Hydrogenation Impairs the Hypolipidemic Effect of Corn Oil in Humans

Hydrogenation, *trans* Fatty Acids, and Plasma Lipids

Alice H. Lichtenstein, Lynne M. Ausman, Wanda Carrasco, Jennifer L. Jenner, Jose M. Ordovas, and Ernst J. Schaefer

The effects on plasma lipoproteins and apolipoproteins of replacing corn oil with corn-oil margarine in stick form as two thirds of the fat in the National Cholesterol Education Program (NCEP) Step 2 diet were assessed in 14 middle-aged and elderly women and men (age range, 44–78 years) with moderate hypercholesterolemia (low density lipoprotein cholesterol [LDL-C] range, 133–219 mg/dl [3.45–5.67 mmol/l] at screening). During each 32-day study phase, subjects received all their food and drink from a metabolic kitchen. Subjects were first studied while being fed a diet approximating the composition of the current US diet (baseline), which contained 35% of calories as fat (13% saturated fatty acids [SFAs], 12% monounsaturated fatty acids [MUFAs; 0.8% 18:1n-9 trans], and 8% polyunsaturated fatty acids [PUFAs]) and 128 mg cholesterol/1,000 kcal. This baseline phase was followed by a corn oil-enriched diet containing 30% fat (6% SFA, 11% MUFA [0.4% 18:1n-9 trans], and 10% PUFA) and 83 mg cholesterol/1,000 kcal, and then a corn-oil margarine-enriched diet containing 30% fat (8% SFA, 12% MUFA [4.2% 18:1n-9 trans], and 8% PUFA) and 77 mg cholesterol/1,000 kcal. All diets were isocaloric. Mean fasting LDL-C and apolipoprotein (apo) B levels were 153 mg/dl (3.96 mmol/l) and 101 mg/dl on the baseline diet, 17% and 20% lower (both p<0.001) on the corn oil-enriched diet, and 10% and 10% lower (both p<0.01) on the margarine-enriched diet. Mean fasting high density lipoprotein cholesterol (HDL-C) and apoA-I levels were 48 mg/dl (1.24 mmol/l) and 134 mg/dl on the baseline diet, 9% and 0.4% lower on the corn oil-enriched diet (p<0.01 for HDL-C), and 10% and 3% lower on the margarine-enriched diet (p<0.01 for HDL-C). No significant effects of diet on triglyceride, apoA-I, or lipoprotein(a) concentrations were noted. Replacing corn oil with a typical corn-oil margarine in stick form, as is currently available, resulted in a 10-fold increase in dietary *trans* fatty acid intake as well as 21% and 14% increases in SFA and MUFA intake, respectively, and a 12% decrease in PUFA intake. These changes resulted in higher plasma concentrations of total cholesterol (p=0.039), LDL-C (p=0.058), and LDL apoB (p=0.068) and a less favorable total cholesterol to HDL-C ratio (p=0.037). Both experimental diets resulted in significant reductions in plasma cholesterol relative to the baseline diet; however, the differences resulting from the substitution of the corn-oil margarine for corn oil were associated with a less favorable lipid profile with regard to coronary heart disease risk. We therefore recommend that hydrogenation be minimized during the processing of foods for use in cholesterol-lowering diets. (Arteriosclerosis and Thrombosis 1993;13:154–161)

**KEYWORDS** • *trans* fatty acids • cholesterol • triglycerides • LDL cholesterol • HDL cholesterol • saturated fat • monounsaturated fat • polyunsaturated fat • diet
process saturates a portion of the existing double bonds in the fatty acyl chain resulting in a decreased content of polyunsaturated fatty acids (PUFAs) and an increased content of saturated and monounsaturated fatty acids (MUFAs). During the hydrogenation process, some of the naturally occurring double bonds are converted from the cis to the trans conformation, which results in a decreased bond angle and an acyl chain with a conformation that physically more closely resembles a saturated fatty acyl chain.

Early work on the effects of human consumption of trans fatty acids on plasma lipids was inconclusive. However, recent studies reported a negative effect on plasma lipoproteins of consuming products enriched with elaidic acid (18:1n-9 trans) as compared with oleic acid (18:1n-9 cis). We chose to study the issue of trans fatty acids and plasma lipids in a middle-aged and elderly population of women and men with moderately elevated low density lipoprotein cholesterol (LDL-C) levels for whom dietary recommendations are most commonly made. We also chose to use as a source of trans fatty acids a product that is frequently incorporated into reduced saturated-fat diets. The product chosen was a standard corn oil–based stick margarine purchased in the supermarket. This product was compared with a commercially available corn oil when both were incorporated into the diet at 20% of calories as fat within the context of a National Cholesterol Education Panel (NCEP) Step 2 diet currently recommended for persons with LDL-C concentrations >130 mg/dl (3.37 mmol/l). Previous work by the authors demonstrated that with respect to plasma lipid and apolipoprotein concentrations, the order in which the diets were consumed did not affect the study outcome (A.H. Lichtenstein et al, unpublished data). Both NCEP Step 2 diets were identical except that two thirds of the fat was derived from commercially available corn oil or corn-oil margarine. All food and drink were provided by the metabolic research unit of the USDA Human Nutrition Center on Aging at Tufts University for consumption on site or packaged for take-out. Subjects were required to report to our metabolic research unit at least three times per week, have blood pressure and weight measured at each visit, and consume at least one meal on site at each visit. The subjects were encouraged to maintain their habitual level of physical activity.

Four times during the last week of each study phase, fasting blood samples (30 ml) after a 14-hour fast were obtained for lipid and apolipoprotein determinations. The mean of these four determinations for each subject was used for statistical analysis. On the last day of each diet phase, all subjects remained in the metabolic research unit, consumed their three meals plus one snack at standardized intervals, and had additional blood samples (20 ml) drawn 5, 8, 10, and 24 hours thereafter. Breakfast was served just after zero hour (8 AM), lunch at noon, supper at 5 PM, and a snack at 8 PM. Data are reported as subject means for each time point, and these data were used for statistical analysis.

The baseline diet was designed to provide 15% of calories as protein, 49% as carbohydrate, 36% as fat (15% saturated fatty acids, 15% MUFAs, and 6% PUFAs), and approximately 150 mg cholesterol/1,000 kcal and was used to stabilize study subjects at a defined level of fat and cholesterol intake. The subjects were then switched to diets approximating the NCEP Step 2 guidelines, which were designed to provide 15% of calories as protein, 55% as carbohydrate, 30% as fat (≤7% saturated fatty acids, 10–15% MUFAs, and up to 10% PUFAs), and less than 80 mg cholesterol/1,000 kcal. Two thirds of the fat in each of the two experimental phases (20% of calories) was provided as corn oil or corn-oil margarine and was incorporated into various food combinations. Triplicate preparations of each complete meal cycle (3 days) for each diet phase were analyzed by Hazleton Laboratories America, Inc., Madison, Wis. The trans fatty acid content of the diet was kindly analyzed by Best Foods Research and Engineering Center, Union, N.J.

The fatty acid profiles of the corn oil and corn-oil margarine reflected those changes that would have been expected to occur as a result of the hydrogenation process. The percentages of 16:0, 18:0, 18:1n-9 cis, 18:1n-9 trans, 18:2n-6, 18:3n-3, and 20:4n-6 in the corn oil were 12.1%, 1.9%, 27.2%, <0.05%, 57.5%, 0.8%, and 0.4%, respectively, and in the corn-oil margarine were 12.4%, 6.1%, 29.1%, 16.1%, 35.3%, 0.6%, and 0.4%, respectively. The preparations used for the study were commercially available at the time the study was conducted. The corn-oil margarine had a higher proportion of 18:0 (32%) and 18:1n-9 (40%) at the expense of 18:2n-6 (39%) than the corn oil. The content of elaidic acid (18:1n-9 trans) was 0.03% in the corn oil and 16.1% in the margarine, representing a 500-fold higher relative amount. In keeping with the

Methods

Subjects

Fourteen subjects (eight women, six men) with a mean age of 62 years (range, 44–78 years) and with screening LDL-C levels >130 mg/dl (range, 133–219 mg/dl [3.45–5.67 mmol/l]) while consuming their usual diets underwent a medical history, physical examination, and had clinical chemistry analyses performed before enrollment in the study. The subjects had no evidence of any chronic illness, including hepatic, renal, thyroid, or cardiac dysfunction. They did not smoke and did not have a history of hypertension, diabetes, or hormones. All women were postmenopausal. An additional male subject did not complete one of the phases, and his data were omitted from all statistical analyses. On the last day of each study phase, all subjects remained in the metabolic research unit, consumed their three meals plus one snack at standardized intervals, and had additional blood samples (20 ml) drawn 5, 8, 10, and 24 hours thereafter. Breakfast was served just after zero hour (8 AM), lunch at noon, supper at 5 PM, and a snack at 8 PM. Data are reported as subject means for each time point, and these data were used for statistical analysis.

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goals of this project, i.e., to describe the effect of substituting corn-oil margarine in stick form for corn oil on plasma lipids, no attempt was made to obtain an unhydrogenated batch of the corn oil used to manufacture the margarine.

The caloric requirement for each subject was estimated using the Harris-Benedict formula (for women, basal energy expenditure [BEE] = 65 + [9.6xW] + [1.7xH] – [4.78xA]; for men, BEE = 66 + [13.7xW] + [5xH] – [6.8xA]; W, weight in kilograms; H, height in centimeters; A, age in years) incorporating a factor of 1.5 to adjust for moderate levels of physical activity.11 The caloric intake was altered when necessary to maintain body weight. If changes were necessary they occurred within the first 1.5 weeks of the study period. The maximum weight change throughout the study was 2 kg. Mean caloric intake was 2,679±608 kcal (range, 2,000-4,000 kcal).

**Biochemical Analysis**

Fasting (14-hour) blood was collected in tubes containing EDTA (0.1%), and plasma was separated by centrifugation at 3,000 rpm at 4°C. Very low density lipoprotein (VLDL, d<1.006 g/ml) was isolated from plasma by ultracentrifugation at 39,000 rpm for 18 hours at 4°C. Plasma and the 1.006 g/ml infranatant fraction were assayed for total cholesterol and triglycerides with an Abbott Diagnostics ABA-200 bichromatic analyzer using [3H]-[6.8A]; for men, BEE = 66 + [13.7xW] + [5xH] – [6.8xA]; W, weight in kilograms; H, height in centimeters; A, age in years) incorporating a factor of 1.5 to adjust for moderate levels of physical activity.11 The caloric intake was altered when necessary to maintain body weight. If changes were necessary they occurred within the first 1.5 weeks of the study period. The maximum weight change throughout the study was 2 kg. Mean caloric intake was 2,679±608 kcal (range, 2,000-4,000 kcal).

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The characteristics of the study subjects are shown in Table 1. As a group they were middle-aged and elderly men and women with somewhat increased body mass indexes. When the subjects were considered for participation in the study, their mean plasma cholesterol concentration was 238±24 mg/dl (6.17±0.62 mmol/l, mean±SD) and mean plasma LDL-C was 164±23 mg/dl (4.25±0.60 mmol/l), confirming that the subjects were from a subset of the population who are prime targets for dietary modification. Mean plasma HDL-C and triglyceride concentrations were within the 10th-90th percentile range of age- and sex-adjusted norms. Mean systolic/diastolic blood pressure at the end of the baseline phase was 112±12/71±6 mm Hg and was not significantly affected by any of the experimental diets.

The composition of the diets based on food analysis is shown in Table 2. The differences observed between the corn oil- and margarine-enriched diets were consistent with the differences observed between the two corn-oil preparations when considering that the experimental fats made up 20% of the caloric content of these two diets. The proportions of saturated fatty acids accounted for by palmitic acid (16:0), stearic acid (18:0), and the MUFA s accounted for by oleic acid (18:1n-9) were higher in the margarine-enriched diets, whereas the proportion of PUFAs accounted for primarily by linolenic acid (18:2n-6) was lower. These two diets were similar with respect to the other dietary constituents. The composition of the diet as assessed by chemical analysis agreed reasonably well with that approximated from the food composition tables.

On average, consumption of the baseline diet resulted in a decrease in the concentrations of total cholesterol, LDL-C, and triglycerides compared with the concentrations of these lipids measured during the screening phase. This observation suggests that under free-living conditions, the mildly hypercholesterolemic middle-aged and older subjects were consuming a diet worse (with respect to fat) than when they were switched to a 35% fat/13% saturated fat diet.

**Table 1. Characteristics of the Study Subjects**

<table>
<thead>
<tr>
<th></th>
<th>Women (n=8)</th>
<th>Men (n=6)</th>
<th>Mean (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67±10</td>
<td>58±13</td>
<td>63±12</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>70±15</td>
<td>80±14</td>
<td>74±15</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>158±4</td>
<td>173±9</td>
<td>165±10</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.1±5.5</td>
<td>26.3±2.5</td>
<td>27.4±4.4</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>226±30</td>
<td>240±14</td>
<td>238±24</td>
</tr>
<tr>
<td>LDL-C</td>
<td>25±7</td>
<td>28±12</td>
<td>26±12</td>
</tr>
<tr>
<td>LDL-C</td>
<td>159±27</td>
<td>170±15</td>
<td>164±23</td>
</tr>
<tr>
<td>HDL-C</td>
<td>52±9</td>
<td>43±11</td>
<td>48±11</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>124±36</td>
<td>149±56</td>
<td>135±46</td>
</tr>
</tbody>
</table>

Values are mean±SD. Cholesterol and triglyceride measurements are milligrams per deciliter. VLDL-C, very low density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol.

Since responses in men and women were similar and since paired t test analysis was used, both groups were pooled.

**Results**

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were calculated as the mean±SD of 14 individual percent changes from baseline. VLDL-C, very low density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; LDL apoB, LDL apolipoprotein B; Lp(a), lipoprotein(a); TC, total cholesterol.

TABLE 3. Plasma Upld and Apollpoprotein Concentrations at the End of Each Study Phase

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Corn oil</th>
<th>Margarine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>223±32</td>
<td>194±20</td>
<td>205±22</td>
</tr>
<tr>
<td>VLDL-C</td>
<td>22±7</td>
<td>24±4</td>
<td>27±6</td>
</tr>
<tr>
<td>LDL-C</td>
<td>153±29</td>
<td>125±20</td>
<td>135±21</td>
</tr>
<tr>
<td>HDL-C</td>
<td>48±10</td>
<td>44±9</td>
<td>43±9</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>108±30</td>
<td>110±30</td>
<td>114±30</td>
</tr>
<tr>
<td>LDL apoB</td>
<td>101±33</td>
<td>79±17</td>
<td>89±18</td>
</tr>
<tr>
<td>ApoA-I</td>
<td>134±22</td>
<td>133±21</td>
<td>138±18</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>14±19</td>
<td>16±21</td>
<td>13±19</td>
</tr>
<tr>
<td>TC/HDL-C</td>
<td>4.83±1.31</td>
<td>4.58±1.04</td>
<td>5.54±1.94</td>
</tr>
<tr>
<td>LDL apoB/apoA-I</td>
<td>0.768±0.214</td>
<td>0.613±0.187</td>
<td>0.714±0.197</td>
</tr>
</tbody>
</table>

Values are mean±SD; n=14 subjects. All dietary variables are milligrams per deciliter (percent change from baseline). Percent changes were calculated as the mean±SD of 14 individual percent changes from baseline. VLDL-C, very low density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; LDL apoB, LDL apolipoprotein B; Lp(a), lipoprotein(a); TC, total cholesterol.
cholesterol, non-HDL-C, and HDL-C, but not for triglycerides. In all cases, HDL-C concentrations were lower in the nonfasting than fasting state as previously reported. The plasma lipids measured at 24 hours were statistically indistinguishable from those measured at the zero-hour time point, indicating that 12 hours of fasting is basically sufficient to assess plasma lipids, and that a 14-hour fast may not be necessary in these types of subjects.

**Discussion**

The intent of this study was to determine the effects of a one-to-one substitution of corn-oil margarine in stick form, a representative source of trans fatty acids, for corn oil in a diet meeting the current guidelines for hyperlipidemic individuals in a clinically relevant population. The preparation of margarine used in stick form is one that is currently available both in the Boston area and in supermarkets throughout the United States. Chemical analysis of the margarine chosen indicated that its elaidic acid content, 16.1%, was similar to previously published values (18.3±5.2%, mean±SD) for corn-oil margarines. Both experimental diets met NCEP Step 2 criteria with respect to the total fat, saturated fat, and cholesterol content, and hence, met the guidelines for treatment of persons with moderately elevated plasma lipids selected for participation in the study, with the exception of the slightly increased saturated fatty acid content of the margarine-enriched diet (0.73% of calories over the maximum recommendation of 7%). As anticipated, both diets had favorable effects on LDL-C and LDL apoB concentrations relative to a diet with a fatty acid profile approximating that currently consumed in the United States.

The actual intake of trans fatty acids in the United States is somewhat uncertain at the current time.
The results of the current study support the concept that the consumption of a diet enriched with a hydrogenated vegetable product, as opposed to an unhydrogenated oil, has unfavorable effects on plasma lipid concentration independent of any other changes resulting from hydrogenation.

The values of various lipids and triglycerides at different time points for each diet are presented in Table 4. These values are expressed as mean±SD; n=14 subjects. The results show significant time effects for triglycerides and HDL-C, and a significant difference between the baseline and the corn-oil margarine diets at 0, 5, 8, and 10 hours for both HDL-C and triglycerides. The baseline values for HDL-C were significantly lower than the corn-oil margarine diet values at 0, 5, 8, and 10 hours. The triglyceride values at 0 and 24 hours were significantly lower than values at 5, 8, and 10 hours.

Hunter and Applewhite published per capita estimates of 7.6 g in 1986 and 8.1 g in 1991. At that time they suggested that even with the trend toward the substitution of vegetable-oil shortenings for beef tallow in frying by fast-food establishments, the increase in per capita consumption of \textit{trans} fatty acids would be only approximately 0.3 g. These figures are lower than the estimate by Eng et al of 13.3 g/person per day. This subject remains highly controversial. The level of \textit{trans} fatty acids consumed in the current study during the margarine phase (12.4±2.8 g/person per day [range, 9.2–18.5]) is a plausible upper level, albeit a worst-case scenario for the United States, but well within the range of a country like The Netherlands.

As a result of substituting corn-oil margarine for corn oil in the diet, in addition to altering the dietary \textit{trans} fatty acid composition, the relative amounts of saturated fatty acid, MUFAs, and PUFAs were also altered, at least in part because of the hydrogenation process. Consistent with the stated intent of our study, no attempt was made to compensate for these inherent differences in the fatty acid composition. Our study design had the advantage of comparing the effects of consuming commercially available food high and low in the \textit{trans} fatty acids on plasma lipids and apolipoproteins but had the disadvantage of not being able to isolate the biological effects of \textit{trans} fatty acid consumption independent of any other changes resulting from hydrogenation.
However, they are the best available tools we have at this point. These data suggest that, consistent with others' concepts, trans fatty acids may have an independent effect on plasma lipids similar to that of saturated fatty acids.3–7,25,26

Work on the effects of hydrogenation of dietary fat on plasma lipids began in the 1950s. Evidence suggested that the hypercholesterolemic effects of hydrogenation were attributable in part to the decreased proportion of PUFAs and the increased proportion of saturated fatty acids.3–7,25–26 Further work done in the 1970s and 1980s on the effects of dietary trans fatty acids on plasma lipids was equivocal.3–8 Renewed interest in the topic was generated by the reports of Katan and coworkers.3,4 Using special preparations of fat that were formulated to maintain constant ratios of saturated fatty acids, MUFAs, and PUFAs, Mensink and Katan3 and later Zock and Katana4 reported that elaidic acid (11% and 7.7% of calories, respectively) resulted in an increase in total cholesterol and LDL-C and a decrease in HDL-C concentrations in normocholesterolemic women and men. Nestel et al reported that consumption of elaidic acid (7% of calories)25 and hydrogenated-oil blends26 resulted in significantly elevated concentrations of total cholesterol and LDL-C in mildly hypercholesterolemic male subjects.

In the current study, both total cholesterol and LDL-C levels were decreased when the subjects consumed the hydrogenated vegetable oil preparation. Similar results have been reported by other investigators.3–7,25–27 However, as in the studies reported by both Laine et al3 and Nestel and coworkers,25,26 we did not observe the decrease in HDL-C concentrations noted by Katan and coworkers.3,4 Differences between the current study and those that reported a decrease in HDL-C concentrations may be attributable to the lower level of total and saturated fat consumed by our subjects (25% versus 42% of calories as total fat, and 7% versus 19% of calories as saturated fat). Our diet depressed HDL-C levels relative to the baseline diet and thereby may have rendered our subjects less responsive to additional perturbations. However, the answer to this question is likely to be more complex because the diets used by the other investigators also had relatively high total and saturated fat contents. This subject clearly warrants further investigation since decreased HDL-C levels and increased total cholesterol/LDL-C ratios have been shown to increase the risk for cardiovascular disease.28

The consumption of either test diet, both of which approximated the current dietary recommendations with respect to total fat, saturated fat, and cholesterol, resulted in significant declines in the plasma cholesterol concentrations of middle-aged and older women and men with mildly elevated plasma lipid levels. The use of a commercially available corn-oil stick margarine, when compared with liquid corn oil, resulted in significantly higher plasma cholesterol concentrations. The differences, whether attributable to differences in either the fatty acid profiles or the trans fatty acid contents of the two preparations of corn oil, were of a magnitude that over the long term would be predicted to have a physiologically significant impact on cardiovascular risk.29,30 However, this is not to imply that currently available alternative products to margarine, higher in saturated fat, should be substituted for butter. As with the general food supply,3,4 the primary trans fatty acid in the margarine-enriched diet was elaidic acid.18 The effects of other trans fatty acids on plasma lipids are not yet clear. In addition, the capacity to alter the fatty acid composition of formulated products in a variety of ways to achieve the same physical characteristics of the product suggests that before large-scale introduction into the food supply, each product should be carefully evaluated.

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