Beyond Saturated Fat: The Importance of the Dietary Fatty Acid Profile on Cardiovascular Disease

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Saturated fat reduction is a primary goal for decreasing the risk of cardiovascular disease. In a recent epidemiologic study, a low-fat diet high in saturated fat (10.6%–16.0% energy) was associated with less progression of coronary atherosclerosis, whereas carbohydrate intake (67% energy) was associated with a greater degree of progression in postmenopausal women.

Key words: cardiovascular disease, fat, fatty acids, saturated fat

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doi: 10.1301/nr.2006.may.257–262

INTRODUCTION

It is well established that dietary saturated fatty acids (SFA) raise total and low-density lipoprotein cholesterol (LDL-C) levels,1-4 and thereby increase the risk of cardiovascular disease (CVD). The first dietary guidelines for the general public were released by the American Heart Association in 1957, and recommended that polyunsaturated fatty acids (PUFA) replace SFA.5 The recommendation to decrease SFA has been supported for over 40 years based on a robust database from both clinical and epidemiologic studies. However, this dietary guidance has been questioned by a recent epidemiologic study conducted in a specific target population.

Mozaffarian et al.6 analyzed data from the Estrogen Replacement and Atherosclerosis (ERA) trial in a population with a lower total fat intake (25% energy), and found that a greater SFA (10.6%–16% energy) intake was associated with less progression of coronary atherosclerosis in postmenopausal women compared to women with a lower intake of SFA (3.5%–7% energy).6 Quantitative coronary angiography was performed at baseline and after a mean follow-up of 3.1 years. Usual dietary intake was assessed at baseline using a validated, semi-quantitative food-frequency questionnaire. Although food-frequency questionnaires tend to underestimate energy and nutrient intakes,7-9 this group validated the questionnaires with plasma fatty acid data, a good biomarker for intake. Thus, the fat and fatty acid intake data presented, albeit somewhat low compared with population data,10 are a reasonable estimate of intake.

The findings reported in this paper are interesting in the context of previous data from women initially free of CVD showing that high intakes of SFA are associated with an increased risk of coronary heart disease (CHD). Using data from the Nurses’ Health Study, Hu et al.11 compared different risk models for energy adjustment when examining the associations between the intake of four major types of fat: SFA, monounsaturated fatty acids (MUFA), PUFA, and trans fatty acids.11 In contrast to the recent results presented by Mozaffarian et al.,6 the Hu study found that SFA and trans fatty acids were associated with an increased risk of CHD. Earlier results from the Nurses’ Health Study indicated that for every 5% increase in energy intake from SFA, as compared with an equivalent energy intake from carbohydrates, the risk of CHD would increase by 17% (relative risk [RR] = 1.17; 95% confidence interval [CI], 0.97–1.41; P = 0.10).12 Further work from the Nurses’ Health Study has demonstrated that a higher intake of long-chain SFAs was associated with an increased risk of CHD (RR = 1.14; 95% CI, 0.93–1.39; P = 0.03), whereas intake of short- and medium-chain SFAs was not (RR=1.07; 95% CI: 0.89–1.30; P = 0.78).13 A more recent multivariate analysis of the Nurses’ Health Study showed no effect of increased levels of SFA on CHD risk (adjusted RRs for increasing quantiles of SFA intake: 1.0, 0.94, 0.96, 1.01, and 0.97; P = 0.93 for trend).14

Previous epidemiologic studies, however, have reported strong positive correlations between SFA intake...
and mortality from CHD. One of the classic epidemiologic studies to show this relationship, The Seven Countries Study, reported a significant association between total SFA intake and levels of serum total cholesterol. In this study, death rates were positively associated with the percentage of dietary energy from SFA; a 5% change in SFA elicited a 4.7% change in the age-adjusted all-cause mortality rate. This work has been supported by numerous studies demonstrating a positive relationship between SFA intake and risk of CHD and CHD mortality. A recent epidemiologic study of about 3500 Danish men and women found that for every 5% increase in energy from SFA, the risk of CHD increased 36% in women. This relationship was not observed among the men in the study.

Numerous clinical trials also have demonstrated the hypercholesterolemic effects of SFA. Using regression analysis of data from many controlled clinical studies, Keys et al. and Hegsted et al. evaluated the effect of individual fatty acids on total cholesterol in humans. The predictive equations that were developed from these analyses showed that SFA raise total cholesterol compared with carbohydrates and MUFA, while PUFA lower total cholesterol. The regression coefficients indicate that SFA are twice as potent in raising total cholesterol as PUFA are in lowering it. In addition, clinical studies have consistently demonstrated that SFA raise LDL-C. More recent studies have developed predictive equations for lipoprotein levels. For every 1% increase in energy from SFA, LDL-C levels increase approximately 0.033 to 0.045 mmol/L. However, relative to the present study, several controlled clinical studies have shown an attenuated effect of reducing SFA on LDL-C lowering in overweight individuals. This could suggest that increasing SFA may have a less than expected LDL-C raising effect in overweight individuals, which was largely the cohort studied by Mozaffarian et al. This might explain in part the unexpected findings reported by Mozaffarian et al. for SFA and athero progression in postmenopausal women. In addition to raising total cholesterol and LDL-C, SFA also increase high-density lipoprotein cholesterol (HDL-C). For every 1% increase in SFA, HDL-C is expected to increase by 0.011 to 0.013 mmol/L.

This impressive body of evidence has been the basis for the current dietary guidance for the prevention and treatment of CVD. The National Academy of Sciences and the Institute of Medicine’s Dietary Reference Intakes for Macronutrients Report recommended that SFA intake be as low as possible within the context of a nutritionally adequate diet. The 2005 Dietary Guidelines for Americans recommends less than 10% of calories from SFA. The Third Adult Treatment Panel of the National Cholesterol Education Program recommends the reduction of SFA to less than 7% of calories as a primary LDL-C lowering strategy. In the present study, SFA intake was presented as quartiles. It is important to note that it is difficult to reliably estimate SFA intake within a quartile because only ranges are presented. For example, in the highest quartile of SFA intake (10.6%–16.0% energy), the only way to estimate average intake is to use the midpoint, which may not accurately reflect the mean intake. Using data presented in the table in the Mozaffarian paper for total cholesterol, PUFA, MUFA, and trans fatty acids, the mean for the highest quartile of SFA intake (calculated by difference) is 10.8% of calories. This intake is by no means excessively high by current recommendations of the 2005 Dietary Guidelines for less than 10% of calories for SFA. Based on data from NHANES 1999-2000, the intake of SFA was 11.1% and 10.9% of calories for women 40 to 59 and 60 to 74 years of age, respectively. Thus, the “high” quartile of SFA intake in the present study is similar to the intake of the US population and does not markedly exceed current recommendations. Usage of the word “high” is relative and may simply reflect the highest quartile of intake and not a high intake defined quantitatively. It is important to emphasize that in this population of subjects with coronary disease, SFA intake should be appreciably less than 10%. The key message from government agencies and professional organizations (e.g., the American Heart Association and the American Diabetes Association) is that SFA intake should be decreased and that high SFA intake (>10%) should be avoided. Nonetheless, in the current paper the highest quartile of SFA intake (10.6%–16% energy) in the context of a low-fat diet is not associated with athero progression; however, there may be a plausible biological basis that explains the outcome.

A second association made in the Mozaffarian study is that an increase in carbohydrate intake is associated with a greater degree of atherosclerotic progression. In the population studied (postmenopausal women), there is a high prevalence of atherogenic dyslipidemia characterized by low HDL-C and high triglycerides, which are significant risk factors for heart disease. A low-fat, high-carbohydrate diet, compared with higher-fat diets, has been shown to induce atherogenic dyslipidemia in some individuals. In the present study, a majority of the study population had hypertension, 25% had diabetes, 75% were overweight, and 50% were obese. Because this response is particularly prevalent in sedentary, overweight, or obese populations, it is not surprising that this population experienced a decrease in HDL-C and an increase in triglycerides on a low-fat, high-carbohydrate diet (lowest quartile of SFA intake). The expected increase in HDL-C due to the increase in SFA may elicit a greater clinical benefit than any adverse
effect of SFA on LDL cholesterol via a reduction in the ratio of total cholesterol/HDL-C. As a result of the increase in HDL-C, there also was a significant decrease in the total cholesterol/HDL-C ratio (5.3 vs. 4.6; P < 0.01). Epidemiologic evidence suggests that for every 1 unit decrease in the total cholesterol/HDL-C ratio, there is a 53% decrease in the risk of myocardial infarction. Current data from the Women’s Health Study indicate that the use of non-HDL-C and the ratio of total cholesterol/HDL-C as predictors of risk for CVD is superior to the use of total cholesterol and LDL-C alone. The total cholesterol/HDL-C ratio (hazard ratio [HR] = 3.81; 95% CI, 2.47–5.86; P < 0.001) was a stronger predictor of risk compared with LDL-C alone (HR = 1.75; 95% CI, 1.30–2.38; P < 0.001), when comparing those in the highest quintile of CVD risk with those in the lowest-risk group. In the Mozaffarian et al. study, the dyslipidemia that is present has an LDL-C that is often not at the level that warrants initiation of therapeutic lifestyle changes, but may indeed be pro-atherogenic, as small, dense LDL particles are a component of atherogenic dyslipidemia. In contrast, HDL-C is low and is considered to be a major risk factor for CHD. Thus, increasing HDL-C levels would be expected to result in a clinical benefit. Moreover, as discussed herein, the possible less than expected LDL-C response to SFA in concert with the HDL-C increase would have a desirable effect on the LDL-C/HDL-C ratio. This in conjunction with expected triglyceride lowering (due to an increase in HDL-C level) and possibly a shift in the density of the LDL particles to larger, buoyant LDL particles might be the biological basis to explain the results reported by Mozaffarian et al. In addition, an increase in SFA decreases lipoprotein a, which could further contribute to the results reported.

While the results of the present study show a beneficial effect of increasing SFA in this at-risk cohort on a low-fat diet, there are other dietary approaches that would be expected to confer better outcomes. Dietary patterns that focus on the inclusion of unsaturated fatty acids, including MUFA and PUFA, have been shown to effectively reduce the risk of CHD. Epidemiologic studies have found inverse associations between MUFA intake and risk of CHD and ischemic heart disease after adjusting for SFA and dietary cholesterol. The Seven Countries Study showed that rates of CHD were low despite moderately high total fat intakes when SFA was replaced with MUFA. Clinical studies also have shown cardioprotective benefits of MUFA when they replace SFA. Grundy and Mattson have demonstrated that replacing SFA with MUFA lowers LDL-C levels without lowering HDL-C. Kris-Etherton et al. demonstrated that replacing SFA with MUFA (37% kcal total fat, 22% kcal MUFA, 47% kcal carbohydrates) versus carbohydrates (30% kcal total fat, 15% kcal MUFA and 54% kcal carbohydrates) resulted in comparable decreases in LDL-C (6.3% and 7.0%, respectively).

In the present study, dietary intakes of SFA and MUFA were strongly correlated (r = 0.83), thus MUFA intake increased with each quartile of SFA intake. As a result of this strong correlation, SFA and MUFA were not included together in the main adjusted model. Although there was no significant association between MUFA and atherosclerotic progression, the authors indicate that slightly larger standard errors of the estimate (SEEs) limited the detection of a possible inverse relationship. Thus, the observed improvement in atherosclerotic progression was also likely due to an increase in MUFA intake.

PUFA also have been extensively studied for their role in the prevention of CHD and CVD. While many studies have shown an association between dietary PUFA and reduced CVD mortality after adjusting for SFA, other studies, such as the Seven Countries Study, have reported no significant association. Clinical studies investigating the effects of PUFA on CHD risk generally have shown beneficial effects. Three studies reported a 13% to 15% decrease in total cholesterol, which was accompanied by a 25% to 43% decrease in CHD events. Predictive equations have demonstrated that a 1% increase in PUFA results in a reduction of total cholesterol by 0.024 mmol/L. In the present study, dietary intake of PUFA was positively associated with a decline in mean minimal coronary artery diameter (P < 0.05 for trend). Although current dietary recommendations suggest that dietary PUFA intake can account for up to 10% of calories, intake in the present study was 5% to 6% of calories across all quartiles of SFA intake. In the cohort studied, a higher PUFA intake may result in a greater beneficial effect on progression of atherosclerosis. Thus, because this population was consuming low levels of PUFA, they likely were not receiving the cholesterol-lowering effect that they might have achieved with a higher dietary PUFA intake.

The cardioprotective effects of marine-derived long-chain n-3 fatty acids, eicosapentanoic acid (EPA) and docosahexanoic acid (DHA), are well established. An inverse association between n-3 fatty acids and coronary artery disease has been found in numerous epidemiologic studies. An inverse correlation was found in the 25-year follow-up of the study with n-3 fatty acid intake and 25-year coronary artery disease mortality rates (r = -0.36). In the Health Professionals Follow-Up Study, a 1% increase in α-linolenic acid (ALA) intake was associated with a 40% lower risk of CHD. Clinical trials testing the efficacy of n-3 PUFA in CHD risk reduction also have demonstrated a beneficial effect. In the GISSI Prevention Study, the largest prospective clinical trial
to test the efficacy of n-3 fatty acids for secondary prevention of CHD, subjects were randomized to the EPA + DHA supplement group (850 mg/d of omega-3 fatty acid ethyl esters), with and without 300 mg/d of vitamin E. Individuals in the supplemented group compared with the control group experienced a 15% reduction in the primary end point of death, nonfatal myocardial infarct, and nonfatal stroke ($P < 0.02$). Current recommendations for ALA are 0.6% to 1.2% of calories for optimal health and to reduce risk of CVD. Intake of ALA in the present study was below the recommended amount, at just 0.1% kcal. If the intake of n-3 PUFA in the present study was at the recommended levels, it is likely that the atheroprogession may have even been less than was observed.

Despite the fact that LDL-C remains the primary target of therapy for the reduction of CVD risk, several other risk factors have emerged as important targets for intervention. These include other lipids/lipoproteins, markers of oxidative stress, inflammation, insulin resistance, and thrombosis. Each of these affect disease processes that are linked to the pathogenesis of CVD, and may provide additional evidence for the causality between dietary factors that affect each of them and those that affect CVD. While the present article brings to light some questions that remain with regard to dietary fats and CVD risk, future research is needed to assess the impact of dietary interventions and different fatty acid profiles on multiple risk factors associated with CVD risk. With this in mind, we must be prudent in making recommendations to target population groups about the nutrient composition of the “ideal” diet that maximally reduces CVD risk. It is clear that CVD risk reduction is not reliant on just one nutrient and is changed in an “ocean” of other nutrients in the diet, many of which modulate risk status. Thus, while the Mozaffarian study does show that SFA intake is associated with a decrease in progression of atherosclerosis in postmenopausal women following a low-fat diet, the regression observed within this quartile was minimal (0.1 ± 1.5% coronary artery stenosis). Results from the Lifestyle Heart Trial demonstrated that an intensive lifestyle intervention program, including a low-fat vegetarian diet, smoking cessation, stress management training, and moderate exercise could elicit a significant regression in the percentage of coronary artery stenosis (40.0 ± 16.9% to 37.8 ± 16.5%) following 1 year of treatment. Collectively, the results from many diet intervention studies with a diversity of diets clearly indicate that better CVD outcomes can be achieved by incorporating the strategies discussed above, which were not evaluated by Mozaffarian et al.

The impressive body of scientific evidence about diet, lifestyle behaviors, and heart disease clearly indicates that we should not have this one finding sway our global understanding of diet and CVD.

**Closing Remarks**

The recent results from the Women’s Health Initiative (WHI), a randomized, controlled trial of over 48,000 postmenopausal women, reported no benefit of a low-fat diet intervention designed to provide 20% of calories from fat on CVD risk, which is likely because the intervention group did not attain their target fat goal (i.e., they consumed 29% of calories from fat). However, in a subgroup analysis, a trend was observed towards a reduced CHD risk in women without existing CVD at the start of the study who attained the lowest levels of saturated fat (<6.1% kcal; adjusted HR = 0.82; 95% CI: 0.67, 0.99; $P = 0.05$) and trans fat (<1.1% kcal; adjusted HR = 0.84; 95% CI: 0.69, 1.02; $P = 0.10$) or the highest intake of fruits and vegetables (>6.5 servings/d; adjusted HR = 0.89; 95% CI: 0.74, 1.06; $P = 0.11$). These results demonstrate the benefits of reducing saturated fat and trans fat in health postmenopausal women. Also of note, however, is that women in the treatment group (28.8% total fat, 9.5% SFA) with existing CVD had an increase in CVD risk (HR = 1.26; 95% CI: 1.03, 1.54). This later cohort and results reported by Mozaffarian et al. are similar. In fact, women in the ERA trial in the lowest quintile of SFA intake (3.5%–7.0% kcal) experienced a 8.0% progression in coronary artery stenosis. Collectively, the results from the WHI, in conjunction with those reported by Mozaffarian et al., are provocative because they raise important questions about whether different diets should be recommended for different groups of postmenopausal women for the prevention and treatment of CVD. Thus, research is needed to identify the optimal dietary pattern(s) that maximally reduce CVD risk in various population groups.

**REFERENCES**

6. Mozaffarian D, Rimm EB, Herrington DM. Dietary fats, carbohydrate, and progression of coronary...


37. Gillman MW, Cupples LA, Millen BE, Ellison RC, Wolf PA. Inverse association of dietary fat with...