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Isomeric Fatty Acids and Serum Lipoproteins

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Unsaturated fatty acids are characterized by the presence of at least one carbon–carbon double bond. Two configurations are possible around such a bond (Figure 1): the two hydrogen atoms on either side can point in the same direction (*cis*) or in opposite directions (*trans*). In addition, the double bond can be located anywhere along the length of the molecule, so that many positional isomers may exist.

Unsaturated fatty acids in plants and vegetable oils typically have the *cis* configuration (but see Houtsmuller[1] for some interesting exceptions), and the double bonds are usually located only at the *n*-3, *n*-6, and/or *n*-9 positions, i.e., at a distance of three, six, or nine carbon atoms from the methyl end of the molecule (Figure 1).

Ruminant animals such as cows or sheep ingest unsaturated fatty acids with their plant foods. Subsequently, bacteria in the rumen use these unsaturated fatty acids as acceptors for excess hydrogen produced during bacterial anaerobic fermentation, thus resulting in saturation of the fatty acids. However, in some cases, the end-product is not a saturated bond but an unsaturated one with a different configuration—*trans* instead of *cis*—or in a different position, or both. As a consequence, the body and milk fat of cows and sheep contain *trans* fatty acids—about 2 to 9% in the case of butterfat.

A similar process, but now using hydrogen gas and a nickel catalyst, is employed industrially to turn liquid edible oils into solid fats. Apart from solidity, this so-called partial hydrogenation process also confers stability and texture. The procedure can be fine-tuned to produce nearly any desired mix of *cis*-unsaturated, *trans*-unsaturated, and saturated fatty acids. Hence, the *trans*-fatty acid content of commercial edible fats may vary from 0% for high-linoleic-acid diet margarines to over 50% of fatty acids for certain shortenings and frying fats. The average U.S. intake of *trans*-fatty acids has been estimated at 8 g per capita per day.[2] Although the actual figure is controversial,[3,4] the average intake of *trans* and other isomeric fatty acids is certainly appreciably lower than that of saturated fatty acids.

The health effects of partially hydrogenated oils have been extensively investigated in several animal species and in multigeneration experiments. No untoward effects on reproduction, longevity, or the occurrence of various diseases, including cancer, have been detected (see Senti[2] for an exhaustive review). However, the effects of diet on blood lipids and lipoproteins show marked differences between species, and we therefore felt it useful to determine the effects of *trans*-fatty acids on serum lipoproteins in healthy volunteers. (Note that wherever this paper refers to *trans*-fatty acids in the diet, the presence of positional *cis* isomers is also implied; both configurations arise during hydrogenation, and any effects ascribed to *trans*-fatty acids may also be due in part to *cis* isomers with a double bond in an unusual position.)

A controlled, clinical trial was carried out in 34 women and 25 men.[5,6] Each subject received three diets for three weeks each, in random order. One diet was rich in the *cis*-monounsaturated fatty acid, oleic acid; one was rich in cholesterol-raising saturated fatty acids; and one was high in *trans*-monounsaturates. Apart from the exchange of one type of fatty acid for another, the diets were identical. The intake of *trans*-fatty acids on the *trans*-diet was fixed at 11% of daily energy intake, which at an energy intake of 10 MJ (2400 kcal) per day would translate into 29 g/day. It was thus appreciably higher in *trans*-fatty acids than average population intakes.

Relative to the diet high in oleic acid, the *trans*-fatty acid-rich diet increased serum total cholesterol by an average of 0.26 mmol/L (10 mg/dL). This was

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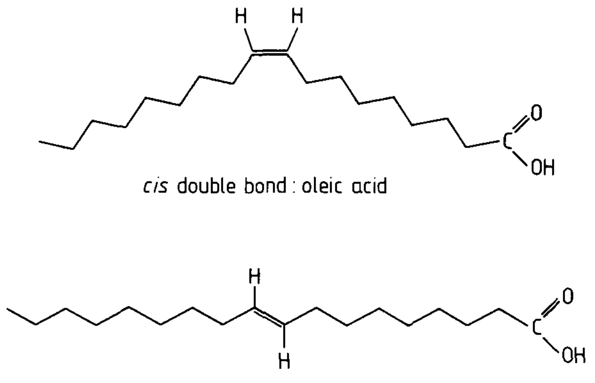

trans double bond: elaidic acid

Figure 1. Structure of *cis*- and *trans*-fatty acids. Hydrogen atoms have been indicated only for the carbons adjacent to the double bond so as to highlight the *cis/trans* isomerism. Both oleic and elaidic acid have their double bond in the *n*-9 position. Note that in partially-hydrogenated oils and in ruminant fats, elaidic acid is only one of several *trans*-fatty acids in which the double bond occurs in various positions.

due to an increase of 0.37 mmol/L (14 mg/dL) in low-density lipoprotein (LDL) cholesterol, an increase of 0.06 mmol/L (2 mg/dL) in very-low-density lipoproteins (VLDL), and a fall of 0.17 mmol/L (7 mg/dL) in the high-density lipoprotein (HDL) fraction. The effects were seen in both men and women, and they were statistically highly significant.[5] In the same subjects, the diet high in saturated fatty acids raised total cholesterol by 0.54 mmol/L (21 mg/dL) and LDL cholesterol by 0.47 mmol/L (18 mg/dL); HDL was unchanged. Thus the LDL-raising effect of *trans*-fatty acids was less, but not much less, than that of cholesterol-raising saturated fatty acids. In addition, the *trans*-fatty acids depressed HDL, whereas saturates did not have this effect. Although there is as yet no formal proof that diet-induced lowering of HDL will increase coronary risk, such changes still appear less than desirable.

The few previous studies that specifically examined the effects of *trans*-fatty acids on total serum cholesterol levels yielded conflicting results. Mattson et al.[7] did not find a hypercholesterolemic effect of *trans*-C18:1 as compared with oleic acid. However, studies by Vergroesen and coworkers[8,9] and by Anderson, Grande, and Keys[10] did suggest that *trans* isomers of oleic acid have a moderate cholesterol-raising effect, though less so than saturated fatty acids. Our recent study[5,6] confirms that *trans*-fatty acids have a cholesterol-elevating effect about half that of saturated fatty acids. The reason for the discrepancy with the study of Mattson et al. is unclear.[6] Effects on individual lipoproteins have not been reported before, and the unfavorable outcomes for LDL and HDL will need to be verified in further studies. More recent findings do suggest that the HDL-lowering effect of *trans*-fatty acids is still present at lower levels of intake that more closely approximate real-life consumption figures.[11] However, the dosage was still fairly high, and the source of *trans*-fatty acids was again a specially manufactured margarine very high in a limited range of isomeric fatty acids.

In view of the limited information available at present, it appears premature to condemn all partially-hydrogenated vegetable oils as cholesterol-raising, let alone hydrogenated marine oils about which very little is known, or to require products to be labeled with their content of *trans*- and other isomeric fatty acids. Likewise, in the dietary treatment of hypercholesterolemia, reducing the intake of saturated fatty acids and cholesterol should remain the primary aim; the efficacy of such measures has been well established. Still, our data do suggest it might be prudent for patients diagnosed with hypercholesterolemia to restrict their intake of foods rich in *trans* isomers of oleic acid. However, this should be a secondary measure only, and it should not distract the patient from the major aim of reducing saturated fatty acid and cholesterol intake.

The notion that margarines have now been shown to be as noxious for cholesterol levels as butter is wrong and should be rectified. Firstly, margarines differ widely in their composition. Some of the diet margarines sold successfully in Europe contain no *trans*-fatty acids at all; they consist of unhydrogenated sunflower oil made semisolid by mixing with a minor amount of saturated fat. Secondly, in margarines that do contain *trans*-fatty acids—which includes most brands consumed in the United States—the *trans* content is usually no more than 10 to 30% of the fat, as opposed to butter, which contains 60% saturated and about 5% *trans*-fatty acids. And finally, vegetable margarines contain no cholesterol, while milk fat has a high cholesterol content—three to four times that of other animal fats. The cholesterol in butter by itself and through a synergistic interaction with the saturated fatty acids present causes an extra rise in total and LDL cholesterol over and above that caused by saturated fatty acids alone.

Thus, recent findings in no way detract from the view that a reduction in saturated fat and cholesterol intake is the primary dietary measure for optimizing blood lipoprotein profiles. However, the range of suitable replacements for butter and other animal fats may be more restricted than previously realized, and it might be necessary to make more use of unhydrogenated vegetable oils, as populations with low rates of coronary heart disease have in fact been doing for centuries.

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