Comparison of the effects on insulin resistance and glucose tolerance of 6-mo high-monounsaturated-fat, low-fat, and control diets\textsuperscript{1–3}

Anette Due, Thomas M Larsen, Kjeld Hermansen, Steen Stender, Jens J Holst, Søren Toubro, Torben Martinussen, and Arne Astrup

ABSTRACT
Background: The effect of dietary fat and carbohydrate on glucose metabolism has been debated for decades.
Objective: The objective was to compare the effect of 3 ad libitum diets, different in type and amount of fat and carbohydrate, on insulin resistance and glucose tolerance subsequent to weight loss.
Design: Forty-six nondiabetic, obese [mean (±SEM) body mass index (in kg/m\(^2\)): 31.2 ± 0.3] men (n = 20) and premenopausal women (n = 26) aged 28.0 ± 0.7 y were randomly assigned to 1 of 3 diets after ≥8% weight loss: 1) MUFA diet (n = 16): moderate in fat (35–45% of energy) and high in monounsaturated fatty acids (>20% of energy); 2) LF diet (n = 18): low-fat diet (20–30% of energy), and 3) control diet (n = 12): 35% of energy as fat (>15% of energy as saturated fatty acids). Protein accounted for 15% of energy in all 3 diets. A 2-h oral-glucose-tolerance test (OGTT) was performed before and after the 6-mo dietary intervention. All foods were provided by a purpose-built supermarket.

Results: After 6 mo, the MUFA diet reduced fasting glucose (<3.0%), insulin (<9.4%), and the homeostasis model assessment of insulin resistance score (<12.1%). Compared with the MUFA diet, the control diet increased these variables [1.4% (P = 0.014), 21.2% (P = 0.030), and 22.8% (P = 0.015), respectively], as did the LF diet [14.4% (P = 0.090), 13.1% (P = 0.078), and 15.5% (P = 0.095), respectively]. No significant group differences were detected in glucose or insulin concentrations during the OGTT, in the Matsudas index, in body weight, or in body composition.

Conclusion: A diet high in monounsaturated fat has a more favorable effect on glucose homeostasis than does the typical Western diet in the short term and may also be more beneficial than the official recommended low-fat diet during a period of weight regain subsequent to weight loss. This trial was registered at clinicaltrials.gov as NCT00274729. Am J Clin Nutr 2008;87:855–62.

INTRODUCTION

The prevalence of obesity and type 2 diabetes is increasing rapidly in both developed and developing countries. Although most of the major environmental determinants of this increase have been attributed to excessive body weight, physical inactivity, and smoking, diet composition has been shown to have an additional impact (1). Observational studies and intervention trials have shown that both the glycemic index (GI) of the diet (1, 2) and the amount and quality of fat in the diet are factors involved in the development of insulin resistance and type 2 diabetes (3, 4).

The official dietary recommendations in the United States and the Nordic countries have, in past decades, been based on the premise that a low-fat, high-carbohydrate diet results in optimal health (5–9). In the Nordic countries, dietary recommendations aim to reduce the total amount of fat in the diet to <30% of energy, increase carbohydrates to 55–60% of energy, increase protein from lean meat and dairy products to 10–20%, and limit the intake of sugar-sweetened soft drinks (5, 6). Meta-analyses of intervention studies have provided good evidence that a low-fat diet can improve risk factors for cardiovascular disease and type 2 diabetes (10, 11). In combination with a slight increase in daily physical activity, an energy-restricted diet with this composition has, in randomized clinical trials, been shown to reduce the incidence of type 2 diabetes by 58% over 4 y (12). However, current dietary recommendations have been challenged by some scientists who have developed new guidelines promoted as a new “Healthy Eating Pyramid” (13). This new recommended diet is higher in vegetable oil, whole grains, nuts and legumes, and fruit and vegetables and lower in carbohydrates with a high GI and in meat and dairy products. There is circumstantial evidence to suggest that this diet, which is high in monounsaturated fat and...
has a low GI could have a beneficial effect on type 2 diabetes (1, 14). However, there is also concern that the increased total fat content will lead to weight gain and, secondarily, to the development of type 2 diabetes. The intake of dietary fat, irrespective of its composition, has been associated with weight gain, but some studies indicate that the intake of unsaturated fat does not lead to the same weight gain as does an isocaloric saturated fat diet (15–17). It should be stressed that recommendations for dietary fat intake in persons with diabetes mellitus are mainly based on studies, including controlled dietary studies and epidemiologic studies, conducted in nondiabetic subjects (18).

The purpose of the present study was to compare the effect on insulin resistance and glucose tolerance of 3 different ad libitum diets consumed in a 6-mo strictly controlled dietary intervention by healthy subjects after weight loss: a diet high in monounsaturated fat (according to Willet’s new Healthy Eating Pyramid), a diet low in fat (official recommended diet), or a control diet high in saturated fat (the average Danish diet and similar to the Western diet).

SUBJECTS AND METHODS

The 4-y controlled dietary intervention trial “MUFObes” (MonoUnsaturated Fatty acids in Obesity) was conducted at the Department of Human Nutrition, Centre for Advanced Food Studies, Faculty of Life Sciences, University of Copenhagen, Frederiksberg, Denmark. The aim of the trial was to compare the long-term effects of 3 diets on body weight, body composition, and risk factors for development of diet-related diseases (see www.mufobes.dk).

Subjects

The present study assessed the effect of the diets on risk markers for insulin sensitivity, insulin resistance, and glucose tolerance in a subgroup of 56 subjects. To be eligible for inclusion, the participants had to be 18–35 y of age, have a body mass index (in kg/m²) of 28–36, have body weight fluctuations ≤3 kg over the previous 2 mo, be nonsmokers, and premenopausal (women). A total of 169 screened subjects were recruited from the areas of Copenhagen and Frederiksberg mainly through advertisements in local newspapers. All subjects signed an informed consent document before the study commenced. The study was approved by the Ethical Committee of the Municipalities of Copenhagen and Frederiksberg and was carried out according to the Helsinki Declaration.

Experimental design

The study was a parallel, randomized, 6-mo dietary intervention trial with 3 diet groups (allocation ratio: 2:2:1). After the initial screening examinations, the subjects completed an 8-wk low-calorie diet (800–1000 kcal/d), which consisted primarily of shakes and bars (Nutrillett; Dansk Droge, Ishøj, Denmark) with a protein, carbohydrate, and fat composition of ≈40%, 40%, and 20% of energy, respectively. Only subjects who lost ≥8% of their initial body weight were allocated to 1 one of the 3 intervention diets and the subgroup with the use of a simple block randomization procedure in which sex and an initial BMI > 31 were used as stratification criteria. To ensure adaptation to the shopping concept and weight stabilization after the weight loss, subjects were instructed to follow the control diet for 3 wk before the examinations at baseline.

Experimental diets and supermarket model

The 3 prescribed ad libitum diets were as follows: 1) MUFA diet: moderate in fat (35–45% of energy) and high in monounsaturated fatty acids (>20% of energy); 2) LF diet: low-fat diet (20–30% of energy); and 3) control diet: 35% of energy as fat (>15% of energy as saturated fatty acids. Protein accounted for 15% of energy in all 3 diets (Table 1). The MUFA diet also included more whole-grain foods, nuts, and legumes than the other diets. Alcohol consumption was allowed in accordance with current Danish guidelines, ie, <14 units/wk for women and <21 units/wk for men (1 unit = 12 g alcohol). Subjects were instructed to maintain their habitual physical activity level (PAL) to achieve energy balance and weight maintenance. PAL was assessed on a scale from 1 to 9 for every 15-min period (19) for 7 d before the dietary intervention.

### TABLE 1

Prescribed dietary composition for the groups randomly assigned to 1 of the 3 diets

<table>
<thead>
<tr>
<th>Diet</th>
<th>MUFA (n = 16)</th>
<th>LF (n = 18)</th>
<th>Control (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total fat (% of energy)</td>
<td>40 (35–45)</td>
<td>25 (20–30)</td>
<td>35 (30–40)</td>
</tr>
<tr>
<td>Monounsaturated fatty acids (% of energy)</td>
<td>&gt;20</td>
<td>10 (5–15)</td>
<td>10 (5–15)</td>
</tr>
<tr>
<td>Saturated fatty acids (% of energy)</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>&gt;15</td>
</tr>
<tr>
<td>Polyunsaturated fatty acids (% of energy)</td>
<td>5–10</td>
<td>5–10</td>
<td>0–10</td>
</tr>
<tr>
<td>Carbohydrate + fiber (% of energy)</td>
<td>45 (40–50)</td>
<td>60 (55–65)</td>
<td>50 (45–55)</td>
</tr>
<tr>
<td>Fiber (% of energy)</td>
<td>&gt;3</td>
<td>&gt;3</td>
<td>&lt;3</td>
</tr>
<tr>
<td>Added sugars (% of energy)</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>5–15</td>
</tr>
<tr>
<td>Protein (% of energy)</td>
<td>15 (10–20)</td>
<td>15 (10–20)</td>
<td>15 (10–20)</td>
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<tr>
<td>Alcohol (% of energy)</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Glycemic index</td>
<td>Low</td>
<td>Medium</td>
<td>High</td>
</tr>
<tr>
<td>Energy density</td>
<td>High</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Energy intake</td>
<td>Ad libitum</td>
<td>Ad libitum</td>
<td>Ad libitum</td>
</tr>
</tbody>
</table>

1 Range in parentheses. MUFA diet, moderate in fat and high in monounsaturated fatty acids; LF diet, low in fat.
2 Variables to be fulfilled before ending each shopping session in the supermarket.
3 The energy value used for fiber was 10 kJ/g.
The aim of the dietary counseling was to motivate the subjects to maintain the weight loss; however, the dietary intake was ad libitum, and no instruction or restriction in energy intake (eg, by calculating energy intake) was given. To control dietary composition strictly, and to monitor energy intake, a validated supermarket model was used (20). A 70-m² shop was established at the Department. The study participants collected all foods free of charge from the supermarket during the 3 wk standardization and the 6-mo dietary intervention. A previously designed computer program (20), adjusted to accommodate the specific diets in this study, was used to register foods and to calculate the nutrient content of each shopping session (A Due et al, unpublished observation, 2007) An appropriate assortment of foods was available to cover the dietary needs and the variability required by the diet groups throughout the 6-mo period. The product database included ≈700 common food items, but alcohol and soft drinks were not included. All foods were bar-coded and registered according to macro- and micronutrient content in the official national food table (FDIR V.5.0; Internet: http://www.foodcomp.dk, accessed September 2003). Values for foods not listed in the food tables were estimated from similar products found in the food tables or from the food manufacturers’ labeling. The estimated loss or increase in weight from preparation or cooking procedures for each food was embedded in the program. Approximately 380 food items that were not available at the study supermarket (nonsupermarket foods) were also incorporated in the computer program.

Educated project personnel scanned the bar codes of all the chosen items and assisted the subjects in altering the selections made to meet the prescribed macronutrient composition. Subjects were not allowed to leave the supermarket until the food selection met the prescribed macronutrient composition, and the energy content was not shown to the subjects. Waste and leftovers from the previous shopping session, and intake of nonsupermarket foods, were registered at the start of each shopping session. All subjects were allowed a 3-wk break from the project (eg, for holidays, disease), where no registration of dietary intake was required; however, they were still instructed to follow the diet. All subjects received dietary counseling during shopping and had a minimum of 2 private counseling sessions with a diettian during the 6 mo.

**Experimental protocol**

Clinical examinations were performed before the dietary intervention (month 0) and at the end of the intervention (month 6). After fasting overnight, the subjects arrived at the Department at 0730 by the least strenuous means of transport. The subjects were weighed while wearing only underwear, and body composition was measured by dual-energy X-ray absorptiometry scanning (Lunar Radiation Co, GE, Madison, WI). Waist and hip circumferences were measured with a tape measure while subjects were standing and wearing only underwear. A Venflon catheter (Terumo Europe NV, Leuven, Belgium) was inserted in an antecubital vein, and a 2-h oral-glucose-tolerance test (OGTT; 75 g glucose in 300 mL water) was performed. The blood samples were drawn in a fasting state (min 0) and during the OGTT (30, 60, 90, and 120 min).

The subjects lay in a supine position for ≥10 min before each blood sample was collected. At other times they were allowed to read, watch videos, or walk quietly around during the test day. The subjects were asked to follow the respective diets closely and to refrain from physical activity or drinking alcohol the day before the test day. Subjects had to consume their evening meal before 0800 and to fast (water was allowed until midnight) on the evening before a test day.

**Laboratory analyses**

Blood samples were kept on ice and centrifuged at 2800 × g for 10 min at 4 °C. All blood samples were kept at −20 °C, except for insulin (−80 °C), until analyzed. Serum glucose concentrations were analyzed with a standard endpoint method using Vitros 950 (Johnson & Johnson, Ortho-Clinical Diagnostics, Birkered, Denmark) with an intraassay CV of 1.1%. Serum insulin concentrations were measured by enzyme-linked immunoassay (21). Adiponectin concentrations were measured by using the Human Adiponectin RIA Kit (catalog no. HADP-61K; LINCO Research Inc, St Charles, MO).

An insulin resistance score, homeostasis model assessment of insulin resistance (HOMA-IR), was computed with the following formula: fasting glucose (mmol/L) × fasting insulin (mU/L)/22.5 (22). A measure for insulin sensitivity was calculated by using the index given by Matsuda and DeFronzo (23) using the OGTT data; Matsuda Index = 10 000(fasting plasma glucose × fasting plasma insulin × mean plasma glucose × mean plasma insulin)1/2. The mean is the mean for the entire OGTT period, including the baseline value.

**Statistics**

The power calculation was based on the primary outcome variable, ie, the difference in body weight change during long-term (>18 mo) dietary intervention between the 2 primary intervention groups (MUFA and LF). For this purpose, an expected number of 25 completing participants in each group gave the study enough power (80%) to detect a significant difference (P < 0.05) in change in body weight of 2.0 ± 2.5 kg (± SD).

To account for an expected dropout during the 8-wk low-calorie diet (≈15%) and during the dietary intervention (≈20%), a minimum of 37 subjects in each group was needed. The sample size was increased to 50 in both the MUFA and LF groups, and 25 subjects were allocated to the control group. The present substudy is based on a group of a total of 56 subjects.

All statistical analyses are based on data for the 46 subjects who completed the OGTT at baseline and after the 6-mo intervention. At baseline, differences between groups in glucose tolerance [fasting, area under the response curve (AUC), and insulin sensitivity] and anthropometric measures (body weight, fat mass, fat-free mass, and waist and hip circumferences) were tested by one-factor analysis of variance. Differences between groups in changes from 0 to 6 mo were also tested with a univariate-adjusted general linear model for multiple comparisons by using Tukey’s test. Differences in sex and in the proportion of dropouts were tested by using chi-square tests. Stepwise multiple regression analysis was performed to examine independent predictors of the changes in glucose tolerance. The statistical analyses were performed after transformation of variables when homogeneity of variance was not achieved. All results are presented as mean values with 95% CIs. Data presented in the figure are means ± SEMs. The level of significance was set at P < 0.05. These statistical analyses were conducted by using SPSS software (version 13; SPSS Inc, Chicago, IL).

Repeated-measures analyses were applied for variables with repeated measures over time (glucose and insulin concentrations...
The subjects shopped an average of 1.5 times/wk, and in the supermarket were found between groups. The dietary intake came from foods from the supermarket, fiber and sugar than did the MUFA and LF groups (P < 0.001) and in the intake of carbohydrate (P < 0.001) were achieved. Pairwise analyses showed that the LF group had a higher intake of saturated fat and a lower intake of polyunsaturated fatty acids (% of energy) (P = 0.001) and the control group (0.028). Furthermore, the control group had a higher intake of saturated fat and a lower intake of fiber and sugar than did the MUFA and LF groups (P < 0.001). The subjects shopped an average of 1.5 times/wk, and ≈87% of the dietary intake came from foods from the supermarket, whereas the remaining 13% came from ordinary shops. No differences in the number of visits or in the amount of foods shopped in the supermarket were found between groups.

### Dietary Intake

Dietary intake during the 6-mo weight-loss maintenance period is shown in Table 2. Dietary composition corresponded to the targeted experimental diets for all 3 groups. In particular, the targeted differences in the amount and type of fat intake between all 3 groups (P < 0.001) and in the intake of carbohydrate (P < 0.001) were achieved. Pairwise analyses showed that the LF group had a less-energy-dense diet than did the MUFA group (P < 0.001) and the control group (0.028). Furthermore, the control group had a higher intake of saturated fat and a lower intake of fiber and sugar than did the MUFA and LF groups (P < 0.001). The subjects shopped an average of 1.5 times/wk, and ≈87% of the dietary intake came from foods from the supermarket, whereas the remaining 13% came from ordinary shops. No differences in the number of visits or in the amount of foods shopped in the supermarket were found between groups.

## RESULTS

### Drop rate

Ten of the 56 subjects (18%) participating in the OGTT at baseline did not complete the 6-mo intervention: 7/23 (30%) in the MUFA group, 3/21 (14%) in the LF group, and 0 in the control group. The drop rate in the MUFA group was significantly greater than that in the control group (P = 0.036).

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### Body weight and body composition

Body weight and body composition at baseline, and after the 6-mo dietary intervention, are shown in Table 3. Before the 6-mo weight-loss maintenance period was initiated, the average weight loss during the low-calorie diet was 10.7 (95% CI: 9.3, 12.0) kg and during the 3-wk standardization the mean regain was 0.77 (95% CI: 0.24, 1.29) kg across groups with no significant group difference (P = 0.927 and P = 0.378, respectively). After the 6-mo dietary intervention, a small weight regain of 1.9 ± 4.3 kg in the MUFA group, of 1.5 ± 4.4 kg in the LF group, and of 3.5 ± 3.3 kg in the control group was found. No significant differences between the groups in changes in body weight, body fat, lean body mass, or waist and hip circumferences were seen at any time.

### Glucose tolerance and insulin sensitivity

Glucose and insulin responses during the OGTT, before and after the 6-mo weight-loss maintenance period, are shown in Figure 1. Before the dietary intervention, the control group had a significantly lower AUC\textsubscript{glucose} response than did the LF group (P = 0.003) and the MUFA group (P = 0.015) (Table 3). After the 6-mo intervention, no differences between groups were found in changes in AUC\textsubscript{glucose} or AUC\textsubscript{insulin}, and no interaction was found between diet and time (in min), even after adjustment for changes in body weight or for the response at baseline. After the 6-mo intervention, reductions of 3% in fasting glucose and of 9.4% in fasting insulin were seen in the MUFA group, whereas increases of 14.4% and 13.1%, respectively, were seen in the LF group; similarly, increases of 14.4% and 21.2%, respectively, were seen in the control group (Table 3). Pairwise analyses adjusted with the use of Tukey’s test showed significant differences in changes in fasting glucose and insulin between the MUFA and control groups (P = 0.014 and P = 0.030, respectively), and nearly significant differences between the MUFA

## Table 2

<table>
<thead>
<tr>
<th>Diet</th>
<th>MUFA (n = 16)</th>
<th>LF (n = 18)</th>
<th>Control (n = 12)</th>
<th>P²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy intake (MJ/d)</td>
<td>12.5 (11.4, 13.5)</td>
<td>12.8 (11.6, 13.9)</td>
<td>12.3 (10.9, 13.8)</td>
<td>0.600</td>
</tr>
<tr>
<td>Energy density (kJ/g)</td>
<td>4.5 (4.3, 5.1)</td>
<td>3.8 (3.6, 4.0)</td>
<td>4.3 (4.0, 4.6)</td>
<td>&lt;0.001 \textsuperscript{f}</td>
</tr>
<tr>
<td>Total fat (% of energy)</td>
<td>38.5 (37.8, 39.3)</td>
<td>23.4 (22.8, 23.9)</td>
<td>32.3 (31.4, 33.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Saturated fatty acids (% of energy)</td>
<td>7.2 (6.8, 7.7)</td>
<td>7.6 (7.2, 7.9)</td>
<td>15.2 (14.7, 15.7)</td>
<td>&lt;0.001 \textsuperscript{f}</td>
</tr>
<tr>
<td>Monounsaturated fatty acids (% of energy)</td>
<td>20.1 (19.5, 20.7)</td>
<td>8.4 (8.0, 8.8)</td>
<td>10.4 (9.8, 11.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Polyunsaturated fatty acids (% of energy)</td>
<td>8.0 (7.6, 8.3)</td>
<td>5.3 (5.1, 5.6)</td>
<td>4.1 (3.6, 4.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Carbohydrate + fiber (% of energy)</td>
<td>43.5 (42.5, 44.4)</td>
<td>57.8 (56.8, 58.8)</td>
<td>49.7 (48.8, 50.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fiber (% of energy)\textsuperscript{g}</td>
<td>3.8 (3.5, 4.0)</td>
<td>3.9 (3.8, 4.1)</td>
<td>2.6 (2.2, 2.9)</td>
<td>&lt;0.001 \textsuperscript{f}</td>
</tr>
<tr>
<td>Added sugars (% of energy)</td>
<td>5.9 (4.9, 7.0)</td>
<td>6.2 (5.3, 7.1)</td>
<td>9.3 (8.0, 10.7)</td>
<td>&lt;0.001 \textsuperscript{f}</td>
</tr>
<tr>
<td>Protein (% of energy)</td>
<td>15.3 (14.7, 15.9)</td>
<td>16.0 (15.5, 16.5)</td>
<td>15.9 (15.1, 16.7)</td>
<td>0.206</td>
</tr>
<tr>
<td>Alcoholic (% of energy)</td>
<td>2.3 (1.4, 3.2)</td>
<td>2.5 (1.6, 3.4)</td>
<td>1.9 (0.7, 3.1)</td>
<td>0.635</td>
</tr>
<tr>
<td>Duration of intervention period (d)</td>
<td>139 (124, 154)</td>
<td>148 (130, 165)</td>
<td>151 (132, 169)</td>
<td>0.573</td>
</tr>
</tbody>
</table>

\textsuperscript{1} All values are \overline{x}; 95% CI in parentheses. MUFA diet, moderate in fat and high in monounsaturated fat; LF, low in fat.

\textsuperscript{2} Test for difference between groups by one-factor ANOVA adjusted for multiple comparisons with Tukey’s test, with diet as a fixed factor, and pairwise analyses.

\textsuperscript{3} LF compared with MUFA (P < 0.001) and LF compared with control (P = 0.028).

\textsuperscript{4} Control compared with LF (P < 0.001), control compared with MUFA (P < 0.001), and MUFA compared with LF (P > 0.1).

\textsuperscript{5} The energy value used for fiber was 10 kJ/g.
Table 3
Clinical and biochemical features of the 3 diet groups at baseline (month 0) and after a 6-mo weight-loss maintenance period

<table>
<thead>
<tr>
<th>Diet</th>
<th>MUFA (n = 16)</th>
<th>LF (n = 18)</th>
<th>CTR (n = 12)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>28.3 (25.5, 31.2)</td>
<td>28.2 (25.6, 30.5)</td>
<td>27.3 (24.6, 29.9)</td>
<td>0.830^2</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>7/9</td>
<td>8/10</td>
<td>5/7</td>
<td>0.988^1</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>1.72 (1.65, 1.79)</td>
<td>1.73 (1.67, 1.78)</td>
<td>1.65 (1.55, 1.75)</td>
<td>0.250^2</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>81.3 (75.1, 87.4)</td>
<td>85.7 (81.0, 90.5)</td>
<td>83.0 (75.7, 90.3)</td>
<td>0.484^2</td>
</tr>
<tr>
<td>Month 0</td>
<td>5.0 (4.8, 5.1)</td>
<td>4.9 (4.7, 5.1)</td>
<td>4.7 (4.4, 5.1)</td>
<td>0.480^2</td>
</tr>
<tr>
<td>Month 6</td>
<td>4.8 (4.6, 5.0)</td>
<td>5.0 (4.8, 5.2)</td>
<td>4.8 (4.6, 5.1)</td>
<td>0.015^4,6</td>
</tr>
<tr>
<td>Glucose AUC (mmol^-1·120 min^-1)</td>
<td>44.9 (34.1, 55.7)</td>
<td>46.5 (40.1, 52.9)</td>
<td>40.1 (26.2, 54.1)</td>
<td>0.641^2</td>
</tr>
<tr>
<td>Month 0</td>
<td>713 (671, 754)</td>
<td>732 (680, 783)</td>
<td>613 (532, 694)</td>
<td>0.10^2</td>
</tr>
<tr>
<td>Month 6</td>
<td>735 (679, 791)</td>
<td>736 (682, 789)</td>
<td>667 (605, 730)</td>
<td>0.094^4</td>
</tr>
<tr>
<td>Insulin AUC (mmol^-1·120 min^-1)</td>
<td>26332 (19889, 32775)</td>
<td>31355 (24458, 38253)</td>
<td>35811 (23246, 48375)</td>
<td>0.253^2</td>
</tr>
<tr>
<td>Month 0</td>
<td>27359 (21493, 33225)</td>
<td>32727 (25492, 39962)</td>
<td>33922 (25499, 42344)</td>
<td>0.928^4</td>
</tr>
<tr>
<td>Matsudas index</td>
<td>23.6 (18.1, 29.1)</td>
<td>19.7 (16.9, 22.4)</td>
<td>25.5 (14.7, 36.2)</td>
<td>0.034^2</td>
</tr>
<tr>
<td>Month 0</td>
<td>23.5 (19.1, 27.8)</td>
<td>18.5 (15.1, 21.9)</td>
<td>21.8 (13.8, 30.2)</td>
<td>0.073^4</td>
</tr>
<tr>
<td>Month 6</td>
<td>1.40 (1.03, 1.76)</td>
<td>1.42 (1.21, 1.62)</td>
<td>1.19 (0.74, 1.65)</td>
<td>0.579^2</td>
</tr>
<tr>
<td>Month 6</td>
<td>1.23 (0.92, 1.54)</td>
<td>1.64 (1.36, 1.91)</td>
<td>1.47 (1.00, 1.94)</td>
<td>0.020^4,7</td>
</tr>
<tr>
<td>Adiponectin (µg/mL)</td>
<td>83.2 (76.8, 89.6)</td>
<td>87.2 (81.8, 92.6)</td>
<td>86.5 (78.5, 94.5)</td>
<td>0.224^2</td>
</tr>
<tr>
<td>Month 0</td>
<td>5.0 (4.8, 5.1)</td>
<td>4.9 (4.7, 5.1)</td>
<td>4.7 (4.4, 5.1)</td>
<td>0.480^2</td>
</tr>
<tr>
<td>Month 6</td>
<td>4.8 (4.6, 5.0)</td>
<td>5.0 (4.8, 5.2)</td>
<td>4.8 (4.6, 5.1)</td>
<td>0.015^4,6</td>
</tr>
</tbody>
</table>

- All values are mean ± 95% CI in parentheses. PAL, physical activity level; HOMA-IR, homeostasis model assessment of insulin resistance [fasting glucose (mmol/L) × fasting insulin (mU/L)/22.5]; Matsudas index [10 000/(fasting plasma glucose × fasting plasma insulin × mean plasma glucose × mean plasma insulin)^1/2], where mean is the mean of the entire oral-glucose-tolerance test period, including the baseline value.
- Test for difference between groups by chi-square test.
- Test for difference between groups at month 0 by one-factor ANOVA.
- Test for difference in changes (month 6 – month 0) between groups after the dietary intervention by general linear model univariate ANOVA and pairwise analyses adjusted for multiple comparisons with Tukey’s test.
- MUFA compared with LF (P = 0.090) and MUFA compared with control (0.014).
- MUFA compared with LF (P = 0.075) and MUFA compared with control (P = 0.030).
- MUFA compared with LF (P = 0.095) and MUFA compared with control (P = 0.015).

and LF groups (P = 0.090 and P = 0.075). The marker for insulin resistance determined by HOMA-IR also improved, by 12.1% in the MUFA group, whereas it was worse in the control group (by 22.8%; P = 0.015) and in the LF group (by 15.5%; P = 0.095). However, without the Tukey adjustment, a significant difference between the MUFA and LF groups in changes in fasting glucose (P = 0.008) and a nearly significant difference in changes in fasting insulin and HOMA-IR (P = 0.055 and P = 0.091, respectively) was seen.

No difference in insulin sensitivity, assessed with the Matsudas index, or in adiponectin concentrations was seen between the groups after the 6-mo intervention. Multiple regression analyses showed that a relatively higher intake of the food category nuts and legumes (defined in the new Healthy Eating Pyramid) explained 9% of the variation between groups in changes in fasting glucose (R^2 = 0.088, P < 0.05).

**DISCUSSION**

The present study showed that a diet high in monounsaturated fat improves glucose metabolism more so than does a typical Western diet and may also be more beneficial than the official recommended low-fat diet. The concentration of both insulin and glucose is known to be positively correlated with body weight and to decline with weight loss (24), although it is hard to predict from the present data. In this weight-loss maintenance study, we found increases in fasting insulin and glucose concentrations along with slight weight regains with the LF and control diets, whereas, despite a similar weight regain with the MUFA diet, reductions in fasting glucose and insulin concentrations were seen. This means that a diet high in monounsaturated fat seems to have a beneficial effect on glucose metabolism independently of a small weight regain. In a post hoc power analysis, a detectable...
difference between the MUFA and LF groups of 0.31 mmol/L in fasting glucose was found. This suggests that the lack of significant difference actually found between these diet groups (0.22 mmol/L) might have been due to insufficient statistical power.

Obviously, weight gain occurring as a result of increased total fat intake might lead to increased insulin resistance and impaired glucose tolerance, but the present substudy was underpowered to pick up possible differences between groups in change in body weight. However, unpublished results from the main trial, which included 104 subjects, showed similar weight regains of 2.3, 2.0, and 3.3 kg in the MUFA, LF, and control groups, respectively (A Due et al, unpublished observations, 2007).

The fact that the subjects, subsequent to a prior weight loss of >10%, had an even better glucose metabolism before the 6-mo weight-loss maintenance period, with only relatively low weight regains, may explain why only small differences were obtained between groups. The relatively high dropout rate of 18% may also have caused a nonsignificant difference between the MUFA and LF groups in the present study.

In a 3-mo isoenergetic, controlled dietary intervention in healthy subjects, Vessby et al (25) found that an exchange of saturated for monounsaturated fat improved insulin sensitivity assessed with an intravenous glucose tolerance test, whereas no improvement in fasting insulin or insulin secretion was seen (25). Interestingly, no beneficial effect was found when the fat intake was >37%. This may explain the lack of improvement in OGTT in the present trial, because the average fat intake in the MUFA group was 38.5%. A reduction in the total fat intake to <37% could possibly have resulted in a more pronounced beneficial effect of the MUFA diet on OGTT. Two other controlled dietary intervention studies performed under isoenergetic conditions in healthy (26) and obese subjects, some of whom had diabetes (27), indicate that an exchange of saturated fat with unsaturated fat in the diet will significantly improve insulin sensitivity. Moreover, an increase in the ratio of polyunsaturated fatty acids (n−6) to saturated fat has been found to improve blood glucose regulation in healthy normoglycemic men (28). It is noteworthy that, in epidemiologic studies, a high proportion of saturated fatty acids in the plasma lipid esters, compatible with a high dietary intake of saturated fat, is related to an increased risk of developing type 2 diabetes (29–31).

The favorable effect of the MUFA diet on glucose metabolism may also have been due to a presumed lower glycemic load of the diet, because a low-GI diet stimulates lower insulin secretion and thereby potentially improves glucose metabolism (32, 33). In the present study, we did not know the GI of the diets; however, we assume that the MUFA diet had a low GI and a low glycemic load because of its high content of unsaturated fat and whole grains and may, at least partly, explain the beneficial effect of this diet on glucose metabolism.

Garg et al (34) tested, in a 14-wk study, the metabolic effects of experimental diets very similar to the MUFA and LF diets in the present trial. They found that a low-fat, high-carbohydrate diet (as recommended by the American Diabetes Association and corresponding to the LF diet in the present study), compared with a high-monounsaturated diet, increased daylong plasma glucose and insulin by 12% and 9%, respectively. The present results also support the results of other studies, which showed that a low-fat, high-carbohydrate diet worsens glycemic control in type 2 diabetic subjects (35–37), whereas other investigations found that an increased intake of carbohydrates, comparable with the amount ingested in our study, is associated with either no change
(38) or a decrease in insulin sensitivity (39). In a recently published study, an inverse association between adherence to the Mediterranean diet (similar to the MUFA diet in the present study) and indexes of glucose homeostasis in a Greek normoglycemic population was found (40). Furthermore, in the present study, a relatively higher intake of nuts and legumes (characteristic food categories of a Mediterranean style diet) turned out to be a predictor of an improved change in fasting glucose and may play a beneficial role in glucose homeostasis in the long term.

The plasma glucose responses to an OGTT in the present trial was the result of both peripheral glucose utilization and hepatic glucose production (41), whereas the hyperinsulinemic glucose clamp technique used in other trials is designed to measure peripheral glucose utilization only (42, 43). The OGTT was chosen because it reflects effects on the whole range of physiologic aspects after dietary intake, including the influence of gastrointestinal hormones, and therefore better reflects free-living conditions.

There is convincing evidence that exchanging dietary saturated fat with monounsaturated fat produces beneficial effects on cardiovascular disease risk factors other than insulin resistance, i.e., it lowers LDL-cholesterol concentrations (44), improves the postprandial lipid profile (45), and lowers the blood pressure (46). Furthermore, adiponectin appears to act on skeletal muscles to promote fat oxidation and on the liver to reduce glucose production (47) and a low-energy Mediterranean-style diet has been shown to increase the concentration of adiponectin compared with a control diet (48). However, this could not be confirmed in the present study.

The larger dropout rate in the MUFA group compared with that in the control group might have been due to the low acceptance of this diet in our Northern European population, in whom a Mediterranean-style diet (high in monounsaturated fat) is unusual. Several subjects following the MUFA diet reported difficulties in adapting to the diet, primarily because of the high intake of vegetable oil. Compliance with a recommended diet is of great importance, and the supermarket model used in the present trial is the best method to ensure high compliance under free-living conditions (20).

In conclusion, 6 mo of a diet conforming to the new Healthy Eating Pyramid, which has a high content of MUFAs, seems to be more effective at improving insulin resistance as measured by HOMA-IR than the typical Western diet and may also be more beneficial than the official recommended low-fat diet during periods of weight regain after weight loss. The study participants in the present trial were young, normoglycemic, overweight or obese, and otherwise healthy, and the beneficial effect of the MUFA diet could be more pronounced in insulin-resistant subjects.

We thank the project staff of the Department of Human Nutrition and especially thank Walter Willett (Department of Epidemiology and Nutrition, Harvard School of Public Health, Boston, MA) and David Ludwig (Department of Medicine, Children’s Hospital, Boston, MA) for participating in the design of the project.

The authors’ responsibilities were as follows—AD: had full access to all of the data in the study and responsible for the integrity of the data and the accuracy of the data analysis; AA, TML, ST, and AD: responsible for the study concept and design; AD and TML: responsible for the data acquisition; AD, TML, KH, SS, JH, TM, ST, and AA: responsible for the data analysis and interpretation; AD and TM: responsible for the statistical analysis; AD, TML, and AA: responsible for the drafting of the manuscript; AD, TML, KH, SS, JH, TM, ST, and AA: responsible for the critical revision of the manuscript and its important intellectual content; AA, TML, ST, and AD: responsible for obtaining funding; and AA: responsible for study supervision. None of the authors reported a conflict of interest.

REFERENCES


