly higher before the high-fat diet than before the high-sucrose diet (11 ± 1 compared with 8 ± 1 pmol/L; P < 0.05), but no significant differences were found on day 15 (Table 4). However, adjustment for changes in body weight resulted in a group difference: GIP was lower in never-obese subjects than in postobese subjects (P < 0.05). Postprandial GIP differed significantly between the groups (diet × time interaction, P < 0.0001), with the high-fat diet resulting in the highest GIP concentration (Figure 8). The AUCs and ΔAUCs were also higher after the high-fat diet than after the high-sucrose or high-starch diets (Figure 8). This remained true after adjustment for differences in energy intake on day 15. There were no differences in postprandial GIP responses between never-obese and postobese subjects.

Plasma glucagon-like peptide 1

Before the dietary periods, no significant differences were found in fasting GLP-1 concentrations (for all groups combined:

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**TABLE 5**

Relative insulin resistance in never-obese and postobese women on day 15 after consuming diets high in fat, starch, or sucrose for 14 d ad libitum.

<table>
<thead>
<tr>
<th></th>
<th>High fat</th>
<th>High starch</th>
<th>High sucrose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting HOMA-R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never-obese</td>
<td>1.50 ± 0.19</td>
<td>1.63 ± 0.15</td>
<td>1.94 ± 0.31</td>
</tr>
<tr>
<td>Postobese</td>
<td>1.11 ± 0.23</td>
<td>1.27 ± 0.19</td>
<td>1.17 ± 0.18</td>
</tr>
<tr>
<td>AUC for HOMA-R</td>
<td>(× 10^3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never-obese</td>
<td>2703 ± 328</td>
<td>2561 ± 329</td>
<td>2611 ± 364</td>
</tr>
<tr>
<td>Postobese</td>
<td>1442 ± 232</td>
<td>1451 ± 275</td>
<td>1607 ± 227</td>
</tr>
</tbody>
</table>

2 ± SEM; n = 10 for never-obese and 8 for postobese. AUC; area under the curve; HOMA-R, relative insulin resistance (25).

2' Overall group effect (never-obese compared with postobese): 2 P < 0.05, 3 P < 0.01.

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**FIGURE 3.** Mean plasma insulin concentrations and mean (±SEM) total areas under the curves (AUCs) and AUCs for the change (Δ) from fasting concentrations in 10 never-obese (NO) and 8 postobese (PO) women after consumption of high-fat (●), high-starch (■), and high-sucrose (▲) diets ad libitum for 14 d each. For the curves, the ANOVA results were significant for time × diet (P < 0.0001), group (P < 0.05; PO < NO), and time (P < 0.0001). For both the AUCs and the ΔAUCs, there was a significant group effect (P < 0.05).
FIGURE 4. Mean serum triacylglycerol concentrations and mean (±SEM) total areas under the curves (AUCs) and AUCs for the change (Δ) from fasting concentrations in 10 never-obese (NO) and 8 postobese (PO) women after consumption of high-fat (●), high-starch (■), and high-sucrose (▲) diets ad libitum for 14 d each. For the curves, the ANOVA results were significant for time × diet × group (P < 0.05), time × diet (P < 0.0001), diet (P < 0.0001; high-fat and high-sucrose diets > high-starch diet), group (P < 0.05; PO < NO), and time (P < 0.0001). For the AUCs, there was a significant group effect (P < 0.05) and diet effect (P < 0.0001). For the ΔAUCs, there was a significant diet effect (P < 0.0001). Diets with different superscript letters are significantly different, P < 0.01.

FIGURE 5. Mean serum nonesterified fatty acid (NEFA) concentrations and mean (±SEM) total areas under the curves (AUCs) and AUCs for the change (Δ) from fasting concentrations in 10 never-obese (NO) and 8 postobese (PO) women after consumption of high-fat (●), high-starch (■), and high-sucrose (▲) diets ad libitum for 14 d each. For the curves, the ANOVA results were significant for time × diet × group (P < 0.05), time × diet (P < 0.0001), diet (P < 0.0001; high-sucrose diet < high-starch and high-fat diets), and time (P < 0.0001). For both the AUCs and ΔAUCs, there was a significant diet effect (P < 0.0001 and P < 0.05, respectively). Diets with different superscript letters are significantly different, P < 0.05.
FIGURE 6. Mean plasma glycerol concentrations and mean (±SEM) total areas under the curves (AUCs) and AUCs for the change (Δ) from fasting concentrations in 10 never-obese (NO) and 8 postobese (PO) women after consumption of high-fat (●), high-starch (■), and high-sucrose (▲) diets ad libitum for 14 d each. For the curves, the ANOVA results were significant for diet × time (P < 0.0001) and time (P < 0.0001). For the AUCs, there was a significant diet effect (P < 0.05). Diets with different superscript letters are significantly different, P < 0.05.

FIGURE 7. Mean plasma glucagon concentrations and mean (±SEM) total areas under the curves (AUCs) and AUCs for the change (Δ) from fasting concentrations in 10 never-obese (NO) and 8 postobese (PO) women after consumption of high-fat (●), high-starch (■), and high-sucrose (▲) diets ad libitum for 14 d each. For the curves, the ANOVA results were significant for diet × time (P < 0.0001) and time (P < 0.0001).
14 ± 1 pmol/L). This was also the case after the diets (Table 4). However, postprandial GLP-1 responses differed between diets (time × diet interaction, \( P < 0.01 \); Figure 9). The AUCs were larger after the high-fat diet than after the high-sucrose diet and were lowest after the high-starch diet, whereas the ΔAUCs were larger after the high-fat diet than after the high-starch diet (Figure 9). There were no differences among subject groups. Adjustment for energy intake on day 15 changed this slightly: AUCs became higher after the high-fat diet than after the high-starch and high-sucrose diets, which were equal to each other (\( P < 0.001 \) for diet effect). Furthermore, AUCs became larger in never-obese than in postobese subjects after the high-sucrose diet (diet × group interaction, \( P < 0.05 \)). There were no significant differences between subject groups.

Body weight

Compared with a change of 0.0 kg, body weight decreased during the high-starch diet by 0.7 ± 0.3 kg (\( P < 0.05 \)) but did not change significantly during the high-sucrose diet (gain of 0.1 ± 0.2 kg; NS) or the high-fat diet (loss of 0.4 ± 0.3 kg; NS). The changes differed significantly between the high-starch and high-sucrose diets (\( P < 0.05 \)). There were no significant differences between postobese and never-obese subjects.

Correlation analyses

For fasting concentrations on day 15 (\( n = 6 \) for the 2 subject groups during the 3 diets), there were positive correlations between lactate and triacylglycerol (\( r = 0.81, P < 0.05 \)), insulin and triacylglycerol (\( r = 0.93, P < 0.01 \)), and glucose and GLP-1 (\( r = 0.84, P < 0.05 \)). No significant correlations were found between the changes (days 15–1) in fasting blood concentrations. The AUCs for insulin and triacylglycerol were positively correlated (\( r = 0.94, P < 0.01 \)). Positive correlations were also seen between the ΔAUCs for GLP-1 and NEFA (\( r = 0.85, P < 0.05 \)) and GLP-1 and glycerol (\( r = 0.87, P < 0.05 \)).

DISCUSSION

Glycemia

Although there were no significant differences among the 3 diets in fasting concentrations, postprandial glucose, lactate, and insulin showed different response patterns on day 15 of the 3 diets. Likewise, Daly et al (31) found a lower AUC for glucose after a sucrose-rich, low-fat diet (50% of energy as sucrose, 5% as starch, and 35% as fat) compared with a starch-rich, low-fat diet (50% of energy as starch, 5% as sucrose, and 35% as fat) in 8 healthy, normal-weight men and women. Both of these findings, therefore, correspond to the lower glycemic index of sucrose compared with starch as reported previously (5, 6). The theory that dietary sucrose reduces insulin sensitivity is therefore not supported by our findings or by the literature.
After both breakfast and lunch, lactate concentrations increased more during the high-sucrose diet than during the high-starch diet. It is likely that the fructose part of the high-sucrose diet caused this effect (7). With the high-starch diet, the increase in lactate must have been caused primarily by anaerobic glucose breakdown in extramuscular tissues (33).

**Lipidemia**

Fasting triacylglycerol concentrations increased with both the high-starch and high-sucrose diets, thereby supporting some previous studies that found increased triacylglycerol after subjects followed carbohydrate-rich diets for a few days or weeks (8, 11). Interestingly, however, these differences between diets disappeared after adjustment for differences in 14-d energy intake, differences in macronutrient intake, or changes in body weight. This highlights the results of a recent meta-analysis that showed positive relations between changes in dietary fat, changes in body weight, and changes in triacylglycerol (10). Triacylglycerol concentrations showed quite different postprandial responses to the 3 diets, especially after lunch. The continued increase in triacylglycerol with the high-sucrose diet could be a result of increased VLDL triacylglycerol synthesis in the liver from the metabolism of fructose during the high-sucrose diet (7, 34, 35). The greater triacylglycerol AUC with the high-sucrose diet than with the high-starch diet also supports the findings of Daly et al (31). The larger incremental AUCs after the high-fat diet than after the high-starch and high-sucrose diets probably reflect the higher fat content of the meals during the high-fat diet (∼80 g) compared with the high-sucrose diet (∼50 g) and high-starch diet (∼40 g). Taken together with the other measurements of risk factors for coronary heart disease that we presented elsewhere (20), substituting a high-sucrose diet for a high-starch diet does not seem advisable. However, different subjects may display different degrees of sensitivity to hypertriglyceridemia induced by sucrose and fructose, and dose-dependent effects probably also occur (7, 36, 37).

In the present study, decrements in total NEFA concentrations were most pronounced after the high-sucrose diet. The same result was found in the study by Daly et al (31) and in another study after 30 d of a high-glycemic, high-sucrose diet compared with a low-glycemic, low-sucrose diet (32). The reason for this was most likely the higher insulin peaks during the high-sucrose diet than during the other diets. On the basis of the NEFA responses, insulin sensitivity was therefore not impaired during a sucrose-rich diet in the studies cited above (31, 32, 38, 39) or in the present study.

**Gastrointestinal hormones**

Both GIP and GLP-1 are potent stimulators of glucose-induced insulin secretion. Furthermore, GLP-1 was shown to reduce gastric emptying rate (40) and is considered a potential therapeutic agent for the treatment of hyperglycemia in type 2 diabetes and hyperphagia in obesity (41, 42). In the present study, GIP increased by ∼30% more after the high-fat diet than after the high-sucrose and high-starch diets, and this was also found after adjustment for differences in energy intake on day 15. This supports the theory that dietary fat is a more potent stimulator of GIP secretion than is carbohydrate (43, 44) and also shows that sucrose and starch apparently had the same effect on GIP. The latter finding is in contrast with an earlier study by Reiser et al (45), but can probably be explained to a large extent by the use of...
different methods or possibly different degrees of adaptation to the diets (44, 45). In the present study, total AUCs for GLP-1 were highest during the high-fat diet and lowest during the high-starch diet. After adjustment for energy intake, however, GLP-1 responses were ~20% higher during the high-fat diet than during both the high-starch and high-sucrose diets. Therefore, fat seems to be a more potent stimulator of GLP-1 than is carbohydrate, with no difference between the types of carbohydrate used here.

**Postobese compared with never-obese subjects**

After the 3 ad libitum diets, we saw no differences between postobese and never-obese subjects in the changes in concentrations of fasting substrates and hormones. However, some interesting postprandial responses were observed. First, postobese women had lower glucose and insulin responses than did never-obese women during all 3 diets. This cannot be explained by differences in energy intake because postobese subjects consumed the same amount of energy or more energy than did never-obese subjects and because energy adjustment had no effect. Instead, this indicates higher insulin sensitivity overall in postobese women, a theory supported by the lower HOMA-R in postobese than in never-obese women. Increased insulin sensitivity in adipose tissue was found previously in similar subjects ([14](#)) and data from Pima Indians also support this finding, in that increased insulin sensitivity was found to be a risk factor for weight gain ([46](#)). Second, we also found lower postprandial triacylglycerol concentrations in postobese women than in never-obese women during all 3 diets. This probably reflects a lipid storage capacity that is higher overall in postobese than in never-obese subjects, which is supported by previous studies ([15–17](#)). Third, no group differences were found in GIP or GLP-1 responses. This suggests that these hormones are not involved in the development of obesity, in contrast with the findings of previous studies ([15, 47, 48](#)).

**Methods**

The design of the present study had some advantages over previous studies. First, not only fasting concentrations, but also postprandial responses, were measured. The measurement of postprandial responses has long been recognized as necessary for evaluation of the risk factors for diabetes, but now is also being recognized as important in evaluations of risk factors for cardiovascular diseases (7). Second, we used 2 test meals instead of only 1 ([15, 49, 50](#)), because a meal given in the morning after a 10–12-h fast may produce a different response than does a meal given for lunch ([51, 52](#)). This was supported by our observations of different response patterns after breakfast and lunch for glucose (especially in never-obese subjects), lactate, triacylglycerol, glycerol, GIP, and GLP-1. Third, the diets were given for 14 d instead of just 1 or 2 d, allowing some habituation to the diets. Fourth, we used an ad libitum design to mimic a more realistic situation than would the use of energy-fixed diets. A disadvantage of the present study design, however, was that we did not measure postprandial blood concentrations before the experimental diets began. We did not collect these data for both practical and theoretical reasons. We were more interested in observing the diet-induced changes after some habituation to the diets than in studying the acute changes, which were studied to some extent before ([15, 31](#)). Whether 14 d of a diet is long enough to habituate subjects is questionable; therefore, longer intervention periods are preferable in future studies.

**Conclusions**

In healthy, normal-weight women, carbohydrate-rich, low-fat diets with large amounts of either starch or sucrose (25% of energy as sucrose) had no adverse effects on postprandial glycemia, insulinemia, or lipidemia compared with a fat-rich diet. Comparison of the high-starch diet with the high-sucrose diet showed lower postprandial glucose concentrations and higher triacylglycerol concentrations during the high-sucrose diet and similar insulin concentrations during the 2 diets. Comparisons of the subject groups indicated that the postobese women were more insulin-sensitive and more efficient at storing triacylglycerol than were the never-obese women, regardless of the diets they were consuming. Conversely, no group differences in concentrations of gastrointestinal hormones (GIP and GLP-1) were seen.

We thank Bente Knap, Inge Timmermann, Jannie Möller Larsen, Charlotte Kosteki, Karina Graff Larsen, Lone Kistrup Larsen, Lis Kristoffersen, Karen Klausen, and Trine Jessen for their expert technical assistance.

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