Changes in plasma lipoproteins during low-fat, high-carbohydrate diets: effects of energy intake\textsuperscript{1–3}

Sidika E Kasim-Karakas, Rogelio U Almario, Wendy M Mueller, and Janet Peerson

ABSTRACT

Background: Low-fat diets can increase plasma triacylglycerol and reduce HDL cholesterol. Changes in energy intake and body weight can influence the lipoprotein response.

Objective: We sought to prospectively examine the effects of euenergetic and ad libitum dietary fat restriction on plasma lipoproteins in healthy postmenopausal women.

Design: Participants first received a controlled euenergetic diet in which dietary fat was reduced stepwise from 35% to 25% to 15% over 4 mo. Thereafter, participants followed an ad libitum 15%-fat diet for 8 mo; 54 women completed the intervention.

Results: During the controlled euenergetic diet, plasma triacylglycerol increased from 1.70 ± 0.10 to 2.30 ± 0.16 mmol/L, total cholesterol decreased from 5.87 ± 0.13 to 5.53 ± 0.13 mmol/L, LDL cholesterol decreased from 3.41 ± 0.10 to 2.87 ± 0.10 mmol/L, HDL cholesterol decreased from 1.76 ± 0.08 to 1.50 ± 0.08 mmol/L, and apolipoprotein (apo) A-I decreased from 5.11 ± 0.14 to 4.78 ± 0.14 mmol/L (\(P < 0.0001\) for all changes). Hormone replacement therapy did not affect the relative change in HDL cholesterol. Plasma glucose, insulin, hemoglobin A\textsubscript{1c}, free fatty acid, and apo B concentrations did not change significantly. During the ad libitum 15%-fat diet, participants lost 4.6 ± 0.4 kg. Plasma triacylglycerol and LDL cholesterol returned to baseline values (1.77 ± 0.12 and 3.31 ± 0.08 mmol/L, respectively), whereas HDL cholesterol and apo A-I remained low (1.40 ± 0.08 and 4.82 ± 0.18 mmol/L, respectively). HDL cholesterol and apo A-I concentrations stabilized in subjects who were not receiving hormone replacement therapy but continued to decline in women who were receiving hormone therapy.


KEY WORDS Low-fat diet, lipoproteins, postmenopausal women, high-carbohydrate diet, lipoprotein response, triacylglycerol, HDL cholesterol, high-density-lipoprotein cholesterol, triglycerides, weight reduction, hormone replacement therapy, apolipoprotein A-I, free fatty acids, glucose, insulin, hemoglobin A\textsubscript{1c}

INTRODUCTION

High plasma total cholesterol and LDL-cholesterol concentrations and a low plasma HDL-cholesterol concentration are associated with increased risk of coronary heart disease (CHD) (1, 2). Although high plasma triacylglycerol concentrations are also associated with increased risk of CHD, this relation may be indirect and may be secondary to the decreased HDL-cholesterol and increased small-dense LDL concentrations that accompany hypertriacylglycerolemia (3, 4). It is well known that low-fat diets lower plasma total cholesterol and LDL-cholesterol concentrations. However, such diets also decrease HDL-cholesterol concentrations and may increase plasma triacylglycerol concentrations (5, 6).

The hypertriacylglycerolemic effect of low-fat diets has been recognized for several decades (7). This effect was most evident during short-term studies in which euenergetic liquid-formula diets were given under metabolic ward conditions (8–10). This secondary hypertriacylglycerolemia can be prevented by decreasing the energy content of the diet (11–13), increasing the complex carbohydrate and fiber contents (14), or gradually restricting the fat content (15).

Here we present the results of a year-long, prospective study that examined the effects of both euenergetic and ad libitum low-fat diets on plasma lipoprotein concentrations. Our goal was to distinguish the effects of weight loss and changes in energy intake from the effects of changes in dietary fat consumption per se. We decided to study postmenopausal women because they are at higher risk of CHD and nutrition-related cancers than are premenopausal women.

SUBJECTS AND METHODS

Subjects

Sixty-four healthy postmenopausal women with a mean (±SD) age of 61 ± 11 y were recruited for the study and signed the

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informed consent forms. The study was approved by the Institutional Human Investigation Committee of the University of California at Davis. All participants underwent a physical examination by the principal investigator and provided blood samples while fasting for a chemistry-20 panel. We excluded individuals with any systemic disease, such as diabetes mellitus, liver or kidney disease, or hypertension requiring medication, and those who had a plasma triacylglycerol concentration > 2.82 mmol/L or an LDL-cholesterol concentration > 4.14 mmol/L. Smokers were also excluded, but obesity was not an exclusion criterion. Menopause was defined as a history of amenorrhea for ≥ 9 mo or surgical removal of both ovaries. Only women who were either not receiving hormone therapy or were receiving continuous hormone therapy were included; women receiving cyclical hormone replacement therapy were excluded. Twenty-five women received hormone replacement therapy; of these women, 15 took estrogen only and 10 took a combination of estrogen and progesterone. The dosages of the hormones and all other medications or supplements remained unchanged throughout the study. The participants’ exercise level was also kept constant and was monitored by using physical activity questionnaires. Four women were excluded from the study during the controlled euenergetic diet because of noncompliance. Six women left the study, 4 during the controlled euenergetic diet and 2 during the ad libitum 15%-fat diet. The remaining 54 women, who had a mean (±SD) age of 59 ± 8 y, completed the entire study.

Diet

The dietary intervention occurred in 2 phases. For the first 4 mo, participants followed a controlled euenergetic diet in which fat intake was reduced in a stepwise manner from 35% to 25% to 15% of energy; all food was provided to the participants. Second, they followed an ad libitum, self-selected, low-fat diet under free-living conditions for 8 mo; participants were told that their goal was to restrict fat intake to 15% of energy. For each participant, the diet consumed before the study was defined as the habitual diet.

Controlled euenergetic diet

Participants ate dinner at the study site 5 d/wk and received take-out, prepackaged breakfasts, lunches, snacks, and weekend meals. The food was prepared in 7-d menu cycles in the study kitchen. The ingredients were weighed to the nearest gram. When participants ate dinner at the study site, their trays were inspected to ensure complete consumption of the food.

During the first 4 wk of the study, the diet contained 35% of energy as fat. The goal was to bring all the participants to the same fat intake and to determine the energy intake required for weight maintenance in preparation for the low-fat diet phases. During this period, the initial energy intake was individualized for each subject’s resting energy expenditure (measured by using indirect calorimetry) multiplied by a factor reflecting her physical activity level (estimated from the physical activity questionnaire). Subjects were weighed 5 times/wk and the energy content of the diet was adjusted when body weight differed by > 1 kg from the weight measured at study entry.

After stabilization of body weight and energy intake during the 35%-fat diet, participants consumed a diet containing 25% of energy as fat for 6 wk, followed by a diet containing 15% of energy as fat for another 6 wk. Participants kept daily records of any additional dietary intake or uneaten foods. Noncompliance was defined as a > 10% difference in energy consumption between the actual dietary intake and the experimental diet on > 1 d during a week. Alcohol was not included in the diet. One alcoholic drink weekly was permitted, as long as this intake was recorded in the food diary. Most of the women did not consume any alcohol. Samples of foods from an entire week during each diet period were homogenized and sent to the Hazelton Laboratory (Madison, WI) for analysis of energy, macronutrient, and micronutrient contents. The actual fat contents of the diets during the 3 phases were 31%, 23%, and 14% and the carbohydrate contents were 53%, 60%, and 67%, respectively.

Ad libitum 15%-fat diet

After completing the 4-mo controlled euenergetic diet, participants continued to consume a 15%-fat diet under free-living conditions by using self-selected, commercially available food products. Subjects were not given any goals for either energy intake or body weight; the only goal of this intervention was to restrict dietary fat intake. To facilitate this goal, participants received education and training about the fat contents of food items, types of fats, calculating the amount of energy obtained from fat, basic principles of low-fat cooking, shopping for low-fat food items, and behavior modification techniques to achieve a change in dietary habits. Each participant also received an individual 3-h counseling session with the dietitian to review the general principles of the intervention diet and to address specific questions about, for example, ethnic foods or eating while traveling. During this 8-mo period, participants attended a potluck participatory dinner once a week. After the dinner, a 30-min session led by the dietitian and attended by the principal investigator was held to provide ongoing reinforcement and support.

Data collection

Dietary data

Seven-day food records were obtained at study entry and once a month during the ad libitum diet. The data were analyzed by using an updated version of NUTRITION DATA SYSTEM 93 (University of Minnesota, Minneapolis). The accuracy of the food records was confirmed by using food-frequency questionnaires.

Anthropometric variables and body composition

To determine the waist-to-hip ratio, waist circumference was measured at the point of smallest girth between the rib cage and iliac crest and hip circumference was measured at < 23 cm (9 in) below the waist. Total fat mass was measured by using bioelectrical impedance (BioAnalgics, British Isles) at the end of each controlled-feeding period and during the second and eighth months of the ad libitum 15%-fat diet. The variability of this measurement was < 1% (16).

Lipid and apolipoprotein determinations

Triacylglycerol and cholesterol concentrations were measured enzymatically with kits from Sigma Chemical Co, St Louis. Each assay included appropriate standards and calibrators. The interassay CVs were 3.6% for triacylglycerol and 1.9% for cholesterol. Plasma fatty acids were measured by using a kit method (WAKO, Richmond, VA) with a CV of 3%. HDL and its HDL₃ subfraction were separated from the plasma by the serial precipitation method of Warnick et al (17) with dextran sulfate and magnesium chloride. The CV for HDL cholesterol was 2% for the normal values and 5% for the extremes. The free and esterified
LIPOPROTEIN CHANGES DURING LOW-FA T DIETS

Changes in weight, percentage body fat, and nutrient intakes at study entry, at the end of the euenergetic diet, and during the ad libitum diet

<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
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<tbody>
<tr>
<td>Changes in weight, percentage body fat, and nutrient intakes at study entry, at the end of the euenergetic diet, and during the ad libitum diet</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study entry (0 mo)</th>
<th>Controlled euenergetic diet (4 mo)</th>
<th>Ad libitum 15%-fat diet</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>75.2 ± 2.4</td>
<td>6758 ± 100</td>
</tr>
<tr>
<td><strong>Percentage body fat (%)</strong></td>
<td>41.2 ± 0.9</td>
<td>6758 ± 100</td>
</tr>
<tr>
<td><strong>Nutrient intake</strong></td>
<td>73.9 ± 2.3</td>
<td>6758 ± 100</td>
</tr>
<tr>
<td><strong>Energy (kcal/d)</strong></td>
<td>71.4 ± 2.2</td>
<td>6758 ± 100</td>
</tr>
<tr>
<td><strong>Total fat (g/d)</strong></td>
<td>41.6 ± 1.0</td>
<td>6758 ± 100</td>
</tr>
<tr>
<td><strong>Carbohydrate (g/d)</strong></td>
<td>6063 ± 100</td>
<td>6758 ± 100</td>
</tr>
<tr>
<td><strong>Cholesterol (mg/d)</strong></td>
<td>73.9 ± 2.3</td>
<td>6758 ± 100</td>
</tr>
<tr>
<td><strong>Total fat (% of energy)</strong></td>
<td>70.8 ± 2.2</td>
<td>6758 ± 100</td>
</tr>
<tr>
<td><strong>Carbohydrate (% of energy)</strong></td>
<td>70.6 ± 2.2</td>
<td>6758 ± 100</td>
</tr>
<tr>
<td><strong>Energy (kJ/d)</strong></td>
<td>69.3 ± 2.1</td>
<td>6758 ± 100</td>
</tr>
<tr>
<td><strong>Total fat (% of energy)</strong></td>
<td>39.8 ± 0.9</td>
<td>6758 ± 100</td>
</tr>
</tbody>
</table>

| **Weight maintenance** | 8646 ± 83 | 6758 ± 100 |
| **Percentage body fat (%)** | 6758 ± 100 | 6758 ± 100 |
| **Nutrient intake** | 8646 ± 83 | 6758 ± 100 |
| **Energy (kcal/d)** | 8646 ± 83 | 6758 ± 100 |
| **Total fat (g/d)** | 8646 ± 83 | 6758 ± 100 |
| **Carbohydrate (g/d)** | 8646 ± 83 | 6758 ± 100 |
| **Cholesterol (mg/d)** | 8646 ± 83 | 6758 ± 100 |
| **Total fat (% of energy)** | 8646 ± 83 | 6758 ± 100 |
| **Carbohydrate (% of energy)** | 8646 ± 83 | 6758 ± 100 |
| **Energy (kJ/d)** | 8646 ± 83 | 6758 ± 100 |

**Notes:** Values in the same row with different superscript letters are significantly different, P < 0.05 (repeated-measures ANOVA followed by Tukey-Kramer adjustment).

Results

Changes in nutrient intake

Although the controlled euenergetic diet was designed to deliver 35%, 25%, and 15% of energy from fat, chemical analysis of the diet showed that the actual dietary fat intakes were 31%, 23%, and 14%, respectively. The corresponding carbohydrate intakes were 53%, 60%, and 67% of daily energy. During the ad libitum diet, fat intake ranged from 11% to 12%, carbohydrate and fiber intakes increased, and cholesterol intake decreased (Table 1). At study entry, self-reported energy intake was 6758 ± 100 kJ, whereas at the end of the 35%-fat phase of the controlled euenergetic diet, the energy intake required for weight maintenance was 8646 ± 83 kJ (data not shown). This difference between the actual and self-reported energy intakes represented an underreporting of 1888 kJ/d, as found previously (20). The magnitude of underreporting did not correlate with the degree of obesity.

Changes in weight

During the controlled euenergetic diet, weight decreased slightly but body mass index (BMI; in kg/m²) and percentage body fat did not change significantly (Table 1). During the ad libitum 15%-fat diet, the mean weight loss was 4.6 ± 0.5 kg, BMI decreased from 27.6 ± 0.9 to 25.5 ± 0.8 (P < 0.01), and percentage body fat decreased from 42.2 ± 1.1 to 39.8 ± 0.9% (P < 0.01). Waist-to-hip ratio did not change during either dietary period; the ratio was 0.87 ± 0.11 and 0.86 ± 0.1 during the controlled and ad libitum diets, respectively.

Changes in plasma glucose, insulin, hemoglobin A1c, and free fatty acid concentrations

Plasma glucose concentrations were lower during the 10th and 12th months of the ad libitum 15%-fat diet (4.94 ± 0.18 and 4.77 ± 0.18 mmol/L, respectively; P < 0.002) than at other times during the study (Table 2). Insulin and hemoglobin A1c concentrations did not change significantly during the study. Plasma free fatty acid concentrations decreased significantly at only one time point, during the 25%-fat phase of the controlled euenergetic diet.

Changes in plasma triacylglycerol, total cholesterol, LDL-cholesterol, and apo B concentrations

During the controlled euenergetic diet, the mean plasma triacylglycerol concentration increased gradually, from 1.70 ± 0.10 mmol/L during the 35%-fat diet to 1.96 ± 0.11 mmol/L during the 25%-fat diet and to 2.30 ± 0.16 mmol/L (P < 0.0001) during the 15%-fat diet (Figure 1). However, 2 mo after participants switched to the ad libitum 15%-fat diet, triacylglycerol concentrations decreased to 1.90 ± 0.15 mmol/L and remained stable for the rest of the study. At the end of the 12-mo study, the plasma triacylglycerol concentration (1.77 ± 0.12 mmol/L) was not significantly different from the value at study entry.
During the controlled euenergetic diet, the total cholesterol concentration decreased from 5.87 ± 0.13 to 5.53 ± 0.13 mmol/L and the LDL-cholesterol concentration decreased from 3.41 ± 0.10 to 2.87 ± 0.10 mmol/L (P < 0.0001 for both; Figure 1). During the ad libitum diet, total cholesterol concentrations remained low. However, the LDL-cholesterol concentrations returned to baseline values within 2 mo and remained stable for the rest of the study.

Apo B concentrations did not change significantly during either the controlled or ad libitum phases of the fat restriction (study entry: 1.94 ± 0.07 mmol/L; end of controlled diet: 2.04 ± 0.07 mmol/L; end of ad libitum diet: 1.96 ± 0.07 mmol/L).

Changes in HDL concentration, HDL composition, and apo A-I concentration

During the controlled euenergetic diet, HDL-cholesterol concentration decreased steadily, from 1.76 ± 0.08 to 1.50 ± 0.08 mmol/L (Table 3), and plasma apo A-I concentration decreased from 5.11 ± 0.14 to 4.78 ± 0.14 mmol/L. During the ad libitum 15%-fat diet, HDL-cholesterol concentrations did not change any further; mean values were 1.37 ± 0.05 mmol/L at 6, 8, and 10 mo and 1.45 ± 0.08 mmol/L at 12 mo. Plasma apo A-I concentrations also remained unchanged, ranging from 4.75 ± 0.18 to 4.82 ± 0.18 mmol/L. HDL composition studies showed that whereas the cholesterol ester, free cholesterol, phospholipid, and apo A-I contents of HDL decreased, HDL triacylglycerol did not change significantly. Of the 2 HDL subfractions, HDL3-cholesterol showed a larger reduction.

Effects of hormone replacement therapy

Women who were and who were not receiving hormone replacement therapy had similar BMIs at study entry and lost similar amounts of weight during the study (Table 4). At base-

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Study entry</th>
<th>35% Fat</th>
<th>25% Fat</th>
<th>15% Fat</th>
<th>Ad libitum 15%-fat diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.44 ± 0.11</td>
<td>5.50 ± 0.11</td>
<td>5.55 ± 0.11</td>
<td>5.16 ± 0.11</td>
<td>4.77 ± 0.11 b</td>
</tr>
<tr>
<td>Insulin (pmol/L)</td>
<td>114 ± 12</td>
<td>96 ± 6</td>
<td>102 ± 12</td>
<td>96 ± 6</td>
<td>96 ± 6 NS</td>
</tr>
<tr>
<td>Hemoglobin A1C (%)</td>
<td>4.6 ± 0.1</td>
<td>4.7 ± 0.1</td>
<td>4.4 ± 0.1</td>
<td>4.5 ± 0.1</td>
<td>4.3 ± 0.1 NS</td>
</tr>
<tr>
<td>Free fatty acids (mmol/L)</td>
<td>0.84 ± 0.06 a</td>
<td>0.91 ± 0.05 a</td>
<td>0.68 ± 0.03 b</td>
<td>0.81 ± 0.04 a</td>
<td>— &lt;0.001</td>
</tr>
</tbody>
</table>

* SEM; n = 54. Values in the same row with different superscript letters are significantly different, P < 0.05 (repeated-measures ANOVA followed by Tukey-Kramer adjustment). To convert glucose to mg/dL, divide by 0.5551; insulin to mU/L, divide by 6.0; and free fatty acids to mg/dL, divide by 0.0355.

![FIGURE 1](image-url). Mean (±SEM) changes in plasma triacylglycerol (TG), total cholesterol (TC), LDL cholesterol (LDL-C), and apolipoprotein (apo) B concentrations during the controlled euenergetic diet and the ad libitum 15%-fat diet in postmenopausal women (n = 54). *Significantly different from the baseline value, P < 0.05 (repeated-measures ANOVA followed by Tukey-Kramer adjustment). To convert cholesterol to mg/dL, divide by 0.02586; triacylglycerol to mg/dL, divide by 0.01129; and apo B to mg/dL, divide by 0.0185.
Weight (kg) 78.4

TG (mmol/L) 2

Percentage body fat (%) 41.6

Apo A-I (mmol/L) 2

women who were and were not receiving hormone replacement therapy (HRT) at study entry and at the end of the euenergetic and ad libitum diets. Differences in weight, percentage body fat, and plasma lipoproteins [triacylglycerol (TG) and total cholesterol (TC)] and apolipoproteins (apo) between women who did and did not take hormone replacement therapy (Table 5) and in women who were receiving hormone replacement therapy (Table 6). The plasma triacylglycerol concentration was positively correlated with dietary carbohydrate intake in women receiving hormone replacement therapy. The HDL-cholesterol concentration was inversely correlated with dietary carbohydrate and starch. The apo B concentration was highly correlated with the dietary variables in the hormone-treated group (Table 6), showing positive correlations with total, saturated, monounsaturated, and polyunsaturated fat intakes and negative correlations with carbohydrate, sucrose, and fructose intakes. The apo A-I concentration was correlated with several dietary variables in the group not receiving hormone replacement therapy (Table 5), showing a positive correlation with saturated fat intake and inverse correlations with carbohydrate and fiber intakes.

**DISCUSSION**

This study had several important findings. First, the hypertriacylglycerolemic effect of fat restriction occurred only during the controlled euenergetic diet, when we tried to prevent weight loss. Second, decreases in HDL-cholesterol and apo A-I concentrations

**TABLE 4**

Differences in weight, percentage body fat, and plasma lipoproteins [triacylglycerol (TG) and total cholesterol (TC)] and apolipoproteins (apo) between women who were and were not receiving hormone replacement therapy (HRT) at study entry and at the end of the euenergetic and ad libitum diets.

<table>
<thead>
<tr>
<th>Substance (mmol/L)</th>
<th>Study entry</th>
<th>Controlled euenergetic diet</th>
<th>Ad libitum</th>
<th>Study entry</th>
<th>Controlled euenergetic diet</th>
<th>Ad libitum</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-C</td>
<td>1.76 ± 0.08&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.63 ± 0.08&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.55 ± 0.08&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.50 ± 0.08&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>HDL-CE</td>
<td>1.19 ± 0.23&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.09 ± 0.21&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.01 ± 0.21&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.98 ± 0.18&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>HDL-FC</td>
<td>0.57 ± 0.10&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.54 ± 0.10&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.54 ± 0.10&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.52 ± 0.08&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>HDL-TG</td>
<td>0.45 ± 0.02&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.44 ± 0.02&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.45 ± 0.02&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.45 ± 0.02&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NS</td>
<td></td>
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<tr>
<td>HDL-PL</td>
<td>39.7 ± 2.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>36.5 ± 2.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>37.1 ± 2.6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>37.5 ± 2.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>HDL-apo A-I</td>
<td>5.14 ± 0.14&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.78 ± 0.14&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.57 ± 0.14&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.39 ± 0.14&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.31 ± 0.02&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.34 ± 0.02&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.26 ± 0.02&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.28 ± 0.02&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NS</td>
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<tr>
<td>HDL-apo A-I</td>
<td>1.45 ± 0.08&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.29 ± 0.05&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.29 ± 0.05&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.22 ± 0.05&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;0.0001</td>
<td></td>
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</table>

<sup>1</sup>Significant (P < 0.05) hormone effect, for the same time periods, without any interaction with diet.

<sup>2</sup>Only HDL-C showed an HRT-group and diet interaction.

<sup>3</sup>Only HDL-C showed an HRT-group and diet interaction.
were independent of changes in weight and plasma triacylglycerol concentrations and persisted even after plasma triacylglycerol returned to baseline values. Third, although LDL-cholesterol concentrations decreased during the controlled euenergetic diet, they returned to baseline during the ad libitum 15%-fat diet. Fourth, hormone replacement therapy exaggerated the hypertriacylglycerolemic response to fat restriction.

It is well recognized that ad libitum low-fat diets cause significant weight loss (21, 22); one reason for this is the decrease in energy intake. As described by Lichtenstein et al (13) and Schaefer et al (11), the lower energy density and higher volume of low-fat diets result in automatic reductions in food and energy intakes; our findings in the present study were similar. When the amount of energy required to maintain weight during the controlled euenergetic diet was compared with the subjects’ self-reported energy intakes, it was clear that the subjects underreported their daily energy intake by ≈1900 kJ on average. The magnitude of underreporting did not correlate with the subjects’ body weight and was consistent. Within the limitations of self-reported data, participants decreased their energy intake by 640 kJ/d during the ad libitum 15%-fat diet. Thus, the calculated energy deficit over this 8-mo period was 153 600 kJ, which should have resulted in a 5.3-kg weight loss. We observed a 4.3-kg weight loss during the ad libitum 15%-fat diet. Although fat restriction may facilitate weight loss through additional mechanisms (22), the self-reported energy deficit was adequate to explain the weight loss seen in our study.

The hypertriacylglycerolemic effect of low-fat, high-carbohydrate diets has been recognized for several decades (5, 7–15). Approaches that have been used to prevent this hypertriacylglycerolemic effect include a gradual increase in carbohydrate intake (14), increases in complex carbohydrate and fiber intakes (14), and restriction of total energy (11–13). We showed that even when carbohydrate intake is increased in a stepwise manner,
plasma triacylglycerol concentrations increase. The etiology of the carbohydrate-induced hypertriacylglycerolemia is not well understood. Although de novo synthesis of triacylglycerol from carbohydrates is well recognized in rodents, this process in humans was shown conclusively only in the past few years (23, 24). An important clinical finding that commonly accompanies hypertriacylglycerolemia is insulin resistance (25), which leads to elevated free fatty acid and insulin concentrations and consequently promotes hepatic triacylglycerol synthesis. In return, preferential use of triacylglycerol and fatty acids in muscle tissue may further impair glucose utilization (Randle hypothesis; 26). We did not see any increases in fasting plasma free fatty acid, insulin, glucose, or hemoglobin A1c concentrations during the controlled euenergetic diet. In addition, hypertriacylglycerolemia may have been caused by decreased clearance of triacylglycerol-rich lipoproteins by lipoprotein lipase (27). We observed previously that postheparin lipoprotein lipase activity, but not hepatic triacylglycerol lipase activity, decreased during dietary fat restriction in premenopausal women (28). A similar decrease in lipoprotein lipase activity may have been responsible for the increase in triacylglycerol concentrations in this study, but we did not measure lipoprotein lipase.

Another significant outcome of the low-fat diet was the decreased concentrations of HDL cholesterol and apo A-I, a finding that we and other researchers (8–15, 28) noted previously. Researchers have reported that decreases in dietary total fat, saturated fat, monounsaturated fat, and even polyunsaturated fat can lower plasma HDL-cholesterol concentrations (29, 30). Kinetic studies of HDL apolipoproteins showed that low-fat diets reduced the transport rate of apo A-I (31) and high-fat diets increased HDL, both by increasing the transport rate and decreasing the fractional catabolic rate of apo A-I and HDL-cholesterol ester (32). Consistent with these kinetic data, we observed decreases, primarily in the apo A-I, cholesterol ester,
and free cholesterol contents of HDL, whereas HDL triacylglycerol was not affected. These findings suggest that low-fat diets decrease not only the cholesterol carried in an individual HDL particle, but probably the entire circulating HDL fraction.

Another significant observation was that the decrease in HDL-cholesterol concentration was not secondary to the increase in plasma triacylglycerol concentration. Cross-sectional studies have shown a strong inverse correlation between plasma triacylglycerol and HDL-cholesterol concentrations that is probably a result of the exchange of core lipids between VLDL and HDL by cholesterol ester transfer protein (33). The fact that the HDL-cholesterol concentration remained low during the ad libitum 15%-fat diet, despite the decrease in plasma triacylglycerol concentration, indicated that the reduced HDL concentration was a direct result of the fat restriction per se.

A disconcerting finding was that during the ad libitum 15%-fat diet, as plasma triacylglycerol concentration decreased, the plasma LDL-cholesterol concentration returned to baseline values. Furthermore, there was no decrease in the plasma apo B concentration throughout the study. This was not a result of dietary noncompliance because the participants lost weight steadily, attended weekly participatory dinners, and kept monthly 7-d food records. In addition, although LDL cholesterol increased, HDL cholesterol and apo A-I did not, providing further evidence of compliance with the fat restriction. A reciprocal relation between plasma triacylglycerol and LDL-cholesterol concentrations was observed in several other clinical settings. For example, treatment of hypertriglyceridemic patients with fibrates or n–3 fish fatty acid–containing oils increased concentrations was observed in several other clinical settings. For example, treatment of hypertriglyceridemic patients with fibrates or n–3 fish fatty acid–containing oils increased LDL cholesterol and decreased plasma triacylglycerol (34, 35).

Similarly, in diabetic patients, antihyperglycemic therapy can increase LDL cholesterol while lowering plasma triacylglycerol (36). In obese subjects, weight loss can elicit similar changes (37). Although our subjects were not hypertriglyceridemic at baseline, they were older women with high percentages of body fat. Therefore, they may have had some metabolic features similar to those of patients with obesity or hypertriglyceridemia.

Several previous studies investigated the effects of dietary fat restriction on plasma lipids. The populations, designs, and durations of these studies were somewhat different from ours. For example, Schaefer et al (11) reported that in 27 (13 men and 14 women) elderly, hypercholesterolemic subjects, a euenergetic 15%–fat diet decreased the LDL-cholesterol concentration by 17%, whereas an ad libitum low-fat diet caused a 24% decrease. Lichtenstein et al (13) reported that, in 5 men and 6 women, a euenergetic 15%-fat diet lowered the LDL-cholesterol concentration by 14% and an ad libitum low-fat diet lowered it by 23%. Recently, Flynn et al (12) reported that in 10 men and 10 postmenopausal women, a euenergetic National Cholesterol Education Program Step II diet increased plasma triacylglycerol and decreased total, LDL, and HDL cholesterol; the apo B concentration did not change. When the same diet was administered with a 15% energy restriction, plasma triacylglycerol decreased and there were additional decreases in total and LDL cholesterol, while HDL cholesterol did not change further (12). Ullmann et al (15) reported that in 2 women and 6 men, LDL cholesterol decreased by 22% when dietary fat intake decreased to 20% of energy. However, when Jeppesen et al (8) compared the effects of a euenergetic 45%-fat diet with those of a 25%-fat diet in 10 healthy postmenopausal women, they found no change in LDL cholesterol. A recent report from the DELTA (Dietary Effects on Lipoproteins and Thrombogenic Activity) Study group (38) stated that in 18 postmenopausal women, reduction of dietary fat from 34% to 25% for 8 wk decreased LDL cholesterol by 11%. Although the absence of a decrease in LDL cholesterol during the ad libitum low-fat phase of the present study was disappointing, our findings may suggest the need for a more focused approach. Our study was conducted in a large group of healthy postmenopausal women over a long time, under both controlled euenergetic and ad libitum conditions. It is clear that both plasma triacylglycerol and LDL cholesterol responded not only to the changes in dietary fat, but also to the changes in energy intake and weight. Therefore, it is not surprising that studies with different populations and dietary interventions reported variable findings, making it difficult to formulate a uniform recommendation for the general population.

The present study confirmed previous reports (39, 40) that women receiving hormone replacement therapy had higher HDL-cholesterol and lower LDL-cholesterol concentrations than did women not taking hormones. Our study contributed to the existing knowledge by showing that hormone therapy did not prevent the decrease in HDL-cholesterol concentration that occurred during dietary fat restriction.

In summary, our long-term, prospective study clarified the role of energy intake in the development of hypertriglyceridemia during low-fat diets and identified the specific changes that occur in the composition of HDL. The decrease in HDL-cholesterol concentration along with the increase in triacylglycerols can be considered unfavorable with regard to risk of CHD. However, a major difference between the fat-restriction-induced lipid changes and genetic dyslipidemia was that the low-fat diet did not seem to cause insulin resistance, whereas genetic dyslipidemia is usually accompanied by insulin resistance (25). Furthermore, at the end of the study, these women still had relatively high HDL-cholesterol concentrations that corresponded to the second-highest quartile of the HDL-cholesterol distribution in the female population (41). Thus, the fat-restriction-induced decrease in HDL cholesterol may not have the same adverse clinical implications in postmenopausal women as would a decrease in HDL caused by genetic dyslipidemia. In addition, a much less appreciated direct relation exists between high HDL-cholesterol concentrations and benign and malignant neoplasms of the breast (42–46). Our findings suggest that recommendations for dietary fat intake need to be individualized. Whereas strict dietary fat restriction may be advisable for weight loss or prevention of nutrition-related cancers (21, 46), it may not be necessary for the prevention of CHD.

REFERENCES


