Dietary trans fatty acids and their impact on plasma lipoproteins

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MB KATAN, RP MENSINK, A VAN TOL, PL ZOCK. Dietary trans fatty acids and their impact on plasma lipoproteins. Can J Cardiol 1995;11(Suppl G): 36G-38G. Foods contain isomers of unsaturated fatty acids that have double bonds in unusual configurations (trans instead of cis) or unusual positions, or both. Such fatty acids arise through biohydrogenation in the rumen of cows and sheep, or catalytic hydrogenation in industrial hardening of oils. The effects of trans-monounsaturates on lipoproteins in man are opposite to those of their cis-isomers: oleic acid, trans fatty acids raise low density lipoprotein (LDL) cholesterol and lipoprotein Lp(a) and lower high density lipoprotein (HDL) cholesterol, all in a dose-dependent fashion. Trans fatty acids raised serum cholesterol ester transfer activity in 52 of 55 volunteers (mean change 18%, P<0.02), and lowered the ratio of cholesterol esters to triglycerides in HDL. Lecithin cholesterol acyl transferase was unchanged. The effects of trans fatty acids on HDL and LDL may thus be mediated through cholesterol ester transfer protein.

Key Words: Dietary trans fatty acids, Lipoproteins

Acides gras trans diététiques et leur influence sur les lipoprotéines plasmatiques

RÉSUMÉ: Les aliments renferment des isomères d’acides gras insaturés qui ont des doubles liaisons de configuration inhabituelle (trans plutôt que cis), des positions inhabituelles ou les deux. Ces acides gras proviennent de la biohydrogénation qui survient dans le rumen des vaches et des moutons ou par l’hydrogénation catalytique lors du durcissement industriel des huiles. Les effets des monoinsaturés de type trans sur les lipoprotéines chez l’homme s’opposent à ceux de leurs cis-isomères: l’acide oléique: les acides gras trans provoquent une élévation du cholestérol LDL et de la lipoprotéine Lp(a) et abaissent le cholestérol HDL de façon dose-dépendante. Les acides gras trans ont élevé l’activité de transfert du cholestérol estérifié sérique chez 52 volontaires sur 55 (modification moyenne 18%, P<0.02) et ont abaissé le ratio cholestérol estér/triglycérides dans le HDL. L’acétyltransferase du cholestérol hépatique est demeurée inchangée. Les effets des acides gras trans sur le HDL et le LDL peuvent donc être modifiés par la protéine de transfert de l’estér cholestérol.

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ISOmeric FATTy ACIDS ARE UNSATURATED fatty acids in which one or more of the double bonds have an unusual spatial geometry, namely trans instead of cis, or an unusual position along the length of the molecule, or both. In foods, geometric and positional isomers almost invariably occur together. As it is analytically easier to distinguish trans from cis isomers than one positional isomer from another, food analyses usually report trans fatty acids only rather than total isomeric fatty acids. Whenever this paper discusses effects of dietary trans fatty acids, the positional cis isomers are implicitly included.

Small amounts of trans fatty acids are continuously formed in the rumen of cows and sheep. Trans fatty acids arise here as intermediates in the hydrogenation (saturation) of dietary unsaturated fatty acids by the hydrogen produced during bacterial fermentation. As a result, the fat in butter, cheese and milk contains some 2 to 8% by weight of trans fatty acids, most of the remainder being saturated. Much higher proportions of trans fatty acids are formed during the industrial hydrogenation of vegetable oils. Such partially hydrogenated vegetable oils have a particular melting range, stability and mouth feel that makes them suitable for incorporation into a wide range of foods, including baked goods and hard margarines. It should be stressed that only particular types of margarines are high in trans, namely brick- or stick-
type hard margarines made from partially hydrogenated oils. In contrast, typical levels of trans in soft margarines are some 3% of total fatty acids in The Netherlands and 11% in North America. Several brands of soft tub margarines sold in Europe and Canada have trans levels of 1% or less, and are also low in saturated fatty acids (1,2).

EFFECTS ON SERUM LIPID AND LIPOPROTEIN CONCENTRATIONS IN MAN

The toxicology of partially hydrogenated vegetable oils has been investigated extensively, and no untoward effects have been detected (3). However, attention was drawn to trans fatty acids when a study in human volunteers (4) showed that trans monounsaturated fatty acids, produced through hydrogenation of oleic acid-rich sunflower oil, lowered high density lipoprotein (HDL) and elevated low density lipoprotein (LDL) cholesterol levels compared with the natural cis isomer, oleic acid. A number of studies have appeared since which have largely confirmed these initial findings (5-7). Figure 1 (8) shows the effects of monounsaturated trans fatty acids relative to their cis isomer oleic acid across five trials. We adjusted for differences in other fatty acids between the trans enriched diets and the reference diets, using regression coefficients from a recent meta-analysis (9). Figure 1 suggests that the effect of trans fatty acids on HDL increases with the amount consumed. Although more experiments would be needed to define the shape of the dose-response curve more precisely, a linear relation appears satisfactory, and there is no evidence for a threshold below which trans fatty acids do not affect HDL cholesterol levels. According to this small meta-analysis, every additional percent of dietary energy as trans fatty acids results in a decrease in HDL cholesterol of 0.013 mmol/L or 0.50 mg/dL (R²=0.86, P=0.0019) and an increase in LDL cholesterol of 0.040 mmol/L or 1.55 mg/dL (R²=0.86, P=0.0028). This effect on LDL is similar to that of saturated fatty acids (9).

Factors that lower HDL cholesterol levels often will also elevate fasting triglyceride levels; dietary carbohydrates are a case in point (9). In view of the HDL-lowering effect of trans fatty acids, one would thus expect a substantial rise in triglycerides. This is indeed confirmed by the results of recent trials for which fasting triglyceride levels were reported. In the three largest trials, serum triglycerides were modestly, but significantly, elevated on the trans fatty acids diets relative to the oleic or linoleic acid reference diets (4, 6,10). In the other recent studies triglyceride levels were also somewhat higher on trans fatty acids, although the changes were not statistically significant within each separate trial (5,7,11). When we apply the same adjustments and linear regression analysis as applied in Figure 1, it emerges that among additional per cent of energy as trans fatty acids increases triglyceride levels by 0.013 mmol/L or about 1 mg/dL (R²=0.60, P=0.04). Thus, in addition to the LDL and HDL lowering effects, monounsaturated trans fatty acids appear to raise modestly fasting plasma triglyceride levels.

EFFECTS ON LIPOPROTEIN(a)

Serum lipoprotein(a) [Lp(a)] is a strong and independent risk factor for coronary artery disease. We therefore examined the effect of trans fatty acids on serum Lp(a) levels in controlled trials.

In our first experiment (4) 10% energy from the cholesterol-mising saturated fatty acids (lauric, myristic and palmitic acid) was replaced by oleic acid or by trans-monounsaturated fatty acids. Each of the 59 participants received each diet for three weeks in random order. The median level of Lp(a) was 26 mg/L on the saturated-fat diet; it increased to 32 mg/L (P=0.001) on the oleic-acid diet and to 45 mg/L (P<0.001) on the trans-fatty-acid diet (10). The second experiment (12) involved 56 subjects, who all received 8% of energy from either the saturated fatty acid stearic acid, from linoleic acid or from trans-monounsaturated, for three weeks each. Median Lp(a) levels were 69 mg/L on both the stearic-acid and linoleic-acid diet, and rose to 85 mg/L (P<0.01) on the trans-fatty-acid diet (10).

Our data thus agree with the finding of Nestel et al (5) in that trans fatty acids appear to raise Lp(a), even though the effect is quite small relative to genetically determined differences in Lp(a) levels. The effect of trans on Lp(a) is relevant for our understanding of lipoprotein metabolism; both satu-
rates and trans fatty acids raise LDL levels in plasma, but trans fatty acids raise Lp(a), while saturates, if anything, tend to lower it (10). This suggests that dietary effects on LDL and on Lp(a) follow different pathways.

**EFFECTS ON CHOLESTERYL ESTER TRANSFER PROTEIN**

Human plasma contains a protein which transfers cholestery esters from VLDL to lipoproteins of lower density. We hypothesized that this cholestery ester transfer protein (CETP) could play a role in the effect of trans fatty acids on HDL and LDL levels. We therefore measured the serum activity levels of CETP (using excess exogenous substrate assays) in sera from our second study on trans fatty acids. The CETP activities measured after the steaarte-di and the linoleate-di were identical, despite the higher VLDL + LDL cholesterol levels seen after the steaarte-di. The trans-diet was accompanied by an 18% increase in CETP activity if all subjects were analysed together. The increase in CETP activity after the trans-diet was seen in 52 of 55 individuals; one individual showed no effect and two showed a decrease in activity (13).

The increase in CETP activity coincided with a low cholesterol ester/ triglycerides ratio in HDL. This was to be expected because CETP removes cholestery esters from HDL and replaces them with triglycerides. The average molar ratio (2SD) was 6.15±1.83 on the trans-diet versus 6.97±2.19 on the linoleate-diet and 6.71±2.25 on the steaarte-diet (P=0.02).

It was previously reported that high concentrations of eladic acid (trans C18:1 n-9), added in vitro, may increase the transfer of cholestery esters from HDL to LDL (14). Therefore, trans fatty acids could act by increasing the serum levels of CETP, as suggested by our data, or by increasing the efficiency of the transfer process, as found in the in vitro experiments. Recently, Abbey and Nestel (11) reported increased CETP activity after substitution of trans-eladic acid for cis-oleic acid in the diet. A significant increase was only detected using a CETP activity assay employing endogenous lipoproteins, but absent if CETP activity was assayed in lipoprotein-deficient plasma. The CETP activity assay used in the present experiments is independent of endogenous lipoproteins and correlates very well with CETP mass. It is therefore possible that dietary trans fatty acids increase the transfer of cholestery esters by increasing CETP mass as well as by changing the structure of plasma lipoproteins, resulting in their acting as better substrates for CETP action.

Diminished levels of plasma CETP activity are often associated with a low risk lipoprotein profile, while increased CETP levels are found in patients with various forms of hyperlipidemia (15). Also, intravenous injection of CETP into rats or introduction of CETP into mice by transgenesis results in a rise in HDL and a fall in LDL cholesterol (15). These changes are similar to those seen in humans consuming high trans fatty acid diets. Experiments with mice and monkeys fed atherogenic diets revealed close correlations between atherosclerosis development, LDL cholesterol concentrations and plasma CETP levels (15). Our present data thus support the notion that the fall in HDL and increase in LDL on trans fatty acids are due to increased CETP activity, and that these lipoprotein changes may contribute to atherogenesis.

**POLICY IMPLICATIONS**

Trans fatty acids raise LDL and lower HDL, and if these changes are due to increased activity of CETP then both the rise in LDL and the fall in HDL might promote atherosclerosis. However, it would be erroneous to conclude that dietary fats high in trans fatty acids should now be replaced by fats high in saturates and cholesterol. The role of saturated fat and cholesterol in coronary artery disease has been abundantly documented. Also, intakes of saturated fatty acids far exceed intakes of trans. It is therefore preferable to count trans fatty acids in with the saturates, and aim for a reduction of the sum of the two. This implies replacement of hard fats by oils and margarines low in both trans and saturated fatty acids. Such margarines are widely available in Europe and Canada (1). Their use will make it possible to reduce trans intake without reverting to products high in saturated fatty acids and cholesterol.

**REFERENCES**