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Review

Trans fatty acids and blood lipid levels, Lp(a), parameters of cholesterol metabolism, and hemostatic factors

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Diets high in trans *fatty acids and/or hydrogenated fat have been reported to increase total and low density lipoprotein (LDL) cholesterol levels, and in some cases decrease high density lipoprotein (HDL) cholesterol levels. More recent evidence supports these observations. The lack of consistency among the data regarding HDL cholesterol levels may be related to differences in the actual level of* trans *fatty acids consumed or the relative decrease in saturated fat accompanying the dietary modification. The decrease in HDL cholesterol levels, when present, has been related to increased cholesterol ester transferase protein (CETP) activity.* Trans *fatty acids have been reported to either increase or have no significant effect on lipoprotein (a) [Lp(a)] levels, whereas saturated fat has been reported to decrease Lp(a) levels. Available data on the effect of* trans *fatty acid intake on cholesterol metabolism other than CETP activity are too limited to draw firm conclusions at this time. The effect of* trans *fatty acids on the susceptibility of LDL to oxidation or on a variety of hemostatic factors suggest no adverse effects. On this basis of the data available it appears prudent to recommend restricting both saturated and* trans *fatty acid intake to reduce the risk of developing cardiovascular disease. Caution needs to be exerted when communicating this message so as to avoid putting undue emphasis on* trans *fatty acids at the expense of saturated fatty acids. Instead patients should be encouraged to reduce intakes of both.* (J. Nutr. Biochem. 9:244–248, 1998) *© Elsevier Science Inc. 1998*

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Introduction

The relationship between hydrogenated fat and/or *trans* fatty acid intake, and blood lipid levels has been a topic of experimental consideration for the past 40 years.[1–4] The majority of early studies in humans suggested that the consumption of partially hydrogenated oil results in higher blood cholesterol levels than oil in the natural state and lower blood cholesterol levels than saturated fat, generally represented by butter.[3] However, much of the early experimental work was limited by factors such as small sample size and inadequate control groups. Little attention was given to hydrogenated fat/*trans* fatty acid and dietary recommendations for either the general population or hyperlipidemic individuals.

This situation changed in 1990 when Mensink and Katan[5] published a pivotal paper that revisited the issue and refocused thinking regarding oil that has been partially hydrogenated and, specifically, *trans* fatty acid containing fats. Their findings suggested that elaidic acid (18:1t), a monounsaturated *trans* double bond containing fatty acid, resulted in higher blood total and low density lipoprotein (LDL) cholesterol levels than oleic acid (18:1c), a monounsaturated *cis* double bond containing fatty acid, and lower blood and LDL cholesterol levels than stearic acid (18:0), a saturated fatty acid of identical chain length to that of

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elaidic and oleic acids. They also reported that high density lipoprotein (HDL) cholesterol levels were comparable after the subjects consumed the high oleic acid and stearic acid diets, but were significantly lower after the subjects consumed the high elaidic acid diet. They concluded that "The effect of *trans* fatty acids on the serum lipoprotein profile is at least as unfavorable as that of the cholesterol-raising saturated fatty acids, because they not only raise LDL cholesterol levels but also lower HDL cholesterol levels."

Subsequent research on the subject, involving either partially hydrogenated fat as the source of *trans* fatty acids or specially synthesized fat differing in only a single fatty acid, confirmed the blood cholesterol raising effects of *trans* fatty acids.[6–13] At relatively high intakes of *trans* fatty acids (8–11% of calories), the HDL cholesterol depressing effect of *trans* fatty acids was also confirmed[6,13]; however, at more modest levels of *trans* fatty acids (≤4% of calories), this differential effect on HDL cholesterol levels was less evident.[6–12] The findings of the post-1990 work and a reassessment of the older literature resulted in general recommendations that, in addition to saturated fat, *trans* fatty acid intake should be limited because of the effects on blood lipid levels and subsequent risk of developing cardiovascular disease.[14–18] A comprehensive review of this material appeared in 1995.[3]

The current review of clinical studies will stress studies that have been performed subsequent to the material previously reviewed (post-1994) and relate that work to the greater body of research in the area of dietary *trans* fatty acids and/or hydrogenated fat and cholesterol metabolism.

Trans fatty acid intake

The difficulties in accurately assessing the nutrient intake of human subjects are well known. These include, but are not limited to, uncertainties in estimating serving size, frequency of consumption, composition of mixed food items, and accuracy of nutrient data available for analysis. Assessing *trans* fatty acid intake is further complicated by dramatic changes in the *trans* fatty acid content of commercially available fats and food products in the past 10 years and by the severely limited databases with which to estimate intake. The most recent estimates, based primarily on food frequency questionnaires, range between approximately 2% and 3% of total caloric intake.[19,20] These data are limited and likely vary widely depending on individual foods habits. In addition, the introduction of *trans* fatty acid free margarines, first in Europe and most recently in the United States, and the potential introduction of *trans* fatty acid free commercial cooking fats for the preparation of processed foods will have an as yet to be determined impact on *trans* fatty acid intake in the coming years.

Blood cholesterol and lipoprotein levels

In a carefully controlled metabolic study, Judd et al.[21] assessed the effects of diets high in *cis* monounsaturated fatty acids and saturated fatty acids (C12:0 to C16:0) relative to diets moderate (3.8%) or high (6.6%) in *trans* fatty acids. The relative relationship of the total and LDL cholesterol levels in response to the different diets were, from lowest to highest: oleic acid, moderate *trans*, high *trans*, and saturated fats. Although the difference between the two levels of *trans* fatty acids was statistically indistinguishable, the other differences were statistically significant. The relative relationship of HDL cholesterol levels in response to the different diets was, from lowest to highest: high *trans*, moderate *trans*, oleic acid, and saturated fats. The HDL cholesterol levels were significantly different after the subjects consumed the saturated fat diet relative to the other diets.

Nestel et al.[22] assessed the effect of a margarine made from an interesterified form of a high-palm oil blend (predominantly lauric, myristic, palmitic, oleic, and linoleic acids) for potential use as a substitute for hardened margarine versus a margarine high in linoleic acid and moderate in *trans* fatty acid versus a margarine high in linoleic acid and moderate in *trans* fatty acid or the high-palm oil blend itself. Total, LDL, and HDL cholesterol levels were higher after subjects used the high-palm oil blend and interesterified form of the high-palm oil blend than after they used the hydrogenated high-linoleic acid-moderate *trans* fatty acid margarine.

Almendingen et al.[23] undertook a metabolic study to assess the relative effects of partially hydrogenated fish oil and partially hydrogenated soybean oil by constructing diets such that butter fat was directly replaced with either of the two partially hydrogenated oils. At the end of the diet periods total and LDL cholesterol levels were similar after the subjects consumed the diets high in butter and hydrogenated fish oil, and lower after subjects consumed the diet high in hydrogenated soybean oil. HDL cholesterol levels were similar after the subjects consumed the diets high in butter and hydrogenated soybean oil, and lower after the subjects consumed the diet high in hydrogenated fish oil.

Matheson et al.[24] altered the diet of individuals associated with an Australian National Antarctic Research Expedition stationed in Antarctica by substituting canola oil and margarine for butter, table margarine (28% saturated fat and 15%. *trans* fatty acids), a polyunsaturated margarine (10% *trans* fatty acids, unreported saturated fatty acids), and vegetable oil in cooking and as a table spread. Total and LDL cholesterol levels were significantly reduced after the subjects consumed the canola oil and margarine. No difference in HDL cholesterol levels was reported.

Chisholm et al.[25] assessed the effect on blood lipid levels of substituting unsaturated *trans* fatty acids containing margarine for butter in moderately hypercholesterolemic individuals. They concluded that LDL cholesterol levels were lower after subjects used the margarine relative to the butter. HDL cholesterol levels were similar regardless of the dietary fat.

In a study designed to assess the relative effect of hydrogenated soybean oil compared with fats rich in oleic, palmitic, or lauric+myristic acids, Sundram et al.[26] reported that consumption of hydrogenated soybean oil elevated total and LDL cholesterol levels relative to the fats high in palmitic and oleic acids, but not lauric+myristic acids, and depressed HDL cholesterol relative to all the fats tested.

Aro et al.[27] quantitated the effect of substituting margarines formulated to be high in either *trans* fatty acids or stearic acid for dairy fat in diets fed to normolipidemic individuals. They reported that the diets high in *trans* fatty acids or stearic acid resulted in lower total cholesterol levels than the diet high in dairy fat. Both experimental fats lowered HDL cholesterol levels; however, the diet high in *trans* fatty acids resulted in lower HDL cholesterol levels than did the diet high in stearic acid. The diet high in *trans* fatty acids resulted in less LDL cholesterol lowering than did the diet high in stearic acid.

Judd et al.[28] recently reported that substituting 8% energy fat in a 39% energy fat diet with *trans* fatty acids, equal parts *trans* fatty acids+stearic acid, or a mixture of lauric+myristic+palmitic acids resulted in higher LDL cholesterol levels than the same amounts of stearic acid, oleic acid, or carbohydrate. HDL cholesterol levels were highest after consumption of the diets high in lauric+myristic+palmitic acids and lowest after consumption of the diets containing *trans* fatty acids and/or stearic acid.

Trans fatty acids have clearly been shown to increase total and LDL cholesterol levels. Issues related to the effect of *trans* fatty acids on HDL cholesterol levels are frequently complicated by concomitant changes in dietary saturated fat intake and are difficult to assess independently. Unclear is(are) the mechanism(s) responsible for the reported changes.

Lipoprotein (a) levels

Initial reports suggested that, in addition to alterations in blood lipid and lipoprotein patterns, *trans* fatty acids increased lipoprotein (a) [Lp(a)] levels in most,[10,29] but not all,[10,12] studies addressing this point. High levels of Lp(a) have been related to increased risk of developing coronary heart disease.[30]

Almendingen et al.[23] reported that consumption of diets that incorporated either hydrogenated soybean or fish oil as the major source of fat resulted in significantly higher Lp(a) levels than diets in which butter was the major fat source. Assessing the effect of diets prepared with margarine relatively high in *trans* fatty acids or stearic acid compared with dairy fat, Aro et al.[27] found that diets high in *trans* fatty acids resulted in the highest levels of Lp(a). Similarly, Sundram et al.[26] reported that diets high in *trans* fatty acids resulted in higher Lp(a) levels than diets high in oleic, palmitic, or lauric + myristic acids.

In contrast, Chisholm et al.[25] reported no difference in Lp(a) levels after periods when subjects used either unsaturated margarine or butter in their habitual diets. Furthermore, when assessing the effect of diets high in oleic acid, moderately high (3.8% energy) in *trans* fatty acids, high (6.6% energy) in *trans* fatty acids, and high in saturated fatty acids, Clevidence et al.[31] found no significant differences in Lp(a) levels among the first three diets, although the high saturated fat diet resulted in lower Lp(a) levels. They noted that a subset of subjects with initially high levels of Lp(a) (>30 mg/dl) responded to the high *trans* fatty acid diet by increasing levels by approximately 5%. In a preliminary report, Lichtenstein et al.[32] demonstrated that substitution of hydrogenated soybean oil for soybean oil had no significant effect on Lp(a) levels. However, substitution of saturated fat (butter) for soybean oil preparations resulted in lower Lp(a) levels.

Small increases in Lp(a) levels have been reported to be attributed to *trans* fatty acid intake. Some of the data are complicated by the Lp(a) lowering effect of saturated fatty acids. Important when interpreting these data is consideration of the magnitude of the reported change and potential of these changes to significantly impact on cardiovascular disease risk.

Cholesterol metabolism

Cholesterol ester transfer protein and phospholipid transfer protein activities

Cholesterol ester transfer protein (CETP) activity is thought to have a direct effect on HDL cholesterol concentrations. *In vitro* enrichment of HDL with *cis* fatty acids has been reported to inhibit CETP activity, whereas enrichment with *trans* fatty acids has been reported to increase CETP activity.[33] Preliminary evidence in animals suggested that *trans* fatty acid intake results in increased CETP activity,[33,34] which may account for the decreased HDL-C concentration observed. Additional evidence to support this in humans is now available.

In order to further investigate the effect of *trans* fatty acids on HDL cholesterol levels, Abbey and Nestel[35] assessed CETP activity after subjects substituted fats contributing approximately 6% energy as elaidic or oleic acids for the habitual fat in their diets. CETP activity was reported to be higher after subjects consumed the elaidic acid-rich relative to the oleic acid-rich diet. An inverse relationship between CETP activity and fall in HDL cholesterol levels was reported. The authors postulated that the altered activity of CETP could be attributed to substrate specificity.

Similarly, van Tol and coworkers[36] assessed the effect on CETP activity of diets high in *trans* fatty acids relative to diets high in linoleic or stearic acids. CETP activity was highest during the period when subjects consumed diets high in *trans* fatty acids relative to the periods when subjects consumed diets high in linoleic or stearic acids. They concluded that the higher CETP activity contributed to the higher LDL and lower HDL levels observed after consumption of the *trans* fatty acid diet.

Aro et al.[27] assessed the effect of diets high in *trans* fatty acids or stearic acid relative to dairy fat on CETP and phospholipid transfer protein (PLTP) activities. They reported no significant effect of the *trans* fatty acid or stearic acid diets on CETP activity. However, the stearic acid diet reduced PLTP activity significantly more than did the *trans* fatty acid diet.

Endogenous cholesterol synthesis

Tracing deuterium oxide incorporation into newly synthesized cholesterol, Cuchel et al.[37] reported that increased rates of endogenous cholesterol synthesis did not contribute to the increase in blood cholesterol levels observed after subjects were provided with diets enriched in corn oil margarine relative to corn oil. The authors concluded that the increase in blood cholesterol levels was attributable, at least in part, to a decreased catabolic rate of cholesterol.

From these data it appears that the mechanism(s) underlying the observed change in blood cholesterol levels have yet to be totally elucidated.

Susceptibility of LDL to oxidation

Nestel et al.[10] initially reported that dietary *trans* fatty acids had no significant effect on the vulnerability of LDL to oxidative change. This observation was later confirmed by Cuchel et al.[37] and Halvorsen et al.[38]

Hemostatic factors

Almendingen et al.[39] assessed the effect on hemostatic factors of two types of hydrogenated fat — soybean oil and fish oil — relative to butter. They concluded that hydrogenated soybean oil had an unfavorable antifibrinolytic effect relative to hydrogenated fish oil and butter. This conclusion was based on higher levels of plasminogen activator inhibitor type 1 antigen and plasminogen activator inhibitor type 1 activity. No differences in the levels of factor VII, fibrinopeptide A, D-dimer, tissue plasminogen activator, or beta-thromboglobulin were found as a result of dietary intervention.

In a comprehensive assessment of coagulation and fibrinolysis factors in response to diets high in *trans* fatty acids or stearic acid, Mutanen and Aro[40] reported no differences in the concentration of plasma fibrin degradation products and D-dimers or factor VII coagulant activity, tissue type plasminogen activity, and plasminogen activator inhibitor activity. Similarly, Turpeien et al.[41] recently reported that *trans* fatty acids and stearic acid had similar effects on platelet function and endothelial prostacyclin production.

On the basis of this recent and comprehensive work it appears that *trans* double bond containing fatty acids do not have a significant effect on blood clotting.

Conclusions

Consistent with previous evidence, recent studies have confirmed that consumption of *trans* fatty acids results in higher total and LDL cholesterol levels relative to unsaturated fatty acids, and lower total and LDL cholesterol levels relative to saturated fatty acids, with the possible exception of stearic acid. HDL cholesterol levels continue to be reported to decrease in response to *trans* fatty acid intake, although not consistently. The lack of consistency among the data regarding HDL cholesterol levels may be related to differences in the actual level of *trans* fatty acids consumed or the relative decrease in saturated fat accompanying the dietary modification. Some researchers have related the decrease in HDL cholesterol levels, when present, to increased CETP activity.

Similarly, *trans* fatty acids have been reported to either increase or have no significant effect on Lp(a) levels, whereas saturated fat has been reported to decrease Lp(a) levels. The lack of consistency among studies regarding Lp(a) levels may be contributed to by coordinate changes of saturated fatty acids when *trans* fatty acid intake is altered. It is important to keep in mind the magnitude of the changes in Lp(a) levels reported relative to the predicted increased risk of developing cardiovascular disease associated with such changes. Available data on the effect of *trans* fatty acid intake on cholesterol metabolism, other than CETP activity, are too limited to draw firm conclusions at this time. The effect of *trans* fatty acids on the susceptibility of LDL to oxidation or on a variety of hemostatic factors suggest no adverse effects.

On the basis of the present review, it appears prudent at this time, as it has been in the past,[14–18] to recommend restricting both saturated and *trans* fatty acid intake to reduce the risk of developing cardiovascular disease. Caution must be exerted when communicating this message so as to avoid putting undue emphasis on *trans* fatty acids at the expense of saturated fatty acids; instead, reduced intakes of both should be encouraged.

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References

1 Emken, E.A. (1994). Nutrition and biochemistry of *trans* and positional fatty acid isomers in hydrogenated oils. *Ann. Rev. Nutr.* **4,** 339–476

2 Mensink, R.P. and Katan, M.B. (1993). *Trans* monounsaturated fatty acids in nutrition and their impact on serum lipoprotein levels in man. *Prog. Lipid Res.* **32,** 111–122

3 Denke, M.A. (1995). Serum lipid concentrations in humans. *Trans* fatty acids and coronary heart disease risk. *Am. J. Clin. Nutr.* **62** (suppl), 693S–700S

4 Zock, P.L. and Katan, M.B. (1997). Butter, margarine and serum lipoproteins. *Atherosclerosis* **131,** 7–16

5 Mensink, R.P. and Katan, M.B. (1990). Effect of dietary *trans* fatty acids on high density and low density lipoprotein cholesterol levels in healthy subjects. *New Engl. J. Med.* **323,** 439–445

6 Flynn, M.A., Nolph, G.B., Sun, G.Y., Navidi, M., and Krause, G. (1991). Effects of cholesterol and fat modification of self-selected diets on serum lipids and their specific fatty acids in normocholesterolic and hypercholesterolemic humans. *J. Am. Coll. Nutr.* **10,** 93–106

7 Fumeron, F., Brigant, L., Parra, H-J., Bard, J-M, Fruchart, J-C., and Apfelbaum, M. (1991). Lowering of HDL_2-cholesterol and lipoprotein A-1 particle levels by increasing the ratio of polyunsaturated to saturated fatty acids. *Am. J. Clin. Nutr.* **53,** 655–659

8 Zock, P.L. and Katan, M.B. (1992). Hydrogenation alternatives: Effects of *trans* fatty acids and stearic acid versus linoleic acid on serum lipids and lipoproteins in humans. *J. Lipid Res.* **33,** 399–410

9 Nestel, P.H., Noakes, M., Belling, B.B., McArthur, R., Clifton, P.M., and Abbey, M. (1992). Plasma cholesterol-lowering potential of edible oil blends suitable for commercial use. *Am. J. Clin. Nutr.* **55,** 46–50

10 Nestel, P., Noakes, M., Belling, B., McArthur, R., Clifton P., Janus, E., and Abbey, M. (1992). Plasma lipoprotein lipid and Lp[a] changes with substitution of elaidic acid for oleic acid in the diet. *J. Lipid Res.* **33,** 1029–1036

11 Wood, R., Kubena, K., O'Brien, B., Tseng, S., and Martin, G. (1993). Effect of butter, mono and polyunsaturated fatty acid enriched butter, *trans* fatty acid margarine, and zero *trans* fatty acid margarine on serum lipids and lipoproteins in healthy men. *J. Lipid Res.* **34,** 1–11

12 Lichtenstein A.H., Ausman L.M., Carrasco, W., Ordovas, J.M., and Schaefer, E.J. (1993). Hydrogenation impairs the hypolipidemic

effect of corn oil in humans. *Arteriosclerosis and Thrombosis* **13,** 154–161

13 Seppanen-Laakso, T., Vanhanen, H., Laakso, I., Kohtamaki, H., and Viikari, J. (1993). Replacement of margarine on bread by rapeseen and olive oils: Effects on plasma fatty acid composition and serum cholesterol. *Ann. Nutr. Metab. 37,* 161–174

14 WHO/FAO. (1993). *Fats and oils in human nutrition. Report of a joint expert consultation. #57 Food and Nutrition Paper. World Health Organization*

15 The British Nutrition Foundation. (1995). *Report of the British Nutrition Foundation Task Force.* Trans *fatty acids.* The British Nutrition Foundation, London

16 Stender, S., Dyerberg, J., Holmer, G., Ovesen, L., and Sandstrom, B. (1995). The influence of *trans* fatty acids on health: A report from The Danish Nutrition Council. *Clin. Sci.* **88,** 375–392

17 Krauss, R.M., Deckelbaum, R.J., Ernst, N., Fisher, E., Howard, B.V., Knopp, R.H., Kotchen, T., Lichtenstein, A.H., McGill, H.C., Pearson, T.A., Prewitt, E., Stone, N.J., Van Horn, L., and Weinberg, R. (1996). Dietary guidelines for healthy American adults. *Circulation* **94,** 1795–1800

18 Lichtenstein, A.H. (1997). *Trans* fatty acids, plasma lipid levels, and risk of developing cardiovascular disease. A statement for healthcare professionals from the American Heart Association. *Circulation* **95,** 2588–2580

19 Hu, F.B., Stampfer, M.J., Manson, F.E., Rimm, E., Colditz, G.A., Rosner, B.A., Hennekens, C.H., and Willett, W.C. (1997) Dietary fat intake and the risk of coronary heart disease in women. *New Engl. J. Med.* **337,** 1491–1499

20 Pietinen, P., Ascherio, A., Korhonen, R., Hartman, A.M., Willett, E.C., Albanes, D., and Viramo, J. (1997) Intake of fatty acids and risk of coronary heart disease in a cohort of Finnish men. *Am. J. Epi.* **145,** 876–887

21 Judd, J.J., Clevidence, B.A., Muesing, R.A., Wittes, J., Sunkin, M.E., and Podczasy, J.J. (1994). Dietary *trans* fatty acids: Effects on plasma lipids and lipoproteins of healthy men and women. *Am. J. Clin. Nutr.* **59,** 861–868

22 Nestel, P.J., Noakes, M., Belling, G.B., McArther, R., and Clifton, P.M. (1995). Effect on plasma lipids of interesterifying a mix of edible oils. *Am. J. Clin. Nutr.* **62,** 950–955

23 Almendingen, K., Jordal, O., Kierulf, P., Sandstad, B., and Pedersen, J.I. (1995). Effects of partially hydrogenated fish oil, partially hydrogenated soybean oil, and butter on serum lipoproteins and Lp(a) in men. *J. Lipid Res.* **36,** 1370–1384

24 Matheson, B., Walker, K.Z., Taylor, D.M., Peterkin, R., Lugg, D., and O'Dea, K. (1996). Effect on serum lipids of monounsaturated oil and margarine in the diet of an Antarctic Expedition. *Am. J. Clin. Nutr.* **63,** 933–938

25 Chisholm, A., Mann, J., Sutherland, W., Duncan, A., Skeaff, M., and Frampton, C. (1996). Effect of lipoprotein profile of replacing butter with margarine in a low fat diet: Randomised crossover study with hypercholerolaemic subjects. *Brit. Med. J.* **312,** 931–934

26 Sundram, K., Ismail, A., Hayes, K.C., Jeyamalar, R., and Pathmanathan, R. (1997). *Trans* (Elaidic) fatty acids adversely affect the lipoprotein profile relative to specific saturated fatty acids in humans. *J. Nutr.* **127,** 514S–520S

27 Aro, A., Jauhiainen, M., Partanen, R., Salminen, I., and Mutanen, M. (1997) Stearic acid, *trans* fatty acids, and dairy fat: Effects on serum and lipoprotein lipids, apolipoproteins, lipoprotein(a), and lipid transfer proteins in healthy subjects. *Am. J. Clin. Nutr.* **65,** 1419–1426

28 Judd, J., Baer, D., Clevidence, B., Kris-Etherton, P., Muesing, R., Iwane, M., Wittes, J., and Lichtenstein, A.H. (1998). Blood lipid and lipoprotein modifying effects of *cis* and *trans* monounsaturated fatty acids compared to carbohydrate, stearic acid and 12:0–16:0 saturated fatty acids in man fed controlled diets. *FASEB J.* **12,** A229

29 Mensink, R.P., Zock, P.L., Katan, M.B., and Hornstra, G. (1992). Effect of dietary *cis- trans*-fatty acids on serum lipoprotein ~~(a) levels~~ in humans. *J. Lipid Res.* **33,** 1493–1501

30 Wild, S.H., Fortmann, S.P., and Marcovina, S.M. (1997). A prospective case-control study of lipoprotein (a) levels and apo(a) size and risk of coronary heart disease in Stanford Five-City Project participants. *Arterioscler. Thromb. Vasc. Biol.* **17,** 239–245

31 Clevidence, B.A., Judd, J.T., Schaefer, E.J., Jenner, J.L., Lichtenstein, A.H., Muesing, R.A., Wittes, J., and Sunkin, M.E. (1997). Plasma lipoprotein(a) levels in men and women consuming saturated, *cis* or *trans* monounsaturated fatty acid enriched diets. *Arterioscler. Thromb. Vasc. Biol.* **17,** 1657–1661

32 Lichtenstein, A.H., Ausman, L.M., Vilella-Bach, M., and Schaefer, E.J. (1997). Hydrogenated vegetable oil results in higher lipoprotein levels than the naturally occurring oil and lower lipoprotein levels than butter. *Circulation* **95,** 1–480

33 Lagrost, L., Persegol, L., Lallemant, C., and Gamvert, P. (1994). Influence of apolipoprotein composition of high density lipoprotein particles on cholesteryl ester transfer protein activity. *JBC* **269,** 3189–3197

34 Lagrost, L. (1992). Differential effects of *cis* and *trans* fatty acid isomers, oleic and elaidic acids on the cholesteryl ester transfer protein activity. *Biochim. Biophys. Acta.* **1124,** 159–162

35 Abbey, M. and Nestel, P.J. (1994). Plasma cholesteryl ester transfer protein activity is increased when *trans*-elaidic acid is substituted for *cis*-oleic acid in the diet. *Atherosclerosis* **106,** 99–107

36 van Tol, A., Zock P.L., van Gent, T., Scheek, L.M., and Katan, M.B. (1995). Dietary trans fatty acids increase serum cholsteryl ester transfer activity in man. *Athero.* **115,** 129–134

37 Cuchel, M., Schwab, U.S., Jones, P.J.H., Vogel, S., Lammi-Keefe, C., Li, Z., Ordovas, J., McNamara, J., Schaefer, E.J., and Lichtenstein, A.H. (1996). Impact of hydrogenated fat consumption on endogenous cholesterol synthesis and susceptibility of low density lipoprotein to oxidation in moderately hypercholesterolemic individuals. *Metabolism* **45,** 241–247

38 Halvorsen, B., Almendingen, K., Nenseter, M.N., Pedersen, J.I., and Christiansen, E.N. (1996). Effects of partially hydrogenated fish oil, partially hydrogenated soybean oil and butter on the susceptibility of low density lipoprotein to oxidative modification in men. *Eur. J. Clin. Nutr.* **50,** 364–370

39 Almendingen, K., Seljeflot, I., Sandstad, B., and Pederson, J.I. (1996). Effects of partially hydrogenated fish oil, partially hydrogenated soybean oil, and butter on hemostatic variables in men. *Arterioscler. Thromb. Vasc. Biol.* **16,** 375–380

40 Mutanen, M. and Aro, J. (1997). Coagulation and fibrinolysis factors in healthy subjects consuming high steraric or *trans* fatty acids diets. *Thromb. Haemo.* **77,** 99–104

41 Turpeinen, A.M., Wubert, J., Aro, A., Lorenz, R., and Mutanen, M. (1998). Similar effects of diets rich in stearic acid or *trans*-fatty acids on platelet function and endothelial prostacyclin production in humans. *Arterioscler. Thromb. Vasc. Biol.* **18,** 316–322