Saturated fat, carbohydrate, and cardiovascular disease¹–⁴

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ABSTRACT

A focus of dietary recommendations for cardiovascular disease (CVD) prevention and treatment has been a reduction in saturated fat intake, primarily as a means of lowering LDL-cholesterol concentrations. However, the evidence that supports a reduction in saturated fat intake must be evaluated in the context of replacement by other macronutrients. Clinical trials that replaced saturated fat with polyunsaturated fat have generally shown a reduction in CVD events, although several studies showed no effects. An independent association of saturated fat intake with CVD risk has not been consistently shown in prospective epidemiologic studies, although some have provided evidence of an increased risk in young individuals and in women. Replacement of saturated fat by polyunsaturated or monounsaturated fat lowers both LDL and HDL cholesterol. However, replacement with a higher carbohydrate intake, particularly refined carbohydrate, can exacerbate the atherogenic dyslipidemia associated with insulin resistance and obesity that includes increased triglycerides, small LDL particles, and reduced HDL cholesterol. In summary, although substitution of dietary polyunsaturated fat for saturated fat has been shown to lower CVD risk, there are few epidemiologic or clinical trial data to support a benefit of replacing saturated fat intake with carbohydrates. Furthermore, particularly given the differential effects of dietary saturated fats and carbohydrates on concentrations of larger and smaller LDL particles, respectively, dietary efforts to improve the increasing burden of CVD risk associated with atherogenic dyslipidemia should primarily emphasize the limitation of refined carbohydrate intakes and a reduction in excess adiposity. *Am J Clin Nutr* 2010;91:502–9.

INTRODUCTION

Saturated fat intake has been linked to an increased risk of cardiovascular disease (CVD), and this effect is thought to be mediated primarily by increased concentrations of LDL cholesterol. Major dietary sources of saturated fatty acids in the United States are full-fat dairy products and red meat (1). Data from clinical trials have shown that substitution of polyunsaturated fat for saturated fat results in a reduced incidence of CVD (2–4); however, as described below, there is little evidence from such trials or from epidemiologic studies that a reduction in saturated fat intake below ≈9% of total energy intake is associated with a reduced CVD risk. Recommendations for further reductions in saturated fat intake (eg, to ≤7% of total energy) (5) are based primarily on the prediction of a progressive reduction in CVD risk associated with greater reductions in LDL cholesterol. However, from the standpoint of implementation, further reductions in saturated fat intake usually involve dietary prescriptions that include an increased proportion of carbohydrate (1, 5). For a large proportion of the population, however, the effect of higher-carbohydrate diets, particularly those enriched in refined carbohydrates, coupled with the rising incidence of overweight and obesity, creates a metabolic state that can favor a worsening of the atherogenic dyslipidemia that is characterized by elevated triglycerides, reduced HDL cholesterol, and increased concentrations of small, dense LDL particles (6, 7). Recent studies point to the beneficial effects of reducing carbohydrate intake, but not saturated fat, on this dyslipidemic state (8). In this review, consideration is given to the implications of these findings for dietary practices aimed at further reducing CVD risk.

CLINICAL TRIALS

As was previously summarized (9), randomized controlled dietary interventions that involved replacement of saturated fat with polyunsaturated fats resulted in reduced CVD risk in some, but not all, studies. The Finnish Mental Hospital Study (4), the

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Los Angeles Veterans Study (2), and the Oslo Diet Heart Study (3) all showed that a high polyunsaturated fat intake (13%, 16%, and 21% of total energy, respectively) in the context of saturated fat intake of ∼9% and total fat intake of 35–40% of energy was associated with significant decreases in CVD events. In contrast, the British Medical Research Council Soy Oil Intervention (10) and the Minnesota Coronary Survey (11) showed nonsignificant effects of replacement of saturated fat with polyunsaturated fat on CVD.

Several clinical trials that involved reductions in saturated fat in the context of reduced total fat and increased carbohydrate intake showed no CVD risk benefit, but these studies may have been limited by a small sample size and/or a limited duration of follow-up (12, 13). Most recently, in the largest controlled dietary intervention trial to date, the Women’s Health Initiative randomly assigned >48,000 postmenopausal women to a low-fat intervention or a comparison group in a free-living setting (14). Saturated fat intake was significantly lower in the intervention group than in the comparison group (means: 9.5% and 12.4%, respectively). Dietary polyunsaturated fat was also lower (difference = 1.5%), and dietary carbohydrate was higher (difference = 8.1%) in the intervention group than in the control group. After 6 y of follow-up, there were no differences between the groups in incidence of fatal and nonfatal coronary heart disease (CHD) and total CVD, including stroke.

In the Lyon Diet Heart Study, adoption of a “Mediterranean” style diet that included an increased intake of the omega-3 (n-3) fatty acid α-linolenic acid, a reduction in saturated fat to 8% compared with 11.7% of energy, and a modest increase in fiber and total carbohydrate was associated with a 72% reduction in recurrent CHD events in patients with prior myocardial infarction (15, 16). Secondary analyses of plasma fatty acid composition in this study indicated that the CHD benefit was most strongly correlated with increased α-linolenic acid. There were no significant differences in traditional risk factors, including results from 6 other studies (24, 27, 29, 44–46) did not yield a statistically significant risk reduction (36). Overall, despite the conventional wisdom that reduced dietary saturated fat intake is beneficial for cardiovascular health, the evidence for a positive, independent association is lacking (36). These conclusions are consistent with a recent review of the relation between dietary patterns and nutrient factors and CVD risk (47).

ROLE OF OTHER NUTRIENTS IN CVD

Replacement of saturated fat with carbohydrate was not significantly associated with a reduced risk of CHD (relative risk: 1.17; 95% CI: 0.97, 1.41) (48). Consistent with this analysis, a low-carbohydrate diet score (a higher score being indicative of higher protein and fat intakes and a lower intake of carbohydrate) in the same cohort was not associated with increased CHD risk in women (49).

Type of dietary carbohydrate, as measured by the glycemic index or glycemic load, has also been suggested to be a relevant determinant of CHD risk in some (50, 51), but not all (52, 53), studies. Glycemic index ranks carbohydrates according to their effects on blood glucose concentrations, and glycemic load is calculated from glycemic index, carbohydrate content, and actual or estimated intake of food items. High glycemic load from refined carbohydrates was shown to be associated with an increased CHD risk independently of known risk factors in the Nurses’ Health Study (51) and was more recently shown to be associated with an increased risk of CHD in a prospective cohort study of >15,000 middle-aged women (50). In line with these observations, replacement of saturated fat with monounsaturated fat rather than carbohydrate was associated with a decreased CHD risk in patients with diabetes (54). A recent meta-analysis showed borderline significant associations of increased glycemic index with heart disease (relative risk: 1.25; 95% CI: 1.00, 1.56) (55). Nonetheless, given the relatively limited number of studies that have been carried out to evaluate the relation of glycemic index and/or load with CVD risk, further research is needed in this area.

DIETARY SATURATED FAT AND CVD RISK FACTORS

Lipids and lipoproteins

The effect of dietary saturated fat on plasma lipoproteins that is felt to most strongly affect CVD risk is elevated LDL-cholesterol concentrations (56). Replacement of saturated fat with polyunsaturated fat has been shown to decrease total, LDL, and HDL cholesterol (57). On the basis of analyses of the effects of substituting individual categories of fatty acids for carbohydrates,
LDL cholesterol can be reduced by both monounsaturated and polyunsaturated fats, with an apparently greater effect of the latter (56). Importantly, the effects of saturated fat on lipids and lipoproteins may be modulated by the content and/or availability of polyunsaturated fatty acids, such that saturated fat only affects LDL cholesterol if the polyunsaturated fat intake is below a threshold level (~5% of energy) (58, 59). LDL cholesterol as well as total cholesterol and apolipoprotein B were not different between women who consumed diets high or low in saturated fat but with similar ratios of polyunsaturated to saturated fat (P:S) (60). Similarly, the amount of cholesterol consumed in the diet has been shown to modulate effects of saturated fat such that, at lower intakes of cholesterol, the effect of saturated fat on LDL cholesterol was minimal compared with significant LDL-cholesterol-raising effects at higher concentrations of dietary cholesterol (61).

Replacement of saturated with polyunsaturated fatty acids in the diets of hyperlipidemic subjects has been reported to lower the LDL-cholesterol production rate (62, 63), although an increase in clearance rate, possibly because of an increased LDL receptor activity, has been reported (64). Replacement of saturated fat with polyunsaturated (65), but not monounsaturated (66), fat has also been shown to decrease coronary atherosclerosis in African green monkeys.

Substitution of saturated fat for carbohydrate results in increases in HDL cholesterol, with no net effect on the total: HDL-cholesterol ratio (67). On the other hand, whereas smaller increases in HDL cholesterol are observed with substitution of monounsaturated and polyunsaturated fats for carbohydrate, these dietary changes result in significant reductions in the total: HDL-cholesterol ratio (67). There are differences between individual types of saturated fatty acids with regard to effects on LDL and HDL cholesterol (67). Specifically, there is a progressively smaller LDL-cholesterol-raising effect with substitution for carbohydrate of saturated fatty acids of increasing chain length, with the largest increase observed for lauric acid (12 carbons), and no significant increase with stearic acid (18 carbons). However, lauric acid substitution also results in the greatest increase in HDL cholesterol, such that there is significant lowering of the total:HDLC ratio (67).

In recent years, there has been increasing concern regarding dietary effects on dyslipidemia, characterized by elevated triglycerides, low concentrations of HDL cholesterol, and increased concentrations of small, dense LDL particles (68). This metabolic profile is considered to be a major contributor to increased CVD risk in patients with the metabolic syndrome, insulin resistance, and type 2 diabetes. Both increased adiposity (69) and higher carbohydrate intakes (6) have been shown to increase the magnitude of each of the components of atherogenic dyslipidemia. In hypercholesterolemic and combined hyperlipidemic patients, fat restriction to <25% and carbohydrate intakes >60% was associated with similar adverse changes in lipids (increased triglyceride and reduced HDL cholesterol) with no further reductions in LDL cholesterol; furthermore, high-carbohydrate feeding led to increased plasma concentrations of palmitate, thus negating the effects of further reductions in saturated fat on palmitate concentrations (70). The induced adverse effects on HDL cholesterol and triglyceride may counteract any benefits of reductions in dietary fat on CVD in men (71). Because HDL cholesterol and triglycerides are stronger risk factors in women, such lipid changes result in a predicted increase in coronary disease incidence in this subgroup (71).

In several studies in which weight loss was induced by very-low-carbohydrate diets, it was observed that LDL-cholesterol concentrations and total:HDL-cholesterol ratios did not increase despite the high intakes of saturated fat on these diets (72, 73). However, these studies did not distinguish between the effects of weight loss and changes in diet composition. We recently conducted a study to evaluate the effects of dietary carbohydrate restriction (from 54% to 26%) with low and high saturated fat (derived primarily from dairy products) in the context of both weight loss and weight stability (8). Carbohydrate restriction under weight-stable conditions reduced total:HDL cholesterol, apolipoprotein B, and the mass of small, dense LDL particles (Figure 1). Weight loss without restriction of carbohydrates led to similar changes (8).

The type of dietary carbohydrate consumed may affect lipid and lipoprotein profiles (74, 75), although a thorough analysis of the evidence for this hypothesis is beyond the scope of this review. Recent studies showed that, compared with dietary saturated fat, the saturated fat to fiber ratio was a stronger predictor of lipoprotein response in persons consuming beef or vegetarian diets (76). Furthermore, the DASH (Dietary Approaches to Stop Hypertension) diet, which reduces saturated fat to 7% and emphasizes an increase in complex carbohydrates rather than simple carbohydrates, lowered total, LDL, and HDL cholesterol without increasing triglyceride concentrations (77).

**Effects of saturated fat on LDL and HDL size and composition**

LDL and HDL particles of different sizes and compositions derive from many metabolic pathways, and smaller and more dense LDL particles have been implicated as being more strongly involved in atherosclerotic CVD than larger LDL particles, as shown in Figure 1.
reviewed elsewhere (78). The reduction in LDL cholesterol known to occur with a decreased saturated fat intake appears to be specific to larger more buoyant particles (79). In persons placed on a baseline high-saturated-fat diet and then switched to a diet high in monounsaturated or polyunsaturated fat, a small but significant reduction in LDL particle size was observed (80). Furthermore, we recently showed that the lower concentrations of small, dense LDL particles resulting from a reduced carbohydrate intake (26% compared with 54% of energy) were similar with diets high (15%) or low (8%) in saturated fat derived primarily from dairy products. In contrast, the higher saturated fat intake raised concentrations of larger, more cholesterol-enriched LDL particles, thus offsetting the reduction in total LDL concentrations that was observed with lower saturated fat intake (8) (Figure 1). These effects were apparent after 3 wk and were independent of weight loss.

Dietary intake of fatty acids can also influence lipoprotein composition. In the acute postprandial response to meals high in saturated fat, high in polyunsaturated fat, or low in total fat, no changes were observed in LDL triglyceride or cholesterol composition, ie, there were no changes in density (77). However, the P:S ratio in the LDL surface monolayer was higher after a meal enriched in polyunsaturated fat than in a meal enriched in saturated fat (81). In contrast, the HDL reduction associated with decreased saturated fat intakes has not been associated with changes in HDL particle composition (82). There is evidence that dietary regimens that lead to the enrichment of LDL with 18:2 polyunsaturated fatty acids are associated with an increased susceptibility of LDL to oxidation (83, 84), an effect associated with an increased CHD risk (85). On the other hand, extensive studies in animal models, particular monkeys, have shown that dietary enrichment of LDL with polyunsaturated fats was associated with reduced atherosclerosis compared with either monounsaturated or saturated fat (86). In these studies, atherosclerosis was associated with the diet-induced enrichment of LDL with cholesteryl oleate. Notably, in humans, the risk of stroke has been related to both the saturated and monounsaturated fatty acid content of plasma cholesteryl esters, which further supports the possibility that the dietary intake of these fatty acids may influence CVD risk by altering cholesteryl ester composition (87).

Factors affecting variation in lipoprotein response to saturated fat

There is considerable interindividual variability in the lipoprotein response to variations in saturated fat intake, and this is related to some extent to variation in response to dietary cholesterol, which suggests a role for intrinsic differences in the regulation of lipid metabolism (88, 89). Baseline LDL-cholesterol concentrations appear to be strongly related to dietary responsiveness, and it was reported that this may be related to differences in the fractional catabolic rates of LDL (90). Other factors that have been reported to be associated with a reduced LDL response to reductions in saturated fat include increased BMI (91), insulin resistance (92), and female sex (93). A relation between triglyceride metabolism and the LDL response to diet is supported by the finding that saturated fats increase LDL cholesterol in normotriglyceridemic but not in hypertriglyceridemic persons (94). Low birth weight has been associated with reduced HDL cholesterol in response to saturated fat in men (95). Genetic factors may also contribute to variability in the dietary response to saturated fat (96–98). Among these, the apoE4 isoform, which is associated with increased plasma LDL cholesterol in comparison with the more common apoE3 isoform, has been most consistently found to be predictive of a greater LDL-cholesterol reduction in response to diet (99, 100).

Finally, there is little information from clinical trials addressing the possibility that the effects of saturated fat on CVD risk factors may be modified by the foods in which they are contained. In this regard, it is of interest that the effects of dairy-derived fat on lipids and lipoproteins have been reported to differ between specific types of dairy food sources (101).

Blood pressure

The effect of saturated fat on blood pressure has not been definitively established, although a study in 162 healthy persons showed that a diet high in monounsaturated fat decreased blood pressure, whereas a diet high in saturated fat led to no change in blood pressure (102). In the Dietary Intervention Study in children, total fat, but not saturated fat, was positively associated with systolic blood pressure, and total and monounsaturated fat, but not saturated fat, was associated with diastolic blood pressure when all nutrients were considered simultaneously in a regression model (103).

More recently, a 1-y weight-loss study that compared the effects of a very-low-carbohydrate, high-saturated-fat diet with those of an isocaloric high-carbohydrate, low-fat diet showed comparable reductions in weight and blood pressure (104). In contrast, a prospective study in children aged from 7 mo to 15 y showed that in those receiving low-saturated-fat counseling throughout childhood, diastolic and systolic blood pressure was 1 mm Hg lower than in control children (105); however, polyunsaturated fat intake was also higher in this group, as was protein intake, which thereby limited the ability to attribute the observed reduction in blood pressure specifically to saturated fat.

Insulin sensitivity

Studies in animal models have indicated that insulin sensitivity is impaired by saturated fat intake and is improved by omega-3 fatty acids (106, 107). Mechanistic studies have suggested that saturated fatty acids impair insulin sensitivity by reducing adiponectin secretion and impairing insulin signaling pathways required for glucose uptake (108) in white adipose tissue. Saturated fatty acids have also been shown to increase lipid accumulation in rat muscle (109).

Some human observational studies have reported positive associations between saturated fat intake and hyperinsulinemia that were independent of body fat (110, 111). In obese patients with type 2 diabetes, consumption of diets high in saturated and trans fats for 6 wk were associated with increased postprandial insulinemia compared with baseline or diets rich in monounsaturated fat (112). However, in the Nurses’ Health Study, total, saturated, and monounsaturated fats were not associated with risk of type 2 diabetes, whereas polyunsaturated fats decreased the risk and trans fats increased the risk (113). Similarly, in the Health Professionals Follow-Up Study, saturated fat was not associated with risk of type 2 diabetes after adjustment for BMI (114). Furthermore, in most human intervention studies, changes in dietary fat quality had no effects on insulin sensitivity (106, 115). However, the effect of saturated fat on insulin...
sensitivity may be modulated by the total amount of fat in the diet (116). In a randomized clinical trial of 162 healthy persons, no differences in insulin sensitivity were observed between persons consuming saturated fat–enriched or monounsaturated fat–enriched diets when total fat intake represented >37% of total energy; in contrast, in persons who consumed lower total fat intakes, saturated fat led to decreased insulin sensitivity compared with monounsaturated fat (116). In other studies, there have been no consistent effects on insulin sensitivity of variations in total fat intake between 20% and 40% of total energy intake without changes in fatty acid composition (107, 117).

Thrombosis, inflammatory markers, and vascular function

Data from experiments in macrophage cell lines from animals (118, 119) and humans (120) have shown that saturated fats, but not unsaturated fats, can induce the activation of nuclear factor-κB (NF-κB) and the expression of Cox2 and other inflammatory markers, including interleukin-6 and tumor necrosis factor-α (TNF-α)—an effect thought to be mediated by the Toll-like receptor 4 (118, 119). More recently, however, stimulation of Toll-like receptor 4 has been attributed to liposaccharide and lipopeptide contamination of bovine serum albumin, a commonly used reagent in cell culture preparations, rather than saturated fatty acids (121). Nonetheless, there is a growing body of evidence from cellular and animal studies that supports the proinflammatory effects of saturated fat, as reviewed extensively elsewhere (108).

In a randomized controlled human feeding trial, Baer et al (122) showed that stearic acid, but not a combination of lauric, myristic, and palmitic acids, increased fibrinogen concentrations relative to controls who consumed carbohydrate. No effects on C-reactive protein, interleukin-6, or E-selectin were observed during consumption of saturated fatty acids compared with carbohydrate. Oleic acid consumption, however, was associated with decreased interleukin-6 and E-selectin relative to consumption of saturated fat (122). In cells obtained from healthy subjects who were given a cream challenge, a delay in the peak of reactive oxygen species as well as a protracted increase in oxidatively damaged lipids compared with challenges with protein or glucose (123) was observed.

An olive oil meal, high in monounsaturated fat, did not lead to NF-κB activation compared with meals of butter or walnuts, which showed comparable responses; notably, the saturated fat contents of the olive oil and walnut meals were similar (124). In a recent study, a butter meal led to increased TNF-α mRNA compared with walnut or olive oil meals, whereas both the butter and olive oil meals led to increased interleukin-6 mRNA compared with the walnut meal (125); however, no differences in plasma concentrations of the inflammatory markers were observed (125).

Isocaloric reductions in total (from ≈35% to ≈15%) and saturated fat (from ≈15% to ≈6%) with replacement by carbohydrate were not associated with changes in plasma concentrations of C-reactive protein in 2 independent diet studies (126, 127). In a double-blind crossover study in 19 persons, consumption of butter over 32 d was not associated with an increased inflammatory cytokine response relative to soybean oil (128). In the same study, however, butter consumption was associated with a reduced cellular immune response as measured by delayed type hypersensitivity (128). Interestingly, saturated fat, but not unsaturated fat, was able to reverse ethanol-induced liver injury, including fibrosis, with reductions in Cox2 and TNF-α in rats (129).

Saturated fat may also affect vascular function, perhaps by increasing the selective uptake of cholesterol in the arterial wall, resulting in increased atherogenesis in mouse models (130). In the acute postprandial phase following a meal enriched in saturated or polyunsaturated fat, HDL collected from individuals after a coconut meal compared with a safflower or unsaturated fat meal was associated with a 50–70% increase in intercellular adhesion molecule and vascular cell adhesion molecule (131). Attribution of this effect specifically to the saturated fat of the coconut meal may, however, be confounded by the high concentrations of tocopherol found in coconut oil (132).

CONCLUSIONS

Evidence from clinical trials and prospective epidemiologic studies support the cardiovascular benefit of substituting polyunsaturated fat for saturated fat, but the benefit of reducing saturated fat below ≈9% has not been evaluated. The benefits of a further reduction in saturated fat to < ≈9% are inferred from extrapolation of epidemiologic data on the effects on LDL cholesterol beyond the range for which the data are informative (5).

Studies of atherogenic lipoprotein concentrations and properties have raised questions about the benefit of lowering saturated fat intakes by increasing carbohydrate intake, which can induce atherogenic dyslipidemia, and the benefit of increasing monounsaturated fat intakes, which does not lead to improvements in the properties of LDL particles that are associated with atherosclerosis in animal models, although substitution with monounsaturated fat rather than carbohydrate has been shown to reduce the ratio of total and LDL cholesterol to HDL cholesterol. Moreover, whereas it is not known whether diet-induced increases in HDL cholesterol confer protection against CVD risk that would be inferred from epidemiologic data, this effect of dietary saturated fat requires consideration when assessing its net effect on CVD risk. In contrast, recent evidence indicates that limitations in carbohydrate intake can improve all features of atherogenic dyslipidemia. Finally, clinical studies have not yielded consistent evidence for adverse effects of saturated fat on CVD risk factors other than LDL cholesterol, although reduced insulin sensitivity and increased inflammation have been reported in animal and cellular studies.

Thus, given the changing landscape of CVD risk factors and the increasing importance of the atherogenic dyslipidemia associated with obesity, insulin resistance, and type 2 diabetes, the relative effect of dietary saturated fat on CVD risk requires reevaluation. This is of particular concern with regard to the implications of further restrictions in total and saturated fat beyond prevailing US dietary guidelines, which call for levels no higher than 10% of total energy, and the recognition that subsets of the population may not benefit, and may even be harmed, by the substitution of high intakes of carbohydrates, especially refined carbohydrates, for fat in the diet. Particularly given the differential effects of dietary saturated fats and carbohydrates on concentrations of larger and smaller LDL particles, respectively, dietary efforts to improve the increasing burden of CVD risk associated with atherogenic dyslipidemia should primarily emphasize the limitation of refined carbohydrate intakes and a reduction in excess adiposity.
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