Saturated and Trans Fatty Acids and Coronary Heart Disease

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Dietary intake of both saturated and trans fatty acids has been associated with an increase in the risk of coronary heart disease (CHD). Evidence comes mainly from controlled dietary experiments with intermediate end points, such as blood lipoproteins, and from observational studies. A few small, randomized controlled trials with clinical end points have been carried out in which saturated fat was replaced with polyunsaturated fat, leading to a reduction in low-density lipoprotein cholesterol and a reduction in CHD risk. However, no such studies exist for trans fatty acids. More high-quality, randomized controlled trials on fatty acids and CHD are required, but public health recommendations to reduce intake of both saturated and trans fatty acids are appropriate based on the current evidence.

Introduction

Coronary heart disease (CHD) is a major cause of morbidity and mortality in the Western world [1]. Well-established risk factors for CHD include age, sex, smoking, blood pressure, total cholesterol and high-density lipoprotein cholesterol (HDL-C), and type 2 diabetes [1]. In terms of nutrition, a diet high in saturated fatty acid (SFA) and trans fatty acid (TFA) intake has been associated with CHD incidence [1]. In this review, the biochemistry and dietary intake of SFAs and TFAs are discussed, the evidence linking them and their food sources with CHD is reviewed, and recent developments in this research area are highlighted.

Biochemistry of Fatty Acids

Fatty acids are hydrocarbon chains with terminal methyl and carboxyl groups. A vast number of fatty acids occur in nature, differing in chain length, number of double bonds, and type of double bonds. However, there are probably less than 20 that are quantitatively important in the human diet.

More than 95% of total dietary intake of fatty acids is in the form of triacylglycerol. Most natural food sources contain a wide variety of saturated and unsaturated fatty acids, and thus a large number of triacylglycerol molecules of different fatty acid composition. Dietary fatty acids fulfill three major roles: acting as an energy source, functioning as structural components of membranes, and acting as precursors to other molecules. Dietary fat represents a convenient energy-rich food source, but the role of fatty acids as energy providers can be adequately fulfilled by carbohydrate, whereas the major fatty acids found in cell membranes can be manufactured in the body. However, linoleic acid and α-linolenic acid cannot be made by animals and are thus described as essential fatty acids. This appears to happen as a result of their necessity in cell membranes and as precursors of eicosanoids, such as thromboxanes, prostaglandins, prostacyclins, and leukotrienes. For the purposes of this review, we focus on two classes of fatty acids—SFAs and TFAs.

Biological Effects of the Various Classes of Fatty Acids

Effect of SFA on serum lipids

Observed epidemiologic associations between cholesterol and fatty acids were confirmed by Keys and Parlin [2] and Hegsted et al. [3], and predictive equations were developed to quantify the effects of fatty acids and dietary cholesterol on plasma cholesterol concentrations. The numerous controlled feeding studies of effects of different fatty acids on cholesterol levels have been summarized in many meta-analyses (most recently by Mensink et al. [4]). These analyses essentially confirm the earlier reports [2,3] that SFAs increase and polyunsaturated fatty acids (PUFAs) decrease total cholesterol and low-density lipoprotein cholesterol (LDL-C). However, not all SFAs affect total and LDL-C concentrations in the same manner. For example, stearic acid has little effect on plasma cholesterol concentrations [3], possibly because stearic acid is rapidly converted in the body to oleic acid.

A more recent meta-analysis shows that fatty acids can also differ in their effects on HDL-C [4]. All three classes of fatty acids (SFA, monounsaturated fatty acid [MUFA], and PUFA) elevate HDL-C when they replace carbohydrate in the diet, but this effect is slightly greater for SFA than the other two classes. However, there is also evidence that the chain length of SFA is related to its effects on HDL-C (ie, the longer the chain length the smaller the effect on HDL-C). Lauric acid increases HDL-C, and palmitic and stearic acid do not affect HDL-C [4]. Triglyceride concentrations also increase when dietary fatty acids are replaced by carbohydrates [4].

Therefore, replacement of SFA with carbohydrate, which reduces both LDL and HDL, has little effect on the LDL to HDL ratio but increases triglycerides, except when low–glycemic index foods are consumed [5]. This change would at most have a minimal beneficial effect on CHD risk. However, replacement of SFA with either MUFA or PUFA would decrease LDL while changing HDL only slightly, hence improving the LDL to HDL ratio, and would have a smaller effect on triglycerides. Therefore, substitution of SFA with unsaturated fat (either MUFA or PUFA) rather than carbohydrate is likely to be more beneficial in terms of CHD risk reduction. These observations have been confirmed in recent intervention studies, in which substitution of carbohydrate with MUFA in a low-SFA diet had no significant effect on LDL, increased HDL, lowered triglycerides, and reduced estimated 10-year CHD risk [6]. In a second study, designed to examine whether carbohydrate or MUFA was the preferred replacement for SFA, LDL was lowered to a similar extent in both groups. The decrease in HDL was smaller in the MUFA group, and triglycerides tended to be lower with the MUFA diet but were significantly higher with the carbohydrate diet. This study concluded that MUFA provided a greater reduction in risk when used as a replacement for SFA than carbohydrate [7].

Effect of TFAs on lipids

The biological effects of MUFAs depend on whether the MUFAs are in the cis or trans configuration. Cis MUFAs are relatively neutral with respect to their effects on LDL and HDL [8], but trans MUFAs have been shown to increase LDL and decrease HDL relative to cis MUFAs [4,8]. Trans MUFAs can also increase plasma levels of lipoprotein(a) [9] and triglycerides [4]. The increase in the ratio of total cholesterol to HDL-C for TFAs is approximately twice that for SFAs [10].

Combined dietary measures to reduce LDL-C

A reduction in SFA, TFA, and dietary cholesterol intake and an increase in soluble dietary fiber and plant sterol/stanol intake have all been shown to independently decrease serum LDL [11]. A combined dietary approach that was low in SFA and high in plant sterols, soy protein, viscous fibers, and almonds has been shown to produce an LDL-C–lowering effect similar to a statin [12].

Other biological effects of SFAs and TFAs

Whereas earlier studies primarily focused on the effects of changes in SFA and TFA on blood lipids, more recent studies have examined effects on other risk markers for CHD [13]. Both SFA and TFA may increase CHD risk by reducing sensitivity to the action of insulin, and therefore may be associated with insulin resistance and type 2 diabetes [14]. There is also evidence that SFA may enhance thrombogenesis, possibly through increased platelet aggregation as a result of inhibition of prostacyclin [15].

Keogh et al. [16] have recently shown that arterial flow-mediated dilatation was impaired more by a high-SFA diet (19% of energy, total fat 37% of energy) than by a low-fat diet (total fat 18% of energy) when the weight of the participants remained stable in the study. However, in a further study, there was no difference in flow-mediated dilatation between a low-carbohydrate, high-SFA weight-loss diet and an isocaloric, high-carbohydrate, low-SFA diet after 8 weeks of intervention [17]. The authors concluded that the overall energy restriction and weight loss may have negated the previously shown adverse effect of SFA, and that longer-term studies would be required [17].

In terms of the association between TFA and vascular function, in a controlled feeding study, increased TFA intake was shown to reduce endothelial function by impairing flow-mediated dilatation [18]. Lopez-Garcia et al. [19] also suggest a potential association between TFA intake, inflammation, and endothelial function based on a cross-sectional analysis that showed associations among TFA and C-reactive protein (CRP), soluble tumor necrosis factor–receptor 2 (sTNF-R2), E-selectin, soluble intracellular adhesion molecule-1 and soluble vascular cell adhesion molecule-1. Similar associations between SFA and sTNF-R1 and sTNF-R2 have also been demonstrated in 823 women from the Nurses' Health Study [20]. In this study, an association with interleukin-6 and CRP was only demonstrated in women with higher body mass index [20]. Some randomized interventions have shown effects of TFAs on inflammatory markers [21,22]. However, another randomized intervention study has shown no effect of TFA content of the diet on CRP [23], and another recent study also showed no effect of increasing TFA intake on a range of inflammatory biomarkers [24]. Therefore, the effects of TFA on inflammation remain to be definitively established.

Several studies have examined the effect of fat intake on blood pressure. Rasmussen et al. [25] carried out a randomized intervention study in which participants in each group consumed 37% of energy from fat, but the diets were either high in SFA (17% of energy) or MUFA (23% of energy). The diet high in SFA had no significant effect on blood pressure, whereas the MUFA diet lowered blood pressure. Appel et al. [6], in the OmniHeart Study, compared three low-SFA diets on blood pressure: one replacing SFA with carbohydrate, one replacing SFA with protein, and one replacing SFA with unsaturated fat. All

diets contained 6% SFA. A lowering in blood pressure was seen in all three groups, but a further lowering of blood pressure was shown with the protein-rich and unsaturated fat–rich diets compared with the carbohydrate-rich diet. Finally, an intervention study examining different dietary intakes of TFA showed no effect of changing TFA intake on blood pressure [23].

Epidemiologic Evidence Linking Consumption of Fatty Acids with CHD

Serum cholesterol and CHD

Serum total cholesterol is accepted as a classical risk factor for CHD. Therefore, the fact that the various fatty acids have different effects on total cholesterol leads to an expectation that they will also have different effects on CHD risk, and this has been tested in a number of observational epidemiologic studies.

SFA and CHD risk

Geographic and migration studies show strong positive correlations between SFA intake and rates of CHD [26,27]. Although these data provide evidence for the importance of environmental factors in the cause of CHD, they are seriously confounded by other dietary, lifestyle, and social factors. Prospective studies have also examined the link between SFA and CHD [14], but only two have found a significant positive association [28,29]. However, the early studies of fat and CHD were limited by small study size, inadequate dietary assessment, and inadequate adjustment for total energy intake, other types of fat, or for trans isomer fat intake [14,30].

The largest study to date of fat intake, which also had four repeated dietary assessments, was carried out in the Nurses' Health Study cohort of 80,082 women followed for over 14 years [31]. This study found a weak but significant positive association between SFA intake and risk of CHD. However, in a recent further analysis, the follow-up has been extended to 20 years, and the association of SFA intake with CHD risk is no longer significant after adjustment for nondietary and dietary risk factors [32••].

A prospective cohort study in Native Americans has suggested that it is only in middle age that SFA intake is associated with CHD mortality in this population. Associations were demonstrated in patients 47 to 59 years of age but not in those 60 to 79 years of age [33].

TFA and CHD risk

The Nurses' Healthy Study found a significant and strong positive association between TFA intake and CHD risk [31], and this was maintained after 20 years of follow-up [32••]. The results of four prospective studies have been combined, and the pooled relative risk of CHD associated with a difference of 2% energy in TFA intake assessed at baseline was 1.25 (95% CI , 1.11–1.40) [34].

There is, however, the possibility of measurement error associated with dietary assessment of TFA intake. Biomarkers of TFA intake have the advantage of not being subject to reporting errors and also allow the assessment of different isomers of TFA. A recent nested case-control analysis of the Nurses' Health Study examined erythrocyte TFA content in 166 CHD patients compared with 327 controls [35••]. Total TFA content in erythrocytes was associated with reported trans fatty acid intake ($r = 0.44$, $P < 0.01$). After adjustment for age, smoking status, and other dietary and lifestyle cardiovascular risk factors, high total TFA content was associated with an elevated risk of CHD (highest vs lowest quartile, relative risk of 3.3; 95% CI, 1.5–7.2), and similar patterns were shown for 18:1 trans isomers and 18:2 trans isomers [35••]. This is an important study because it confirms previous observations based on self-reported intake using objective biomarkers of intake.

Fatty Acid Intervention Studies and CHD

A number of early intervention studies either lowered total fat intake or replaced SFA with PUFA, leaving total fat intake unchanged [14,30]. The two trials testing total fat reduction, which were both in the secondary prevention setting, showed no effect on serum cholesterol or CHD risk [14,30]. The trials that replaced SFA with PUFA showed mostly reduced CHD risk [14,30].

A meta-analysis by Truswell [36] has shown that there was a direct relationship between the level of serum cholesterol lowering in diets in which PUFA replaced SFA and the effect on coronary events and all-cause mortality. The average reduction in serum cholesterol in 14 trials was 10%. This was associated with a 13% reduction in coronary events and a 6% reduction in all-cause mortality. In the five trials with the largest reduction in serum cholesterol (13%), a 30% reduction was observed for coronary events and 11% reduction was observed for all-cause mortality [36].

Whole dietary changes that lead to alterations in SFA or TFA intake

A number of studies have examined whole diet changes that affect not only fat intake but also intake of other macro- and micronutrients.

The Dietary Approaches to Stop Hypertension (DASH) intervention study [37] originally showed that a diet rich in fruits, vegetables, and low-fat dairy foods (a diet that was overall low in SFA and total fat) could lower blood pressure. A recent study has developed and tested a DASH-style diet adherence score and related this score to CHD and stroke risk [38]. Adherence to the DASH-style diet was associated with reduced SFA and TFA intake and was also associated with a lower risk of CHD and stroke among middle-aged women during 24 years of follow-up. This diet pattern is clearly associated

with many other changes in nutrient intake other than differences in fat intake, and therefore these reductions in risk cannot be exclusively associated with the reductions in TFA and SFA.

Only one study to date has examined the effect of a Mediterranean-type diet on clinical end points. In the Lyon Diet Heart Study [39], a randomized controlled trial with free-living participants, those in the intervention group had a 50% to 70% reduction of cardiac end points. In the final report of this study, de Lorgeril et al. [39] reported significant reductions in three composite outcomes (CO): CO1 (cardiac death and nonfatal myocardial infarction), CO2 (CO1 plus unstable angina, stroke, heart failure, pulmonary or peripheral embolism), and CO3 (CO2 plus minor events requiring hospital admission), with adjusted risk ratios ranging from 0.28 to 0.53. In terms of dietary change, individuals in the control group averaged 34% of calories from total fat, 12% from SFA, 11% from MUFA, 6% from PUFA, and 312 mg/d from cholesterol. In contrast, individuals on the Mediterranean-style diet averaged 30% of calories from total fat, 8% from SFA, 13% from MUFA, 5% from PUFA, and 203 mg/d from cholesterol. Plasma fatty acid analysis conducted after 52 weeks of follow-up confirmed the dietary fatty acid data [40]. Therefore, total cholesterol and SFA intake was reduced on the Mediterranean diet, although blood levels of TFA did not change [40].

The Women's Health Initiative has recently published results of their Dietary Modification Trial [41•]. This was a randomized controlled trial of 48,835 postmenopausal women to either an intervention or comparison group, with participants being followed for a mean of 8.1 years. The intervention group was given intensive behavior modification in group and individual sessions designed to reduce total fat intake to 20% of calories and increase intake of fruit and vegetables to 5 servings per day and grains to at least 6 servings per day. The control group received general dietary advice in written form. The diet had no significant effect on incidence of CHD (hazard ratio of 0.97; 95% CI, 0.90–1.06). However, there was a trend towards a reduction in CHD risk in those who adhered more closely to the intervention and had lower intakes of either SFA or TFA [41•]. It must be remembered that this study was primarily designed to test for effects on breast and colorectal cancer risk, and that the focus was on total fat reduction rather than on reduction of specific fat types. Women in the intervention group achieved reductions of 2.9% of energy in SFA and 0.6% of energy in TFA, but also had intakes of PUFA that were lower than recommended, leading to a minimal change in LDL-C concentrations.

Outstanding Issues

Industrial versus ruminant TFAs

An outstanding issue in TFA and CHD research that has received recent attention is whether both dietary sources of TFA in the food supply (ie, industrial production [in which TFAs are mainly derived from partially hydrogenated vegetable oil] and natural sources [in which TFA are found in smaller amounts in ruminant-derived food products]) equally affect lipids and CHD risk. It has been suggested that the positive association observed between TFA intake and CHD risk is primarily accounted for by industrially produced TFA, and that ruminant TFA intake may even protect against CHD [42]. A recent prospective cohort study has shown no association between ruminant TFA intake and CHD risk, with a trend towards a protective effect among women [43], and similar null or even protective effects have been observed in other studies [44].

Two carefully controlled feeding studies in healthy volunteers have recently compared the effects of ruminant-derived versus industrially derived TFA on blood lipids. The studies differed slightly in their methodologies, but Chardigny et al. [45] showed that the industrial TFA diet lowered HDL-C and LDL-C more than the ruminant TFA diet, although these effects were only observed in women. Motard-Belanger et al. [46] showed that the diet high in ruminant-derived TFA (3.7% of energy) lowered HDL-C and LDL-C, whereas the diet moderate in ruminant-derived TFA (1.5% of energy) had similar effects to the control diet (0.8% of energy). General conclusions were similar in the two studies in that, at the amounts present in usual diets, ruminant TFAs are unlikely to contribute in a major way to cardiovascular risk. An accompanying editorial points out that although this question is interesting scientifically, it is unlikely to have critical public health or policy relevance because adherence to guidelines for SFA intake would ensure low total consumption of ruminant TFA [44].

Reducing TFAs in the food chain

What is of crucial public health importance is the response of industry and governments in reducing and regulating TFAs in the food supply. Numerous expert committees have recommendations regarding limiting dietary TFA intake, and these have been reviewed [42]. With the possible exception of conjugated linoleic acid (CLA) found naturally in animal products [42], TFAs have no intrinsic health value above their caloric value, and therefore consumption of TFAs has no apparent benefit but does carry the potential for considerable harm [9].

Governments have responded in different ways to this [42], with the Danish government passing legislation in 2003 stating that industrially produced TFAs should be limited to 2% of the total amount of fat or oil in a food. This will require the development of TFA alternatives by the food industry [42]. In contrast, countries such as the Netherlands have not opted for government legislation yet it has made significant progress in reducing TFA in the food supply through efforts actually initiated by the food industry. In the United States, trans fats in food products are still considered under the category "generally regarded as safe." The US Food and

Drug Administration, however, ruled that as of January 2006, the TFA content of foods needed to be included on the food label. However, CLA is exempt from trans fat labeling regulations in the United States. An important consumer education issue is that only products with TFA content greater than 0.5 g per serving need to be included on a food label [42]. If the TFA content is less than 0.5 g per serving, it is expressed as 0 g per serving. Therefore, products listed as containing 0% TFA are not necessarily free of trans fats, and consumers, even if they read the label, may unwittingly consume substantial amounts of trans fats in multiple servings of such foods [9].

The potential for a reduction in TFA content of foods leading to a decrease in CHD events has been highlighted by a recent study that examined the association between TFA intake and CHD risk before and after efforts to reduce industrially produced trans fats in Costa Rica [47••]. Prior to industrial modification, TFA intake in the highest quintile was associated with an increased risk of MI (odds ratio of 4.76; 95% CI, 2.24–10.11), but after industrial modification the median intake in the highest quintile dropped from 2.02 g per 100 g to 1.4 g per 100 g, overall mean intake dropped from 4.1 g/d to 2.9 g/d, and the association with CHD risk disappeared (odds ratio of 1.15; 95% CI, 0.80–1.64).

Differential response to modifications in SFA and TFA intake

Another area of particular interest is whether all individuals will react to alterations in fat intake in a similar manner. Lefevre et al. [48••] examined the effects of alterations in SFA, total fat, and dietary cholesterol intakes on lipids and also examined whether the lipid response depended on adiposity or insulin resistance. Insulin resistance was associated with a reduced LDL-C reduction and an increased triglyceride elevation in response to reductions in total fat, SFA, and dietary cholesterol. The authors conclude that persons who might already be at increased risk of cardiovascular disease because of insulin resistance may be less likely to benefit from dietary intervention.

Genetic factors may also modulate the association between SFA, TFA, and CHD. Little research has been carried out in this area, but it has been suggested that the apoE genotype may interact with fat intake to influence CHD risk [49]. It remains to be seen whether genetic variation can meaningfully distinguish responders from nonresponders, and the extent of response to diet is likely to be influenced by many different genes.

Public Health Benefits of an Alteration in Fatty Acid Intake

This review of the relationships between SFA, TFA, and CHD shows that much evidence has been collected in controlled feeding studies, observational studies, and clinical trials. An expert committee of the World Health Organization judged that evidence linking SFA, TFA, and the omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid with CHD is convincing [50]. However, there are no randomized controlled trials with clinical end points of suitable size and duration to properly determine the potential public health benefits of a reduction in either TFA or SFA.

Nevertheless, a number of investigators have attempted to quantify the potential public health benefits of changes in SFA and TFA [5,9,51]. For example, Mozaffarian et al. [9] have estimated that, on the basis of predicted changes in total cholesterol and HDL-C levels alone, reducing the intake of industrially produced TFAs (calculations carried out for either halving or near-elimination of intake) would translate to a 3% to 6% reduction in CHD events. However, they believe that this is an underestimate due to the ability of TFAs to influence CHD through other mechanisms (eg, inflammatory or endothelial effects). Therefore, they also calculate the potential reduction in CHD events based on the prospective studies of TFA intake and CHD risk, which they predict would produce a 10% to 19% reduction in CHD events. These figures may, however, also be an underestimate, as they are based on replacing TFAs with carbohydrates; in general, TFAs would most commonly be replaced with cis-unsaturated fats, which may have additional CHD benefits [9]. Based on these estimates, there is potential for a large reduction in CHD event rates worldwide as a result of reduced consumption of industrially produced TFAs.

A recent study carried out in the United States examined secular trends in diet quality for CHD prevention in the past two decades (data collected at regular intervals between 1980 and 1982 and between 2000 and 20022) as part of the Minnesota Heart Survey, with dietary data collected using 24-hour diet recalls [52]. An overall improvement in dietary compliance was observed over the 20-year period, but improvements with respect to fatty acid composition of the diet, particularly SFA, TFA, and cholesterol intake, plateaued in the years 1995 to 1997. This emphasizes the importance and need for reinforcement of public health messages.

Conclusions

Evidence from controlled feeding studies, epidemiologic studies, and clinical trials suggest a potential for alteration in fatty acid composition of the diet to reduce CHD risk. SFAs and TFAs increase CHD risk, whereas unsaturated fatty acids decrease CHD risk. Although simply lowering the percentage of energy from fat in the diet is unlikely to improve lipid profile or reduce CHD incidence, optimization of the fatty acid composition of the diet could have major public health benefits. It is likely that replacing SFAs and TFAs with unsaturated fats would be effective in preventing CHD, but a combination of this approach with increased consumption of omega-3 fatty acids and a

diet high in fruits, vegetables, nuts, and whole grains and low in refined grains would confer greater benefits.

Disclosures

No potential conflicts of interest relevant to this article were reported.

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