Trans fatty acids, lipoproteins, and coronary risk

Peter L. Zock and Martijn B. Katan

Abstract: Most dietary fatty acids contain at least one double bond, which is usually in the cis configuration. However, bihydrogenation in the rumen of cows and sheep, or catalytic hydrogenation of vegetable oils in the food industries, will convert some of the cis double bonds to the trans configuration. Trans fatty acid intake in western Europe and North America probably ranges from 5 to 15 g/day. Major dietary sources are frying fats used in industrial food preparation, margarines, and other spreads. In the past, margarines contained up to 50% trans fatty acids; however, these are now being phased out. Trans fatty acids raise serum low density lipoprotein (LDL) cholesterol and lower high density lipoprotein (HDL) cholesterol in humans when substituted for cis unsaturated fatty acids in the diet. These effects may be mediated by the cholesteryl ester transfer protein. Trans fatty acids also increase lipoprotein (a) levels relative to other fatty acids. The effects of trans fatty acids on the risk profile for coronary heart disease are thus unfavorable, and labels of food products should state the trans fatty acid content.

Key words: trans fatty acids, diet, lipoproteins, cholesterol, coronary heart disease.

Résumé : La plupart des acides gras contiennent au moins une double liaison, généralement en position cis. Toutefois, la bihydrogénation dans le rumen de vaches ou de brebis, ou l’hydrogénation catalytique des huiles végétales dans les industries alimentaires, convertissent une partie des doubles liaisons cis en configuration trans. On estime que les apports d’acides gras trans se situent dans la plage de 5-15 g/jour en Europe occidentale et en Amérique du Nord. Les acides gras trans se retrouvent principalement dans les graisses à friture utilisées dans les préparations industrielles, les margarines et autres produits à tartiner. Toutefois, ils sont en voie d’être éliminés des margarines qui, dans le passé, en contenaient jusqu’à 50%. Les acides gras trans augmentent le taux de cholestérol LDL sérique et diminuent le taux de cholestérol HDL chez les humains lorsqu’ils remplacent l’acide gras insaturé cis dans le régime alimentaire. Ces effets pourraient être induits par la protéine de transport des esters de cholestérol. Les acides gras trans augmentent aussi les taux de lipoprotéine (a) comparativement aux autres acides gras. Ainsi, les acides gras trans augmentent les facteurs de risque de maladie coronarienne; par conséquent, la teneur en trans devrait apparaître sur les étiquettes des produits alimentaires.

Mots clés : acides gras trans, régime alimentaire, lipoprotéines, cholestérol, maladie coronarienne.

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Introduction

In the past few years, possible adverse health effects of trans fatty acids have stimulated considerable discussion. Two recent reports have summarized the nature and health effects of trans fatty acids; a report from The British Nutrition Foundation (1995) gives a clear and balanced overview. An industry-sponsored report by the International Life Sciences Institute (Expert Panel on Trans Fatty Acids and Coronary Heart Disease 1995) extensively reviews the link between trans fatty acids and coronary heart disease risk, but its conclusions have been subject to some criticism (Willett and Ascherio 1995; Katan 1995a). The present paper summarizes recent human studies that investigated the effects of trans fatty acids on serum lipoprotein levels. The nature of trans fatty acids and their occurrence in the diet is briefly addressed.

Structure and formation of trans fatty acids

In Western diets, about 20–25% of total daily energy intake is provided by fatty acids that contain at least one double bond. Such fatty acids are called unsaturated, because under certain conditions they can take up hydrogen atoms, which are added to the double bonds. After all the double bonds have been converted into single bonds, the fatty acid stops taking up hydrogen and it is then called saturated. The most common configuration of double bonds in dietary fatty acids is cis (Fig. 1). Bihydrogenation in the rumen of cows and sheep, or catalytic hydrogenation of vegetable oils by the food industry, converts unsaturated fatty acids into saturated fatty acids, but unsaturated fatty acids with one or sometimes two double bonds in an unusual geometric configuration (Fig. 1; trans instead of cis) or position (positional cis isomers) may also be created. Geometric (cis-trans) and positional isomers usually occur together; therefore, in theory, effects ascribed to trans could also partly be due to positional cis isomers. Figure 1 shows elaidic acid with the trans double bond in the Δ9/Δ9 position. In fact, partially hydrogenated fats contain a broad range of positional trans isomers, with the position of the trans double bond ranging from position Δ6/Δ12 to position Δ16/Δ12.
Fig. 1. Structure of cis and trans monounsaturated fatty acids with 18 carbon atoms. Both oleic (cis) and elaidic (trans) acids have their double bond in the Δ9/Δ9-9 position. Partially hydrogenated fats also contain isomers of these two fatty acids, with the position of the double bond ranging from position Δ6/Δ2 to position Δ16/Δ2 (Expert Panel on Trans Fatty Acids and Coronary Heart Disease 1995).

**STRUCTURE OF CIS AND TRANS FATTY ACIDS.**

![Cis and trans fatty acids structure](image)

Fig. 2. Intake of trans fatty acids with chain lengths of 16 or 18 carbon atoms in seven countries: assessment by chemical analysis in 1987 of diets as reported in 1960 (De Vries et al. 1997). In addition to C16 and C18 trans fatty acids, diets in The Netherlands and Finland contained appreciable amounts of trans isomers with chain lengths of 20 and 22 carbon atoms, formed during partial hydrogenation of fish oils.

![Intake of trans fatty acids](image)

(Expert Panel on Trans Fatty Acids and Coronary Heart Disease 1995), and elaidic acid is not always the predominant trans fatty acid in such fats (Sampugna et al. 1982).

**Intake of trans fatty acids**

There are no recent reliable figures for the intake of trans fatty acids in various countries. Estimates from per capita disappearance data indicate that about 10–15 years ago average intake in western Europe and the United States probably ranged from about 5 to 15 g/day, or 2–5% of total daily energy intake (Senti 1985; British Nutrition Foundation’s Task Force 1987; Enig et al. 1990; Hunter and Applewhite 1991), but estimates

<table>
<thead>
<tr>
<th>Type of fat</th>
<th>Total fatty acids (g/100 g)</th>
<th>No. of grams/14 g serving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full-fat margarinea</td>
<td>20.8 (11.7–32.1)</td>
<td>2.1 (1.0–3.1)</td>
</tr>
<tr>
<td>Reduced-fat spreadsb</td>
<td>11.2 (3.2–15.2)</td>
<td>0.5 (0.2–1.0)</td>
</tr>
<tr>
<td>Shorteningsc</td>
<td>19.5 (14.8–24.3)</td>
<td>2.6 (2.0–3.3)</td>
</tr>
</tbody>
</table>

**Table 1. Trans fatty acid content of commonly used spreads and shortenings sold in the United States.**

Note: Products were purchased in April 1995 in Boston, Mass. Values are means of analyses using Fourier transform infrared spectroscopy and gas-liquid chromatography after preparation of cis and trans isomers with silver ion thin layer plates (Department of Human Nutrition, Wageningen Agricultural University, The Netherlands). Values in parentheses are ranges.

aAverage of 6 brands: Promise spread, Fleischmann’s soft spread, Fleischmann’s, Kraft Parkay, Star, and Mazola margarines.

bAverage of 3 brands: Land O’Lakes light (40% fat), Shedd’s (50% fat), and Nucoa smart beat “trans-Free” (14% fat) spreads.

cAverage of 2 brands: Crisco and Star shortenings.

of intake levels of up to 27 g/day, depending on the type of diet, have been reported (British Nutrition Foundation’s Task Force 1987). Chemical analysis of the diets of men reported in the Seven Countries Study (De Vries et al. 1997) showed considerable differences in the intake of trans fatty acids from ruminant fats and partially hydrogenated vegetable oils between countries, with levels in The Netherlands and Finland being high and those in southern Europe being low (Fig. 2). In addition, diets in The Netherlands and Finland contained appreciable amounts of trans isomers from partially hydrogenated fish oils (Brussaard 1986). In view of the rapid changes now occurring in fat processing (Katan 1995b), per capita intake in these countries will probably fall to levels of about 5 g/day or less.

Major sources of trans fatty acids are partially hydrogenated fats in the form of shortenings and frying fats used in industrial food preparation, in margarines and other spreads, and from dairy products and meat. About 3–8% of the fatty acids in butter, cheese, milk, beef, and mutton are trans (Pflanzgraf et al. 1994). Much larger amounts can be formed during the partial hydrogenation (hardening) of vegetable and fish oils. Table 1 gives the trans fatty acid content of popular margarines and shortenings sold in the United States in 1995; up to 32% of the fatty acids in these products are trans. In the past, margarines and shortenings could contain up to 50% trans fatty acids (Rice et al. 1962); however, these are now being phased out (Fig. 3), and in western Europe and Canada most margarines will soon contain little or no trans fatty acid (Katan 1995b). Shortenings high in trans fatty acids will continue to be produced and will find their way into baked goods, convenience foods, and fats for commercial deep-fat frying.

**Effect of trans fatty acids on serum lipids and lipoproteins**

Trans fatty acids cannot be considered foreign substances; they are present in the meat and milk of animals and they are formed transiently in human tissues during the breakdown of cis fatty acids. In addition, animal studies have yielded some evidence of toxic effects (Senti 1985). Several studies have examined the effects of trans fatty acids on serum total cholesterol levels. However, the results of older studies are often

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difficult to interpret, because fatty acid intake between the different dietary regimens was not well balanced. Two of the older studies did directly compare the effects of trans and cis monounsaturated fatty acids (trans-C18:1 and cis-C18:1) on serum total cholesterol levels, but results were not consistent. Mattson et al. (1975) found no difference in effect between trans-C18:1 and cis-C18:1, while the studies of Vergeer and Gottenbos (1975) showed that trans-C18:1 might be hypercholesterolemic. The discrepancy between these two well-controlled studies remains unexplained.

More recently, it has been suggested that, compared with cis-C18:1, a high intake of trans-C18:1 increases levels of cholesterol in LDL (low density lipoprotein) but lowers those in HDL (high density lipoprotein) (Mensink and Katan 1990). However, volunteers consumed about 11% of energy from trans-C18:1, and it was questioned whether the results could be extrapolated to lower intake levels (Reeves 1991). Since then, several groups have studied the effects of trans fatty acids from partially hydrogenated vegetable oils (Zock and Katan 1992; Nestel et al. 1992; Lichtenstein et al. 1993; Judd et al. 1994). When the data are combined into a linear model (Fig. 4), each additional percent of dietary energy as trans fatty acids results in an increase in LDL cholesterol of 0.040 mmol/L or 1.5 mg/dL (95% confidence interval, 0.021–0.058 mmol/L) and a decrease in HDL cholesterol of 0.013 mmol/L or 0.4 mg/dL (95% confidence interval, −0.018 to −0.007 mmol/L) (Zock et al. 1995). Figure 4 suggests that our studies (Mensink and Katan 1990; Zock and Katan 1992), which used higher doses of trans fatty acids, somewhat underestimated the effect on LDL cholesterol. We employed a feeding period of 3 weeks, assuming that this period was long enough for lipoprotein levels to stabilize after a dietary change. It may be possible that 3 weeks is not long enough for LDL and HDL cholesterol levels to stabilize after a change in trans intake. An alternative explanation is that the dose–response relation between trans fatty acid consumption and lipoprotein cholesterol is not linear, with the effects levelling off at higher intake levels (Fig. 4). On the other hand, a preliminary report from a Malaysian study (Sundram et al. 1995) suggests that a diet supplying 7% of energy as trans-C18:1, fed for 4 weeks, raises LDL cholesterol levels and lowers HDL cholesterol levels more than was observed by Zock and Katan (1992). Obviously more experiments are needed to define the precise shape of the dose–response curve. Nevertheless, the data clearly indicate that diets containing trans-C18:1 fatty acids raise LDL cholesterol and lower HDL cholesterol relative to diets containing the cis isomer oleic acid. In addition, there seems to be no evidence for a threshold below which trans fatty acids do not affect lipoprotein cholesterol levels.

Thus, dietary studies in humans show that trans fatty acids from partially hydrogenated vegetable oils raise the level of atherogenic LDL cholesterol and lower the level of the “good” or HDL cholesterol when compared with cis fatty acids. However, trans fatty acids formed by industrial hydrogenation are derived not only from vegetable oils but also, in some countries, from fish oils. In contrast with vegetable oils, hydrogenated fish oils also contain trans fatty acids with 20 and 22 carbon atoms and one or more double bonds. In a recent Norwegian study, Almendingen et al. (1995) compared the effects of partially hydrogenated fish oil, partially hydrogenated soybean oil, and butter on serum lipoprotein levels. Serum LDL cholesterol levels were similar for the butter and the partially hydrogenated fish oil diets. The partially hydrogenated soybean oil diet, however, lowered serum LDL cholesterol relative to the partially hydrogenated fish oil diet and butter diets. Serum HDL cholesterol levels were the same for the butter and partially hydrogenated soybean diet, but significantly lower for the partially hydrogenated fish oil diet. Thus, this study shows that the unfavourable effects of trans fatty acids are not limited to those with 18 carbon atoms, as trans fatty acids with 20 or 22 carbon atoms also have an adverse effect on the serum lipoprotein profile. Figure 5 shows the effects of

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Table 2. Effect of \(\text{trans}\)-rich diets on blood \(\text{Lp(a)}\) levels in recent trials.

<table>
<thead>
<tr>
<th>Reference</th>
<th>(%)</th>
<th>(\text{Trans fatty acids})</th>
<th>(\text{Lp(a) levels on (\text{trans})-rich diets relative to other diets})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nestel et al. 1992</td>
<td>7</td>
<td>Rapeseed and palm oils</td>
<td>(\dagger) vs. palmitic acid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>= vs. oleic acid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(\dagger) vs. baseline saturated fat</td>
</tr>
<tr>
<td>Mensink and Katan 1992</td>
<td>11</td>
<td>High oleic acid sunflower oil</td>
<td>(\dagger) vs. saturated fat</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>High oleic acid sunflower oil</td>
<td>(\dagger) vs. palmitic acid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(\dagger) vs. oleic acid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(\dagger) vs. stearic acid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(\dagger) vs. linoleic acid</td>
</tr>
<tr>
<td>Lichtenstein et al. 1993</td>
<td>4</td>
<td>Corn oil</td>
<td>(\dagger) vs. unmodified corn oil</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(=) vs. baseline saturated fat</td>
</tr>
<tr>
<td>Almendingen et al. 1995</td>
<td>9</td>
<td>Soybean oil</td>
<td>(\dagger) vs. butter</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Fish oil</td>
<td>(\dagger) vs. butter</td>
</tr>
<tr>
<td>Aro et al. 1996</td>
<td>9</td>
<td>Vegetable oil</td>
<td>(\dagger) vs. stearic acid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(\dagger) vs. baseline milk fat</td>
</tr>
</tbody>
</table>

Note: \(\dagger\), \(\text{Lp(a)}\) levels higher with \(\text{trans}\)-rich diet; \(=\), no significant difference.

\(\text{Trans fatty acids}\) and other risk factors for coronary heart disease

Another plasma lipoprotein thought to produce cardiovascular disease is lipoprotein \((a)\) (\(\text{Lp(a)}\)). There is now appreciable evidence that \(\text{trans fatty acids}\) tend to raise \(\text{Lp(a)}\) levels (Table 2). Nestel et al. (1992) measured \(\text{Lp(a)}\) levels by radio-immunoassay and found that \(\text{Lp(a)}\) levels were higher with \(\text{trans fatty acids}\) than with palmitic or oleic acid, but the difference with oleic acid failed to reach statistical significance. Mensink et al. (1992) measured \(\text{Lp(a)}\) levels by enzyme-linked immunosorbert assay (ELISA). They found that \(\text{trans fatty acids}\) resulted in higher \(\text{Lp(a)}\) levels than saturated fat, oleic acid, linoleic acid, and stearic acid. Lichtenstein et al. (1993) did not observe an increase in \(\text{Lp(a)}\) levels measured with ELISA. This suggests that \(\text{trans fatty acids}\) in lower doses do not affect \(\text{Lp(a)}\). However, the statistical power of this trial may have been limited, owing to the lower dose or relatively small number of subjects. Almendingen et al. (1995) found that \(\text{trans fatty acid}\) from partially hydrogenated soybean oil, as well as from partially hydrogenated fish oil, raised \(\text{Lp(a)}\) levels compared with a diet rich in butter. A preliminary report by Aro et al. (1995b) indicates that \(\text{trans fatty acids}\) increase \(\text{Lp(a)}\) relative to stearic acid or milk fat. Thus, \(\text{trans fatty acids}\) seem to be one of the rare dietary factors that affect \(\text{Lp(a)}\) levels, even though the effect is modest compared with genetically determined differences.

Fig. 5. Effects of saturated, \(\text{trans}\) monounsaturated, \(\text{cis}\) monounsaturated, and \(\text{cis}\) polyunsaturated fatty acids on LDL and HDL cholesterol. Values were obtained by meta-analysis of 32 controlled dietary trials in humans (Mensink and Katan 1992; Zock et al. 1995).

**Evidence from epidemiologic studies**

The experiments described above indicate that \(\text{trans fatty acids}\) have adverse effects on blood lipoproteins. Cross-sectional observations showed that in free-living subjects, habitual consumption of \(\text{trans fatty acids}\) is also associated with higher LDL cholesterol and lower HDL cholesterol levels (Trevisi et al. 1992; Siguel and Lemann 1993). The question then becomes whether high intake levels of \(\text{trans fatty acids}\) indeed promote coronary heart disease (CHD) in the population. In the absence of controlled clinical trials on \(\text{trans fatty acids}\) and...
CHD, one must rely on epidemiologic observations. Several case-control studies have shown a higher intake of trans fatty acids or margarines in CHD patients than in control subjects (Thomas 1992; Tzonou et al. 1993; Siguel and Lerman 1993; Ascherio et al. 1994), although this could not be confirmed by others (Aro et al. 1995a; Roberts et al. 1995). In two large cohort studies, one of women (Willett et al. 1993) and one of men (Ascherio et al. 1996) in the United States, the intake of trans fatty acids was an independent predictor of CHD. In the Framingham study (Gillman et al. 1995), consumption of margarine at entry was associated with the incidence of CHD in men in the following 20 years.

Consumption of foods high in trans fatty acids may be part of a lifestyle that involves many other factors that affect CHD; such confounders are difficult to exclude. Thus, epidemiologic studies cannot prove that trans fatty acids cause CHD. Nevertheless, the effects of trans fatty acids on plasma lipoproteins are unmistakable, and together with the positive associations between trans fatty acid intake and CHD observed in epidemiologic studies, they give credence to a causal link.

Conclusions

Dietary trans fatty acids raise plasma LDL cholesterol levels and lower HDL cholesterol levels when exchanged for cis unsaturated fatty acids. The exact dose–response relationship between the amount of trans fatty acids and their effect on lipoproteins needs further study, but there is no evidence for a threshold below which trans fatty acids do not affect lipoprotein cholesterol. Trans fatty acids also raise Lp(a) levels relative to other fatty acids. Those effects seem to be shared by trans fatty acids from various sources and with different isomer compositions. The effects of trans fatty acids on blood lipoproteins and the risk of cardiovascular disease are thus unfavourable, and labels of food products should state the trans fatty acid content. Claims for other adverse health effects of trans fatty acids remain to be substantiated.

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References


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