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Influence of Trans Fatty Acids on Health

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Abstract
The contribution of dietary trans fatty acids (TFAs) on the risk of ischemic heart disease (IHD) has recently gained further support due to the results from large, prospective, population-based studies. Compared to saturated fat, TFAs are, gram to gram, associated with a considerably (2.5- to >10-fold) higher risk increment for IHD. A negative effect on the human fetus and on newborns and an increase in colon cancer risk in adults are possible but, however, still equivocal. Recent findings justify further studies concerning the effect of TFAs on allergic diseases in children and on the risk of type-2 diabetes in adults. The intake of industrially produced TFAs in European countries is decreasing. However, determination of the TFA content in various popular food items collected in Danish shops showed that it is likely that persons with a frequent intake of, e.g., French fries, microwave oven popcorn, chocolate bars, fast food, etc., consume industrially produced TFAs in amounts far exceeding the average intake, and are thereby exposed to an unnecessary health risk. The Danish government has decided that oils and fats containing more than 2% industrially produced TFAs will not be sold in Denmark after the January 1, 2004.

Introduction

Trans fatty acids (TFAs), as they appear in human food, are mainly generated by industrial hardening of edible oils, and by bacterial hydrogenation of polyunsaturated fatty acids in the rumen of ruminants.

Industrial hardening of oils aims to produce stable products and to make the products solid at room temperature, thus making transportation and storage easier. The industrial process results in the formation of predominantly monounsaturated TFAs, of which elaidic acid (Δ9-*trans*-18:1) is a major component. The bacterial process in the rumen results mainly in the formation of trans vaccenic acid (Δ11-*trans*-18:1), but also of isomers of linoleic acid, the so-called conjugated linoleic acids, e.g. Δ9*cis,* 11-*trans*-18:2 [1].

TFAs and Ischemic Heart Disease

The fatty acid content in plasma reflects intake during previous weeks, in erythrocytes during the previous months, and in adipose tissue during the previous year. Studies relating these markers for TFA intake to the incidence of ischemic heart disease (IHD) have so far given contradictory results. The results of 1 large study, including 671 men with myocardial infarction from 9 European countries, were inconclusive [2] and considered difficult to interpret [3].

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A Norwegian case-control study [4], including 100 first-time myocardial infarction patients and 98 control persons, demonstrated a significantly higher TFA content in the adipose tissue of patients than controls. Comparing the 20% with the highest TFA content in adipose tissue with the 20% with the lowest content, the odds ratio for myocardial infarction adjusted for age and gender was 2.8 (95% CI 1.16–6.84).

The most evident epidemiological data that relate TFAs in the diet to the risk of IHD are 4 extensive prospective population-based studies including about 145,000 persons in all, with a follow-up for 6–14 years. After adjustment for several confounders, the relative risk of IHD associated with an increase in TFA intake corresponding to 2% of the total energy intake (E%) was 1.36 (1.03–1.81) in the Health Professionals' Follow-up Study [5]; 1.14 (0.96–1.35) in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study [6]; 1.93 (1.43–2.61) in the Nurses' Health Study [7], and 1.28 (1.01–1.61) in the Zutphen Elderly Study [8]. The pooled results give a relative risk of 1.25 (1.11–1.40) [8] associated with a 2E% increase in TFA intake.

According to 3 of the 4 prospective studies [5–7], the relationship between the intake of TFAs and the risk of IHD was stronger than that between the intake of saturated fatty acids and the risk of IHD. Even if unknown confounding factors in epidemiological studies could be the causative factor in the associations, the 4 prospective studies, including both men and women in different age groups living in 3 different countries, constitute a rather firm basis for applying the results to populations in general.

Ascherio et al. [9] summarized randomized studies that compared the influence of isocaloric amounts of saturated fatty acids and industrially produced TFAs on high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol concentrations in blood. They concluded that an increase in the intake of industrially produced TFAs has an unfavorable influence on the LDL/HDL cholesterol ratio. An increase in TFAs of 2E% increases the ratio by 0.1, whereas 2E% saturated fatty acids increase the ratio by 0.04 [9]. An increase in the LDL/HDL cholesterol ratio of 0.1 corresponds to a 5% higher risk of IHD and an increase of 0.04 to a 2% higher risk of IHD [9].

Due to an increase in LDL/HDL cholesterol ratio, a 5% increase in risk by a TFA intake equivalent to 2E% is less than the fully adjusted risk increment of IHD (25%) for an increase of 2E% in TFA intake according to prospective population-based studies [8]. This discrepancy between 5 and 25%, respectively, may be due to the influence of TFAs on lipoprotein(a) (Lp(a)), triglycerides, and endothelial function.

Comparing the increments in the relative risk of IHD, 25 and 2% associated with TFA and saturated fat intake, respectively, thus suggest a >10-fold greater effect of TFAs gram-to-gram. The risk association between the intake of saturated fat and IHD is fully predicted by the effect on blood cholesterol concentrations [10]. This estimate is rather crude. The most conservative estimate based on the effects of blood cholesterol only means that gram-for-gram the intake of TFAs is associated with 2.5 times the risk increment of saturated fatty acids [9].

Lp(a) in plasma is increased when TFAs replace saturated fat [11]. Another result of high intakes of TFAs is an increased concentration of triglycerides in plasma [9], which is independently associated with an increased risk of IHD [12].

A recent study [13] that examined the effect of replacing 9.2E% of saturated fatty acids with TFAs resulted in a 20% reduction in HDL cholesterol and a concomitant reduction in flow-mediated vasodilatation of 30%, an effect that might be caused by lowering HDL. Impairment in flow-mediated vasodilatation suggests that TFAs increase the risk of IHD through an effect on endothelial function as well.

A supplementary explanation is that a daily intake of a few grams of industrially produced TFAs leads to an incorporation of TFAs in the cells involved in cardiac rhythm regulation, with a subsequent decrease in the threshold for cardiac arrhythmias, a major cause of sudden cardiac death. This hypothesis is derived partly by analogy with the beneficial effect of n–3 fatty acids on IHD. About 1 g/day of n–3 fatty acids apparently has a preventive effect against cardiac arrhythmia [14]. The hypothesis is supported by studies of fatty acids incorporated in cultured heart myocytes [15, 16] and by a recent case-control study demonstrating a higher TFA content in erythrocytes from patients with primary cardiac arrest compared to controls [17]. The association between primary cardiac arrest and TFA intake related, however, only to nonconjugated *trans*-linoleic acid isomers.

The Nurses' Health Study showed that the association between IHD and TFAs was due to partially hydrogenated vegetable fat rather than to isomers from ruminant sources [18]. The same pattern was observed in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study [6], whereas there was no difference in risk association in the smaller Zutphen Study [8]. Taken together the results suggest that the harmful effect of TFAs on IHD is primarily derived from industrially produced TFAs.

TFAs and the Human Fetus and Newborns

TFAs are transferred from the mother to the fetus [19]. Animal experiments suggest that high intakes of TFAs inhibit the formation of long-chain polyunsaturated fatty acids (LCPUFAs) [20]. In theory the same can happen in humans [21]. LCPUFAs are important in fetal and infant growth, and in visual and central nervous system development.

A negative association between birth weight and TFAs in plasma was reported in a study including premature children [21]. Two studies have shown an inverse relationship between LCPUFAs and TFAs in cord blood lipids of full-term infants [22, 23]. Elias and Innis [22] further found that the level of TFAs, including conjugated linoleic acid, was inversely related to the length of gestation, and to birth weight and length.

An opposite effect between TFAs and n–3 fatty acids on the threshold of muscular contraction may be valid not only for the heart but also for the uterus. A few grams of n–3 fatty acids daily prolong gestation [24], whereas the opposite seems to occur for a few grams of TFAs [22].

TFA intake has been reported to be associated with the development of preeclampsia. Preeclamptic women had 30% higher amounts of TFAs in red blood cells than women without toxemia [25].

Although the present data rather weakly support a harmful effect of TFAs on the fetus and newborn, any harmful effect has enormous public health implications.

TFAs and Cancer

The EURAMIC study, which investigated the association between TFAs in adipose tissue and the incidence of cancers of the breast, prostate, and colon, demonstrated a positive association between TFAs and the incidence of cancers of the breast and colon, but not of the prostate [26, 27].

A smaller study found a negative association between TFAs in adipose tissue and the incidence of metastasis in lymph nodes as a measure of the prognosis of breast cancer [28]. There was no association between TFAs and survival. Holmes et al. [29] found no association between TFA intake and breast cancer in the Nurses' Health Study. In a case-control study including 500 index and 500 control persons, there was no association between the self-reported intake of TFAs and the incidence of polyps in the colon [30].

Another case-control study examining the association between TFAs and colon cancer in approximately 2,000 index and 2,000 control persons found suggestions of an increased risk related to the intake of TFAs in subsets of this population [31].

The effect of TFAs on cancer is thus still equivocal. However, there are suggestions of increased risk caused by TFAs.

TFA and Allergy

The increasing prevalence of allergic rhinitis, atopic diseases, and asthma are associated with the spread of a Western lifestyle [32]. The ISSAC examined the prevalences of asthma, allergic rhinoconjunctivitis, and atopic eczema in children aged 13–14 years from 155 centers around the world [33]. The results showed a positive association with the intake of TFAs estimated as the content of a representative market basket [34]. In no way do ecological studies like this prove causality.

TFA and Diabetes

An analysis of a 14-year follow-up of the Nurses' Health Study considering the relative risks of type-2 diabetes [35] demonstrated that the risk of diabetes was positively associated with the intake of TFAs. The authors estimated that an increase in TFAs of 2E% from TFAs was associated with a relative risk of type-2 diabetes of 1.39. However, this association was not present in the Iowa Women's Study [36] or in the Health Professionals' Study [37]. Several studies suggest that the fatty acid composition of muscles and dietary fatty acids modulate the action of insulin. In these studies TFAs appear to increase insulin resistance [38–40]. This may be due to an effect of TFAs on ion channels in the cell membranes. The relation – if any – between the intake of industrially produced TFAs and the appearance of type-2 diabetes has not yet been settled. There are, however, some indications.

Intake of TFAs

The average intake of TFAs in Denmark was 2.6 g/person/day in 1996 [41], which is about 50% of the intake in 1991, and corresponds to the average intake in Europe [41]. The average intake of ruminant TFAs is about 1.3 g/person/day. This means that only small amounts,

probably about 1 g/day, originate from industrially produced TFAs, representing a substantial decrease compared with 6 g in 1976 [42].

Margarine and shortenings have been the main contributors to the intake of industrially produced TFAs. The content of TFAs in table margarines in Denmark has been considerably reduced and was less than 1% in 1999, while it was approximately 3% in 1996.

The TFA content in baking margarines and industrial margarines has not changed. But 20% were 'trans fat free' in 1999, compared with none in 1996 [43].

In 2000 the Danish Nutrition Council analyzed 49 randomly collected snack, cake, and candy products which were all labelled as containing 'partially hardened fat' or similar terms [44]. Twenty-four products contained less than 1 g industrially produced TFAs/100 g, 11 contained 1–2 g TFAs/100 g, and 8 contained more than 2 g/100 g. Two products contained 7.4 and 18 g/100 g, respectively. A random sample of popcorn products for microwave ovens was also analyzed. This showed a maximum content of industrially produced TFAs of 40% of the fat content. A bag equivalent to a serving that contains 30 g of fat has a content of approximately 12 g of TFAs [44]. The deep fat frying of foods in some fast-food chains can contribute considerably to the intake of TFAs because the fat often contains more than 10% industrially produced TFAs. Finally a random sample of 31 products produced in the EU and labelled as containing 'vegetable fat' only and not with 'partially hydrogenated fat' etc., was analyzed. This included products with industrially produced TFAs of up to 16% of the total fat content (Danish Nutrition Council, unpublished data). This obvious mislabelling shows that even for the informed consumer, exposure to industrially produced TFAs is unavoidable.

The above results demonstrate that considerable amounts of industrially produced TFAs are presently incorporated in a variety of products. A doughnut can contain 3.2 g TFAs, and a large serving of chips 6.8 g of TFAs [45]. A bag of popcorn, a doughnut, and a large serving of chips contain altogether more than 20 g TFAs. A similar 'meal' consisting of 100 g of biscuits (10 g TFAs), a chocolate bar (3 g TFAs) and a bag of popcorn for a microwave oven (12 g TFAs) also contains more than 20 g TFAs.

Labelling of TFAs in Food

In Canada and the US

On January 1, 2003, Canada as the first country in the world introduced a labelling of the content of TFAs in food products [46].

On July 11, 2003, the Food and Drug Administration (FDA) published its regulations on nutrition labelling. These require that TFAs be declared in the nutrition label of conventional foods and dietary supplements on a separate line immediately under the line for the declaration of saturated fatty acids, to be effective by January 1, 2006 [47]. FDA has decided not to separate between industrially produced TFAs and TFAs of ruminant origin. Consequently dairy products will be labelled with content of TFAs.

In the EU

Processed and packaged food should be labelled with a list of ingredients ranked according to the amounts in grams in the product. If a product contains some partially hydrogenated fat, it should appear on the label, but not how much TFAs it contains.

If food is provided with a health claim concerning its content of industrially produced TFAs, e.g. 'free of trans fatty acids', a declaration is required of the fat composition in the product, stating the amounts of mono-, poly-, and saturated fatty acids.

In March 2003, after consultations with the member states of the EU, the Danish government decided that oils and fats with a more than 2% content of industrially produced TFAs will not be sold in Denmark after the January 1, 2004.

Conclusion

There is now strong supporting evidence that industrially produced TFAs promote IHD and some supporting evidence of other harmful effects of TFAs on health [48]. By contrast, there is no evidence to suggest that removal of these TFAs will have any negative effects on health or the quality of foods. The use of industrially produced TFAs is primarily due to marginal economic reasons. Present data suggest that industrially produced TFAs in the diet compared to saturated fat gram-to-gram give a >10-fold higher increment in IHD risk. This calculation is rather crude and is not based on direct comparison of the risk increment for IHD by saturated and TFAs, but by a combination of results from observation and

intervention studies. However, the results of direct comparisons in the Nurses' Health Study [7] and in the 7-country study [49] show an even greater difference.

The decrease in intake of industrially produced TFAs in Denmark from 6 g in 1976 to less than 1 g in 1996 occurred concomitant with a >50% decrease in deaths from IHD [42, 50]. Even if many other changes in lifestyle have taken place during the last 80 years, it is tempting to relate the increase and the following decrease in deaths from IHD in the Western hemisphere to a similar trend in the intake of industrially produced TFAs during the same period [50]. Likewise, to relate the increase in deaths from IHD in the Eastern hemisphere and Eastern Europe [50] to the increase in intake of TFAs [51]. With a hypothetically destabilizing effect on heart rhythm [52], the lag time between a change in intake and a change in deaths from IHD should be rather short.

Despite the low average intake of industrially produced TFAs in Western Europe, certain popular food items contain more than 10 g/serving. Similar products are available either as organic or as traditionally produced products without TFAs, and with the same quality of taste.

The intake of TFAs from ruminant sources, e.g. beef and dairy products, constitutes a low and more uniform exposure, i.e. less than 5% of ruminant fat in contrast to much higher, i.e. up to 60%, TFAs in industrially hydrogenated fats. Even with the same harmful biological effect per gram as industrially produced TFAs, ruminant TFAs in the food would constitute a minor health problem.

Information about the content of industrially produced TFAs in food can be considered as a label warning. Scandinavian authorities consider that label warnings are in general ill-judged measures that push the responsibility for ensuring the safety of the food from the authorities and the producers onto the consumer. Such labelling may confuse, or even frighten, and result in a general skepticism with respect to food. Instead it seems sensible to make such label warnings unnecessary through legislation, for example by setting product and process requirements.

Ideally, industrially produced TFAs in our food should be replaced by *cis*-unsaturated fat. However, despite the negative effect of saturated fat on blood lipids, even replacement of industrially produced TFAs with saturated fat will, according to present knowledge, lead to a considerable reduction in IHD risk and other health risks. Right now it is likely that population groups within Western societies, with dietary habits that are different from the average, and populations outside the Western hemisphere consume considerable amounts of industrially produced TFAs and are thereby exposed to an unnecessary, presently unavoidable but easily eliminated health risk.

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