Impact of Myristic Acid Versus Palmitic Acid on Serum Lipid and Lipoprotein Levels in Healthy Women and Men

Peter L. Zock, Jeanne H.M. de Vries, Martijn B. Katan

Abstract The cholesterol-raising effect of dietary saturated fatty acids is largely accounted for by lauric, myristic, and palmitic acids. Dairy fat is a major source of myristic acid, and palm oil is especially rich in palmitic acid. Myristic acid is suspected of being much more cholesterolemic than palmitic acid, but direct comparisons have been lacking. We therefore fed 36 women and 23 men three diets that differed from each other in palmitic, oleic, and myristic acid content by about 10% of total energy. We used palm oil, high-oleic acid sunflower oil, and a specially produced vegetable oil that is high in saturated fatty acids, is low in medium-chain saturates (C6:0, C8:0, and C10:0) or stearic acid.10 In humans lauric acid is less potent than palmitic acid in raising total cholesterol and LDL-cholesterol.8-9 These effects are seen in experimental animals, saturated fatty acids raise plasma cholesterol through downregulation of low-density lipoprotein (LDL) receptor activity and subsequent accumulation of LDL cholesterol (LDL-C) in plasma and increased LDL production from its precursor, very-low-density lipoprotein (VLDL).89 These effects are seen with lauric, myristic, and palmitic acids but not with medium-chain saturates (C6:0, C8:0, and C10:0) or stearic acid.10 In humans lauric acid is less potent than palmitic acid in raising total cholesterol and LDL-C.89 Myristic acid and palmitic acid together make up about 25% to 30% of the fat in Western diets (D. Kromhout, unpublished data, 1988), but their relative cholesterol-raising potencies have not been clearly defined in humans. Meta-analyses of dietary trials that employed commercially available fats indicate that myristic acid might be four to six times more cholesterolemic than palmitic acid.413 Some recent studies also suggest that palmitic acid lowers cholesterol relative to a mixture of lauric acid and myristic acid.14-16 However, others have found that palmitic acid strongly increases cholesterol levels.5712-17 A problem in studies with natural fats is that the amount of myristic acid is linked with either the amount of lauric acid, such as in coconut oil, or with that of palmitic acid, such as in dairy fat. The effects of different saturates are therefore hard to examine. An early study with specially synthesized fats by McGandy et al11 did not resolve the issue. Synthetic fats are expensive, and the effort has not been repeated until now.

Myristic acid is the third most common saturated fat in the diet. Average intake levels are about 1 g/d in Japan, 6 g/d in the United States, 8 g/d in the Netherlands, and 14 g/d in eastern Finland (D. Kromhout et al, unpublished data, 1988). Major sources are butter fat, which is also rich in palmitic acid, and two vegetable oils, coconut oil and palm kernel oil; the latter two also contain large amounts of lauric acid. Palm oil, another vegetable oil that is high in saturated fatty acids, is low in myristic acid and high in palmitic acid. Palm oil is the number one edible oil worldwide, and its consumption is rising. If much of the cholesterol-raising effect of saturated fatty acids is indeed specifically due to myristic acid, then palm oil would be a suitable substitute for animal fats and hydrogenated vegetable oils in a wide range of products for cholesterol-lowering diets. Moreover, modern biotechnology could be applied to replace myristic acid with palmitic acid in other fats.

To investigate the relative potencies of myristic and palmitic acids, we produced a fat high in myristic acid and compared its effects with those of palmitic and oleic acid.
acids on lipoprotein levels in humans. Serum lipids have an important role in the atherosclerotic process in both women and men, but data on the differences in dietary effects on serum lipids between women and men are scarce. To determine whether women and men have similar lipoprotein responses to dietary saturated fat, we included enough female subjects to allow detection of gender-specific responses.

Methods

Hypotheses, Design, and Statistical Analysis

The objective of the trial was to estimate the effects of myristic and palmitic acids relative to each other and to oleic acid on serum lipids and lipoproteins in healthy women and men. The study was designed to detect a significant ($P<.05$) effect of myristic acid versus palmitic acid on total cholesterol and LDL-C with a power of 80% if the real population effect exceeded 0.13 mmol/L. The a priori power was also 80% for detecting a difference in response of total cholesterol and LDL-C of 0.30 mmol/L between women and men.

The trial consisted of three consecutive 3-week periods, during which each participant consumed each of the three diets. Our experience agrees with that of earlier workers in that serum lipid and lipoprotein levels stabilize within 2 weeks after a dietary change. One diet was high in palmitic acid, another high in myristic acid, and the third high in oleic acid. Thus, there were six possible treatment sequences. Each of the six diet sequence groups had the same ratio of men to women and of women using and not using oral contraceptives. In this way, bias due to the order in which the diets were consumed or to drift of variables over time was eliminated.

Subjects

Seventy-nine persons responded to calls via local newspapers and posters in university buildings. Five women and 2 men withdrew before or during the screening procedure. Of the remaining 42 women and 30 men, 2 men were excluded because they consumed over 10% of daily energy intake as alcohol, 3 men and 3 women because their serum cholesterol levels exceeded 7.1 mmol/L, or their blood pressure was over 140/90 mm Hg, and 2 women for medical reasons as judged by an independent physician. One man and 1 woman withdrew after the screening because their partner was excluded for one of the reasons mentioned above and one man for unstated reasons. The 36 women and 23 men who entered the study were all apparently healthy, as indicated by a medical questionnaire. None had anemia, glycosuria, or proteinuria, and none were taking medications known to affect blood lipids. Eleven women used oral contraceptives, and 6 women and 2 men smoked cigarettes. Preexperimental fasting serum cholesterol levels ranged from 3.67 to 7.10 mmol/L (mean, 5.06 mmol/L). The women were between 18 and 55 years old (mean, 29 years) and weighed between 53 and 83 kg (mean, 65 kg); their body mass index ranged from 19.0 to 26.8 kg/m$^2$ (mean, 22.4 kg/m$^2$). The men's ages ranged from 18 to 62 years (mean, 28 years), they weighed between 59 and 97 kg (mean, 76 kg), and their body mass index was 17.9 to 32.4 kg/m$^2$ (mean, 22.3 kg/m$^2$).

Approval for the study was obtained from the Ethics Committee of the department, and the protocol and aims of the study were fully explained to the subjects, who gave their written informed consent. No reward was given except for the food, which was free.

Diet

The diets consisted of conventional solid foods; 21 different menus were provided over the course of each 3-week cycle. The nutrient composition of each diet was similar, except that approximately 10% of total energy intake was provided by either myristic acid, palmitic acid, or oleic acid. These differences were achieved by the use of special margarines (Table 1). To prepare a fat high in myristic acid, 46 parts myristic acid were mixed with 10.8 parts glycerol, 10.8 parts stearic acid, and 3.5 parts linoleic acid. This mixture was then heated under reduced pressure with 0.2% by weight tetraethyl titanate as a catalyst until the reaction was complete, cooled, refined with diluted sodium hydroxide, dried, and filtered. The resulting product was free of titanium (detection limit, 5 mg/kg). Subsequently, the triglycerides were dissolved at 45°C in

Table 1. Fatty Acid Composition of Margarines Used in the Three Study Diets

<table>
<thead>
<tr>
<th>Fatty Acid</th>
<th>Myristic Acid Rich</th>
<th>Palmitic Acid Rich</th>
<th>Oleic Acid Rich</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saturated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lauric acid (C12:0)</td>
<td>65.5</td>
<td>58.5</td>
<td>19.2</td>
</tr>
<tr>
<td>Myristic acid (C12:0)</td>
<td>0.3</td>
<td>0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Palmitic acid (C16:0)</td>
<td>50.7</td>
<td>1.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Stearic acid (C18:0)</td>
<td>13.4</td>
<td>11.2</td>
<td>12.0</td>
</tr>
<tr>
<td>Monounsaturated</td>
<td>28.4</td>
<td>30.2</td>
<td>71.4</td>
</tr>
<tr>
<td>Oleic acid (cis C18:1)</td>
<td>25.4</td>
<td>29.6</td>
<td>69.8</td>
</tr>
<tr>
<td>Elaidic acid + isomers (trans C18:1)</td>
<td>3.0</td>
<td>0.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Polyunsaturated</td>
<td>4.6</td>
<td>11.2</td>
<td>9.4</td>
</tr>
<tr>
<td>Linoleic acid (cis,cis C18:2)</td>
<td>3.8</td>
<td>10.9</td>
<td>9.3</td>
</tr>
<tr>
<td>trans Isomers of C18:2</td>
<td>0.7</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Others</td>
<td>1.5</td>
<td>0.1</td>
<td>0.1</td>
</tr>
</tbody>
</table>

The special margarines supplied 53% of the total fat in the myristic acid, 66% in the palmitic acid, and 54% in the oleic acid diets.
By guest on June 27, 2017.

Choice items were coded, and their energy and nutrient pools and analyzed after the study. Records of the free-supplied (Table 2).

In all 59 subjects the proportion of myristic acid in the cholesterol esters was higher on the myristic acid diet in 58 of 59 subjects relative to the myristic acid diet. Neither the questionnaires nor the diaries revealed any deviations from the protocol that might have affected the results. The largest deviation reported in the questionnaire was the consumption by one subject of two herrings over the full 9-week study period. Adherence to the study diets was confirmed by the fatty acid composition of the serum cholesterol esters, which uniformly followed the dietary composition (Table 3). In all 59 subjects the proportion of myristic acid in the cholesterol esters was higher on the myristic acid diet than on either the palmitic acid or oleic acid diet. The proportion of palmitic acid increased on the palmitic acid diet in 58 of 59 subjects relative to the myristic acid or oleic acid diets, and all 59 subjects showed the highest proportion of oleic acid in their cholesterol esters when on the oleic acid diet. All these differences were highly significant (P<.0001).

**Blood Sampling and Analysis**

All participants were assigned a random number that was used for labeling blood and serum tubes. In this way the laboratory technicians were unaware of the subjects' diet sequence. Blood samples were taken after a 12-hour fast on days 1, 17, and 21 (period 1), days 38 and 42 (period 2), and days 59 and 63 (period 3). All venipunctures were performed by the same technician, in the same location, and at the same time of the same days of the week. Serum was obtained by low-speed centrifugation within 1 hour of venipuncture, stored at −80°C, and analyzed enzymatically for total cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol (HDL-C), and triglycerides.24-26 All samples from a particular subject were analyzed within one run. The coefficient of variation within runs was 1.1% for total cholesterol, 1.3% for HDL-C, and 1.9% for triglycerides. Mean bias with regard to the target values of serum pools provided by the Centers for Disease Control and Prevention, Atlanta, Ga, was −0.10 mmol/L for total cholesterol, 0.0 mmol/L for HDL-C, and 0.07 mmol/L for triglycerides. LDL-C was calculated by using the Friedewald equation.31

Apolipoproteins were measured by Dr A. von Eckardstein at the Institut f"ur Klinische Chemie und Laboratoriumsmedizin, M"unster, FRG, by using a turbidimetric method on microtiter plates as described.32 Lipoprotein and apolipoprotein values obtained at the two sampling days at the end of each dietary period were averaged for data analyses.

Specific Saturated Fatty Acids and Lipoproteins

The analyzed composition of the diets agreed with our objectives: about 10% of daily energy from oleic acid was replaced by palmitic acid or myristic acid, and other dietary constituents, notably lauric acid and trans fatty acids, were virtually unchanged. Fifty-seven of the 59 subjects returned the anonymous questionnaire that they received at the end of the trial. The blinding was successful with respect to the myristic and palmitic acid diets, but most subjects had recognized the oleic acid diet. Neither the questionnaires nor the diaries revealed any deviations from the protocol that might have affected the results. The largest deviation reported in the questionnaire was the consumption by one subject of two herrings over the full 9-week study period. Adherence to the study diets was confirmed by the fatty acid composition of the serum cholesterol esters, which uniformly followed the dietary composition (Table 3). In all 59 subjects the proportion of myristic acid in the cholesterol esters was higher on the myristic acid diet than on either the palmitic acid or oleic acid diet. The proportion of palmitic acid increased on the palmitic acid diet in 58 of 59 subjects relative to the myristic acid or oleic acid diets, and all 59 subjects showed the highest proportion of oleic acid in their cholesterol esters when on the oleic acid diet. All these differences were highly significant (P<.0001).

**Serum Lipids and Lipoproteins**

The mean levels of serum total and lipoprotein cholesterol and triglycerides on the three diets are shown in Table 4. Fig 1 depicts the changes in serum cholesterol levels on the myristic acid and palmitic acid diets.
TABLE 2. Mean Daily Intake of Energy and Nutrients of the Subjects While on the Three Study Diets

<table>
<thead>
<tr>
<th>Energy/Nutrient</th>
<th>Myristic Acid</th>
<th>Palmitic Acid</th>
<th>Oleic Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy/MJ/d</td>
<td>11.9±2.6</td>
<td>11.7±2.6</td>
<td>11.7±2.7</td>
</tr>
<tr>
<td>kcal/d</td>
<td>2841±627</td>
<td>2807±624</td>
<td>2806±634</td>
</tr>
<tr>
<td>Protein, % of energy</td>
<td>13.2</td>
<td>12.6</td>
<td>12.4</td>
</tr>
<tr>
<td>Fat, % of energy</td>
<td>39.2</td>
<td>39.6</td>
<td>38.5</td>
</tr>
<tr>
<td>Saturated fatty acids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lauric acid (C12:0)</td>
<td>0.4</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Myristic acid (C14:0)</td>
<td>11.3</td>
<td>1.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Palmitic acid (C16:0)</td>
<td>4.7</td>
<td>14.9</td>
<td>5.0</td>
</tr>
<tr>
<td>Stearic acid (C18:0)</td>
<td>4.3</td>
<td>4.1</td>
<td>3.8</td>
</tr>
<tr>
<td>Monounsaturated fatty acids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oleic acid (cis C18:1)</td>
<td>10.9</td>
<td>11.6</td>
<td>20.9</td>
</tr>
<tr>
<td>Elaidic acid (trans C18:1)</td>
<td>0.7</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Polyunsaturated fatty acids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linoleic acid (cis,cis C18:2)</td>
<td>4.2</td>
<td>4.7</td>
<td>4.4</td>
</tr>
<tr>
<td>trans Isomers of C18:2</td>
<td>0.1</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Carbohydrates, % of energy</td>
<td>46.9</td>
<td>47.2</td>
<td>48.3</td>
</tr>
<tr>
<td>Alcohol, % of energy</td>
<td>0.7</td>
<td>0.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Cholesterol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mg/d</td>
<td>344.9</td>
<td>358.9</td>
<td>351.8</td>
</tr>
<tr>
<td>mg/MJ</td>
<td>29.0</td>
<td>30.6</td>
<td>30.0</td>
</tr>
<tr>
<td>Dietary fiber</td>
<td>g/d</td>
<td>g/MJ</td>
<td></td>
</tr>
<tr>
<td></td>
<td>42.0</td>
<td>43.0</td>
<td>39.9</td>
</tr>
<tr>
<td></td>
<td>3.5</td>
<td>3.7</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Each subject consumed each diet for 3 weeks in random order. Values are based on chemical analyses of duplicate diets plus the calculated contribution of free-choice items (see 'Methods'). Each value represents the mean of three independent duplicates collected in three different periods during which each diet was consumed by one third of the subjects. Variations between periods were negligible.

Diets relative to the oleic acid-rich diet. Compared with the level on the oleic acid diet, total cholesterol increased by 0.66 mmol/L (P < .0001; 95% confidence interval [CI], 0.54 to 0.79 mmol/L) on the myristic acid diet and by 0.43 mmol/L (P < .0001; 95% CI, 0.30 to 0.56 mmol/L) on the palmitic acid diet. The difference in total cholesterol between the myristic acid and palmitic acid diets was 0.23 mmol/L (P < .0001; 95% CI, 0.11 to 0.35 mmol/L).

TABLE 3. Fatty Acid Composition of Serum Cholesterol Esters on the Three Study Diets

<table>
<thead>
<tr>
<th>Fatty Acid</th>
<th>Myristic Acid</th>
<th>Palmitic Acid</th>
<th>Oleic Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>C14:0</td>
<td>2.83±0.82†</td>
<td>0.65±0.17</td>
<td>0.66±0.16</td>
</tr>
<tr>
<td>C16:0</td>
<td>9.25±0.64†</td>
<td>10.67±0.54*</td>
<td>9.18±0.65</td>
</tr>
<tr>
<td>C16:1 (n-7)</td>
<td>2.67±0.57*</td>
<td>2.71±0.56*</td>
<td>2.24±0.86</td>
</tr>
<tr>
<td>C18:0</td>
<td>0.95±0.15†</td>
<td>0.91±0.16*</td>
<td>0.83±0.12</td>
</tr>
<tr>
<td>C18:1 (n-9)</td>
<td>16.76±1.11*</td>
<td>16.89±1.01*</td>
<td>23.15±1.83</td>
</tr>
<tr>
<td>C18:2 (n-6)</td>
<td>54.56±2.95†</td>
<td>56.12±2.77*</td>
<td>51.34±3.14</td>
</tr>
<tr>
<td>C20:4 (n-6)</td>
<td>6.35±1.20†</td>
<td>6.03±1.07*</td>
<td>6.64±1.20</td>
</tr>
<tr>
<td>Other</td>
<td>6.63±0.83</td>
<td>5.83±0.76</td>
<td>5.96±1.00</td>
</tr>
</tbody>
</table>

Values are mean±SD. The 59 subjects consumed each diet for 3 weeks each in random order. *Significantly different from oleic acid diet, P < .02. †Significantly different from the palmitic acid diet, P < .02.
Table 4. Serum Lipid and Lipoprotein Cholesterol Levels on the Three Study Diets

<table>
<thead>
<tr>
<th></th>
<th>Myristic Acid</th>
<th>Palmitic Acid</th>
<th>Oleic Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total cholesterol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>5.19±0.90†</td>
<td>4.96±0.85*</td>
<td>4.53±0.81</td>
</tr>
<tr>
<td>Women</td>
<td>5.27±0.79†</td>
<td>5.03±0.78*</td>
<td>4.67±0.75</td>
</tr>
<tr>
<td>Men</td>
<td>5.08±1.04†</td>
<td>4.85±0.96*</td>
<td>4.32±0.87</td>
</tr>
<tr>
<td><strong>HDL cholesterol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>1.65±0.37†</td>
<td>1.52±0.33</td>
<td>1.50±0.30</td>
</tr>
<tr>
<td>Women</td>
<td>1.76±0.31†</td>
<td>1.63±0.29</td>
<td>1.62±0.25</td>
</tr>
<tr>
<td>Men</td>
<td>1.46±0.38†</td>
<td>1.34±0.32</td>
<td>1.32±0.28</td>
</tr>
<tr>
<td><strong>LDL cholesterol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>3.09±0.78†</td>
<td>2.98±0.72*</td>
<td>2.60±0.71</td>
</tr>
<tr>
<td>Women</td>
<td>3.07±0.75*</td>
<td>2.96±0.71*</td>
<td>2.63±0.71</td>
</tr>
<tr>
<td>Men</td>
<td>3.14±0.83*</td>
<td>3.01±0.75*</td>
<td>2.55±0.73</td>
</tr>
<tr>
<td><strong>HDL-LDL ratio</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>0.56±0.17†</td>
<td>0.54±0.17*</td>
<td>0.62±0.20</td>
</tr>
<tr>
<td>Women</td>
<td>0.51±0.17*</td>
<td>0.58±0.16*</td>
<td>0.66±0.19</td>
</tr>
<tr>
<td>Men</td>
<td>0.49±0.15*</td>
<td>0.47±0.15*</td>
<td>0.56±0.20</td>
</tr>
<tr>
<td><strong>Triglycerides</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>0.99±0.52</td>
<td>1.00±0.55</td>
<td>0.95±0.43</td>
</tr>
<tr>
<td>Women</td>
<td>0.96±0.42</td>
<td>0.95±0.39</td>
<td>0.93±0.36</td>
</tr>
<tr>
<td>Men</td>
<td>1.05±0.65</td>
<td>1.10±0.72</td>
<td>1.00±0.54</td>
</tr>
</tbody>
</table>

Values are mean±SD and are expressed in millimoles per liter. The 23 men and 36 women consumed each diet for 3 weeks in random order. To convert values for total, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol to milligrams per deciliter, multiply by 38.67. To convert values for triglycerides to milligrams per deciliter, multiply by 88.54.

†Significantly different from the palmitic acid diet, P<.02.
*Significantly different from the oleic acid diet, P<.02.

0.36 mmol/L). LDL-C rose by 0.50 mmol/L (95% CI, 0.40 to 0.60 mmol/L) on the myristic acid diet and by 0.38 mmol/L (95% CI, 0.28 to 0.48 mmol/L) on the palmitic acid diet compared with the level on the oleic acid diet (P<.0001 for both comparisons). The difference in LDL-C of 0.11 mmol/L between the two saturated fat diets was also statistically significant (P=.0086; 95% CI, 0.01 to 0.22 mmol/L). The mean HDL-C level on the myristic acid diet was higher than on the two other diets (Table 4 and Fig 1), increasing by 0.12 mmol/L (95% CI, 0.05 to 0.18 mmol/L) compared with the palmitic acid diet and by 0.15 mmol/L (95% CI, 0.10 to 0.19 mmol/L) compared with the oleic acid diet (P<.0001 for both comparisons). The HDL-C-raising
effect of myristic acid was evident in 51 of the 59 subjects. Mean HDL-C levels on the palmitic and the oleic acid diets were the same. The HDL-C to LDL-C ratio on the myristic acid diet was significantly lower than that on the oleic acid diet ($P < .0001$) but slightly higher than that on the palmitic acid diet ($P = .0133$). Serum triglyceride levels did not differ significantly between any of the diets (Table 4).

The rise of apolipoprotein (apo) A-I (Table 5) paralleled the change observed in HDL-C (Table 4), although not to the same extent; the mean ratio of apoA-I to HDL-C was 994 mg/mmol on both the palmitic acid and oleic acid diets, but it decreased significantly to 966 mg/mmol on the myristic acid diet ($P < .0006$). ApoB levels on the myristic acid and palmitic acid diets were both higher than on the oleic acid diet ($P < .0001$), but unlike LDL-C, apoB levels did not differ between the two saturated fat diets (Table 5).

The responses of lipid, lipoprotein, or apolipoprotein levels to the diets did not differ significantly between men and women or between women using and not using oral contraceptives.

**Discussion**

**Myristic Acid Versus Palmitic Acid**

The relative cholesterol-raising potential of the various saturated fatty acids has been controversial for many years. Several reports indicate that the cholesterol-raising saturated fatty acids (lauric, myristic, and palmitic acids) differ in their effects on cholesterol levels. No study has directly examined myristic acid except that of McGandy et al., who conclude that both myristic acid and palmitic acid raise total cholesterol. However, a consistent difference between the two could not be detected, in part because the number of subjects was small. In the present trial a large group of healthy volunteers consumed three strictly controlled diets in which either myristic acid or palmitic acid was exclusively substituted for oleic acid. Our data show that myristic acid is about 1.5 times as cholesterol-raising as palmitic acid, which is much less than the factor of 4 to 6 that meta-analytical studies suggest. The high values found in meta-analyses could be a statistical artifact, because in experiments that use natural fats the intake of myristic acid is strongly correlated with that of either lauric acid or palmitic acid. Such "collinearity" may produce unreliable outcomes of multiple regression analyses. Other investigators report that palm oil, which is rich in palmitic acid, causes remarkably lower cholesterol levels than coconut oil, which is rich in lauric acid and myristic acid. Ng et al therefore suggest that myristic acid is the major contributor to the cholesterol-raising effect of saturated fatty acids and that palmitic acid may be neutral, like stearic acid and oleic acid. This hypothesis, however, was not confirmed by the present study. Hayes and Khosla propose that palmitic acid might have a conditional effect on serum cholesterol, with palmitic acid being cholesterol-raising in hypercholesterolemic subjects (total cholesterol, >5.8 mmol/L or 225 mg/dL) but not in normocholesterolemic subjects. Our findings did not support this: the increase of total cholesterol on the palmitic acid diet relative to the oleic acid diet of subjects in the lowest tertile of initial cholesterol level (initial level, 3.78 mmol/L; increase, 0.37 mmol/L) was similar to that of subjects in the highest tertile (initial level, 5.97 mmol/L; increase, 0.42 mmol/L). Myristic acid did raise total cholesterol more than palmitic acid, but about one half of the effect was due to HDL-C. Both myristic and palmitic acids markedly raised LDL-C and apoB levels compared with oleic acid. This accords with other well-controlled studies in which palmitic acid was shown to raise LDL-C relative to that produced by oleic acid.

It must be noted that we investigated a synthetic myristic acid–rich fat in which myristic acid is randomly attached to glycerol molecules. In contrast, the triglycerides in natural coconut oil or dairy fat have a specific fatty acid distribution that might modulate the effect of myristic acid on cholesterol metabolism. However, in our experience two dietary fats with equal total fatty acid composition but contrasting positional distribution of saturated fatty acids resulted in highly similar serum lipid and lipoprotein levels in volunteers (P.L., unpublished data, 1993). It is therefore unlikely that myristic acid in synthetic fats would have a totally different effect on serum lipoproteins than in coconut oil or dairy fat.

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### Table 5. Serum ApoA-I and ApoB Levels on the Three Study Diets

<table>
<thead>
<tr>
<th>Diet</th>
<th>Myristic Acid</th>
<th>Palmitic Acid</th>
<th>Oleic Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoA-I, mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>154.6±21.0†</td>
<td>147.4±21.1</td>
<td>145.8±18.9</td>
</tr>
<tr>
<td>Women</td>
<td>160.8±19.7†</td>
<td>154.9±20.6</td>
<td>153.0±17.8</td>
</tr>
<tr>
<td>Men</td>
<td>145.0±19.7†</td>
<td>135.7±16.1</td>
<td>134.5±14.8</td>
</tr>
<tr>
<td>ApoB, mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>74.6±16.5*</td>
<td>74.3±15.9</td>
<td>68.6±16.6</td>
</tr>
<tr>
<td>Women</td>
<td>73.6±15.6*</td>
<td>74.0±15.5*</td>
<td>68.5±16.3</td>
</tr>
<tr>
<td>Men</td>
<td>76.1±18.3*</td>
<td>74.7±16.7*</td>
<td>68.6±17.6</td>
</tr>
</tbody>
</table>
Changes in HDL-C

Myristic acid increased HDL-C by about 9% compared with palmitic acid and oleic acid. The apoA-I to HDL-C ratio was lower on the myristic acid diet than on both other diets, which indicates an increase in the less dense HDL particles and suggests that the change in HDL-C occurred mainly in HDL2. A specific HDL-C-raising effect of myristic acid has not been reported before, but myristic acid–rich coconut oil diets, apart from increasing total cholesterol and LDL-C, generally produce higher HDL-C levels than other saturated fat diets.23,24,25 A large cross-cultural study26 reports that men in Finland, who consume large amounts of myristic acid from dairy fat,41 not only have high total cholesterol but also very high HDL-C concentrations. Although these epidemiological data provide no direct evidence, they are in line with the present observation that myristic acid raises HDL-C. In spite of their high HDL levels, the Finnish men still had very high rates of coronary heart disease. Thus, the beneficial effect (if any27) of raising HDL-C through diet is evidently more than undone by the unfavorable effect on LDL-C, a lipoprotein that is clearly known to be atherogenic.

Gender-Specific Effects

It is often believed that women are less suitable subjects for studying dietary effects on serum lipids because of confounding effects of the menstrual cycle43,44 or the use of oral contraceptives.45 With a proper study design, however, this is not the case. In our study different women entered the trial at different points of their cycle; moreover, the diets were fed in random sequence. In this way the effects of menstrual cycle canceled each other and averaged out and thus could not have systematically biased the comparisons of the diets. Unlike the means, one would expect the SDs of the responses to be enlarged because cyclic effects add a random positive or negative term to each lipid data point of an individual woman. However, we found that the SDs of the mean responses of the 36 women to the diets did not differ significantly from those of the 23 men or were even smaller (on average, 0.42 mmol/L versus 0.41 mmol/L for total cholesterol; 0.16 versus 0.14 mmol/L for HDL-C; and 0.23 versus 0.28 mmol/L for triglycerides). Moreover, the SDs of the mean serum lipid changes of the women using oral contraceptives (0.45 mmol/L for total cholesterol, 0.16 mmol/L for HDL-C, and 0.22 mmol/L for triglycerides) were similar to those of the men. The present observation that women show no substantially larger within-subject variation in their serum lipid levels than men is in accord with our previous studies and again shows that female volunteers are as suitable subjects as men for studies on diet and lipoproteins.26

The mean responses of total cholesterol and LDL-C to the two saturated fat diets tended to be nonsignificantly higher for men than for women, whereas the HDL-C levels of men and women responded similarly. We have earlier reported gender-specific effects of dietary fats on HDL-C levels.25,26 It is possible that we missed small gender-specific effects in the present study. However, in other trials both sexes were also found equally responsive to changes in dietary fat saturation.15,16,18,20,47 At the very least, the lipoprotein levels of both sexes respond in the same direction and with the same order of magnitude. It therefore appears that diets low in saturated fat can be recommended for both male and female patients. Furthermore, mean effects of diet on lipoproteins in the 11 women using and the 25 women not using oral contraceptives were identical. Oral contraceptives may influence absolute serum lipid levels,45 but apparently they do not affect responsiveness of lipoproteins to diet. This agrees with our previous experience.26

Dosage

The differences in intake of myristic acid and palmitic acid between the diets amounted to about 10% of total daily energy. For palmitic acid this is a realistic amount; it is similar to the difference between an affluent high–saturated fat diet and the American Heart Association Step I diet.46 The difference in myristic acid, however, was much higher than is achievable with natural fat sources. Thus, when extrapolating our findings for myristic acid to low levels of intake one must assume that the amount of myristic acid in the diet and its effects on serum lipids and lipoproteins are related in a linear way. Such a linear relation has in fact been observed for saturated fatty acids in general.23,24,13

Comparison With Other Dietary Fatty Acids

Fig 2 puts our findings into the context of other studies that directly compare the effects of individual fatty acids in humans. It must be noted that Fig 2 merely summarizes data currently available from a few well-controlled trials; it is not meant to quantify the exact differences in cholesterolemic effect between the various fatty acids. Nevertheless, the estimates suggest that myristic and palmitic acids are the most important cholesterol-raising saturated fatty acids. Palmitic acid appears to be more potent than lauric acid12 but less potent than myristic acid. trans Fatty acids17,18,26 raise total cholesterol less than lauric, myristic, and palmitic acids, but they simultaneously raise LDL-C and lower HDL-C, which also results in an unfavorable lipoprotein risk profile. Stearic acid27-29 produces lower cholesterol levels than the other saturates and nearly equals oleic acid; ie, it is approximately neutral in its effects on serum total and lipoprotein cholesterol. The effects of different fatty acids on LDL levels in humans summarized in Fig 2 correspond well with the effects of dietary fatty acids on LDL metabolism in the model developed by Spady and coworkers.8 In this model LDL-C levels are affected through changes in the activity of the hepatic LDL receptor. The liver enzyme acyl coenzyme A:cholesterol acyl transferase, which converts free cholesterol into cholesterol esters, has a much lower activity toward saturated than toward unsaturated fatty acids. As a consequence, feeding saturated fatty acids to hamsters decreases the hepatic cholesterol ester content.49,50 It is assumed that at the same time the amount of free cholesterol increases in certain hepatocyte compartments, including the putative pool that controls the expression of the LDL receptor, presumably via the LDL receptor mRNA level in the cell. This leads to downregulation of receptor activity and the accumulation of LDL in plasma and increased formation of LDL from its precursor, VLDL.51,52 In this way, saturated fatty acids raise
Fig 2. Bar graph showing an overview of the effects of individual dietary fatty acids on serum total, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol in recent trials, expressed as the changes that occur when 1% of dietary energy as carbohydrates is replaced by a specific fatty acid. The values for lauric acid (12:0) were obtained by direct comparison with oleic acid; values for myristic acid (14:0) are those of the current study (Table 3). The estimates for palmitic acid (16:0) are averages of results from the present plus three other strictly controlled trials in which palmitic acid was isoenergetically exchanged for oleic acid. The values for monounsaturated trans fatty acids (trans isomer, elaidic acid) might explain why trans fatty acids result in higher LDL-C levels than oleic acid. The exact mechanisms involved in regulating plasma lipoprotein cholesterol levels in humans, however, require additional investigation.

Limitations of the data presented in Fig 2 need to be stressed. First, estimates are based on a limited number of studies and for lauric and myristic acids on only one trial each. The precise differences in cholesterolemic effects among the various saturated fatty acids still need to be established. Second, we assumed a linear dose-response relation between the amount of fatty acids in the diet and their effects on serum total and lipoprotein cholesterol. Previous studies support this assumption. Third, the values for lauric, myristic, and stearic acids are based on studies in which the fatty acids were supplied as synthetic or interesterified fats.

In conclusion, both myristic and palmitic acids are dietary constituents that powerfully raise serum total cholesterol and LDL-C levels. Myristic acid as well as palmitic acid should be reduced in diets for the treatment of hypercholesterolemia.

Acknowledgments

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