Saturated fats: what dietary intake?[1–3]

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ABSTRACT

Public health recommendations for the US population in 1977 were to reduce fat intake to as low as 30% of calories to lower the incidence of coronary artery disease. These recommendations resulted in a compositional shift in food materials throughout the agricultural industry, and the fractional content of fats was replaced principally with carbohydrates. Subsequently, high-carbohydrate diets were recognized as contributing to the lipoprotein pattern that characterizes atherogenic dyslipidemia and hypertriacylglycerolemia. The rising incidences of metabolic syndrome and obesity are becoming common themes in the literature. Current recommendations are to keep saturated fatty acid, *trans* fatty acid, and cholesterol intakes as low as possible while consuming a nutritionally adequate diet. In the face of such recommendations, the agricultural industry is shifting food composition toward lower proportions of all saturated fatty acids. To date, no lower safe limit of specific saturated fatty acid intakes has been identified. This review summarizes research findings and observations on the disparate functions of saturated fatty acids and seeks to bring a more quantitative balance to the debate on dietary saturated fat. Whether a finite quantity of specific dietary saturated fatty acids actually benefits health is not yet known. Because agricultural practices to reduce saturated fat will require a prolonged and concerted effort, and because the world is moving toward more individualized dietary recommendations, should the steps to decrease saturated fatty acids to as low as agriculturally possible not wait until evidence clearly indicates which amounts and types of saturated fatty acids are optimal? *Am J Clin Nutr* 2004; 80:550–9.

KEY WORDS Saturated fat, saturated fatty acids, dietary recommendations, LDL, HDL, coronary artery disease

INTRODUCTION

The study of lipids and their major structural elements, the fatty acids, remains one of the most enigmatic research fields in biology and nutrition. As a specific component in the diet, fat provides essential fatty acids and dissolves and assists in the absorption of fat-soluble vitamins and essential nutrients. Fats in the diet also produce metabolic effects that are a complex consequence of fat content, fatty acid composition, timing, and individual variation. Fatty acids are required not only for membrane synthesis, modifications of proteins and carbohydrates, construction of various structural elements in cells and tissues, production of signaling compounds, and fuel, but also for solubilizing a variety of nonpolar and poorly soluble cellular and extracellular constituents.

In the absence of sufficient dietary fat, the body is apparently capable of synthesizing the saturated fatty acids that it needs from carbohydrates, and these saturated fatty acids are principally the same ones that are present in dietary fats of animal origin. However, not all saturated fatty acids are the same molecule. Recent compositional analyses have shown remarkable specificities for particular saturated fatty acids in cellular compartments (1). Because the biosynthetic pathways for each lipid differ and because the specificity of the enzymes that metabolize fatty acids varies significantly, it has been difficult to assign specific functions to particular fatty acids by examining the phenotypes of animals or humans when they are deficient in even the essential polyunsaturated fatty acids, eg, linoleic acid. Most of what is known about the functions of fatty acids is fragmented and biased by the assumptions made within the experimental investigations in which the fatty acids were studied. This bias is particularly true for studies of the saturated fatty acids, most of which have been examined solely for their tendency to alter lipoprotein metabolism and to influence the concentrations of lipoproteins that carry cholesterol in blood.

The complexity of structure and diversity of function of all fatty acids in biological cells and tissues remain poorly understood. In only a few biological situations have the actions of fatty acids been well described, and scientific knowledge of the structures and functions of biological lipids is narrow. Research on fatty acids consumed in the diet has focused principally on their role in lipoprotein metabolism, although how saturated fatty acids increase lipoprotein cholesterol is not completely understood at the molecular level, and which saturated fatty acids have this capacity is still being debated. However, the evidence that dietary saturated fats generally increase blood cholesterol concentrations is the basis for recommendations to decrease the intake of saturated fats (2, 3). The decision to focus on the role of saturated fat in the diet and on lipid metabolism is reasonable given the cost of cholesterol-related diseases in the population. However, the apparent breadth of studies of saturated fats and lipid metabolism should not obscure the fact that little is known

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about metabolic aspects of individual dietary saturated fatty acids. Although both clinical and epidemiologic evidence indicates that diets inordinately rich in saturated fats are deleterious to health, there is still the question of what the most healthful overall mixture of the different classes of dietary fats is. The agricultural enterprise and food industries are being guided by recommendations to the public to decrease saturated fatty acid contents as low as possible. The response has been gradual but continuous, and saturated fats are disappearing from the food supply. How low should saturated fatty acids in the diet go? This review summarizes a variety of research findings and biological observations on the disparate functions of saturated fatty acids and seeks to bring balance to the debate on dietary saturated fat.

RECOMMENDATIONS FOR INTAKE OF DIETARY FATS

Reduction in fat intake

In 1977 public health recommendations to reduce the intake of fat were made for the US population, especially adults, and some recommendations were for a reduction in total fat to <30% of calories (4). In the American Heart Association Step I and Step II diets, the percentages of calories from total fat were 28.6% and 25.3%, respectively, and the percentages of calories from saturated fat were 9% and 6.1%, respectively. Step I and Step II diets were recommended for treatment of high blood cholesterol. Initial dietary recommendations for patients consuming the Step I diet were similar to those advocated by the American Heart Association. However, 40 y after the much-cited Framingham Heart Study was carried out, persons with high triacylglycerol concentrations (>1.7 mmol/L) and low HDL-cholesterol concentrations (<1.03 mmol/L) were reported to have a significantly higher rate of coronary artery disease (CAD) than were persons with lower triacylglycerol and higher HDL-cholesterol concentrations (5). In addition, studies on the long-term health benefits of consuming a low-fat diet—particularly after variation in human responses is taken into account—are lacking, and low-fat diets have been shown to exert a potentially deleterious effect on lipoprotein profiles in some persons (6, 7). As an example, in a study in which healthy, nondiabetic volunteers consumed diets that contained either 60% of total calories from carbohydrate (25% from fat and 15% from protein) or 40% from carbohydrate (45% from fat and 15% from protein), the 60%-carbohydrate diet resulted in higher fasting plasma triacylglycerol, remnant lipoprotein, and remnant lipoprotein triacylglycerol and lower HDL cholesterol without changing LDL-cholesterol concentrations. These diets were consumed in random order for 2 wk, with a 2-wk washout period between them. The effect of the low-fat diet was not limited to higher fasting plasma triacylglycerol and lower HDL cholesterol, but also included a persistent elevation in remnant lipoproteins (8). These findings led the investigators to question whether it is wise to recommend that all Americans replace dietary saturated fat with carbohydrate.

Individual response to low-fat diets

A key factor that is often not taken into account in studies of the response to dietary fats is individual variation. Within a population of hypercholesterolemic subjects, groups of consistent hyperresponders and minimal responders arise as a consequence of changing dietary saturated fat intake, and this phenomenon is not explained by the dietary compliance of the subjects (9). In consistent responders, changes in total cholesterol in response to increasing dietary saturated fat correlate with baseline cholesterol ester transfer activity, total cholesterol, triacylglycerols, and apolipoprotein (apo) B (9). Men and women differ in their response to dietary fat changes. This was shown by a greater response of total plasma cholesterol to a decrease in the intake of saturated fat in men than in women (10, 11). There are also differential responses in persons who consume low-fat diets (12) and in persons with different levels of cardiorespiratory fitness; the latter result might be explained by reduced hepatic fatty acid and lipoprotein synthesis and enhanced muscular lipid utilization in the physically active subjects who exhibited a higher level of fitness (13). A series of studies showed that very-low-fat (10%), high-carbohydrate diets enriched in simple sugars increase the synthesis of fatty acids, especially palmitate, and that differences between subjects in increased triacylglycerol concentrations vary considerably (14). The results led the investigator to conclude that public health recommendations to reduce dietary fat must take into account the highly variable effects that different carbohydrates may have on increasing plasma triacylglycerol and fatty acid synthesis. These differences in response are examples of why it is important to take into account individual differences in response to both dietary fat and carbohydrates when studies of the effects of either low-fat diets or diets with reduced saturated fat or studies of the effects of specific dietary saturated fatty acids are pursued.

Aftermath of dietary recommendations to decrease fat intake

To assist the public in following the guidelines for a lower intake of dietary fats, the food industry reformulated commodities and processed foods. Despite these changes in the food supply, the results of the National Health and Nutrition Examination Survey data-collection studies in the US indicate that the replacement of dietary fat with dietary carbohydrate failed to reverse the trend of an increasing incidence of obesity in the population. Although a reduction in dietary fat is logically matched to increased dietary carbohydrate, the role of carbohydrates in weight gain is unclear. However, carbohydrates increase blood glucose concentrations, which stimulates insulin release, which in turn promotes the growth of fat tissue that can cause weight gain. Increased obesity is associated with the metabolic syndrome and hypertriacylglycerolemia, a recognized atherogenic risk (15–18; for review *see* reference 19).

Because of the changing emphasis in the fields of diet and health to include the tendency of populations to develop chronic diseases such as heart disease, obesity, and cancer, for the past 15 y, dietary fat has been considered by the scientific community and the public to be a health problem. Despite the long-standing recommendations about diet, many reports stress that there is a widespread epidemic of obesity (20, 21). Still, many investigators claim that the global obesity epidemic is a result of environmental factors (21), including dietary fat (22), supersized portions (23), insufficient energy expenditure (20), and social causes (24). Such hypotheses are the basis of sound scientific debate; however, they are not the basis of sound public health policy.

Controversy over saturated fat intake

In the average American diet, 34.3% and 15% of calories were calculated to come from total fat and saturated fat, respectively

(25), although according to the third National Health and Nutrition Examination Survey (26) and information from the US Department of Agriculture (27), an average of only 12% of calories is derived from saturated fat. High-fat diets usually mean increased intakes of saturated fat. Epidemiologic data suggest that saturated fats increase the concentration of LDL cholesterol in the bloodstream of some persons and that elevated cholesterol concentrations heighten the risk of heart disease (28). However, from a pragmatic food-choice perspective, it is impossible to achieve a nutritionally adequate diet that has no saturated fat (3).

Controversy exists about the roles that dietary fat and cholesterol play in the risk of heart disease. Confounding factors influence the interpretation of results of epidemiologic studies. For example, over the years, France and Finland—populations that have similar intakes of cholesterol and saturated fat—have consistently had very different mortality rates from CAD (29). Some epidemiologic evidence suggests that consumption of high amounts of saturated fat and cholesterol lead to high blood cholesterol and thus to an increased risk of heart disease (for review *see* reference 30). Reviews of studies that linked dietary cholesterol and fats and high serum cholesterol with atherosclerosis and cardiovascular disease aptly pointed out that the results of the epidemiologic and experimental studies are inconclusive or even contradictory (31–33). The conclusion of an analysis of the history and politics behind the diet-heart hypothesis was that after 50 y of research, there was no evidence that a diet low in saturated fat prolongs life (34). The proposition that dietary fat is unhealthy is based on the fact that high intakes of saturated fat elevate blood cholesterol and thus increase the incidence of atherosclerosis, which then increases the risk of CAD (35, 36). However, dietary saturated fats are not the only cause of heart disease—the causes are multifactorial. The results of studies on the etiology of heart disease are inconclusive and sometimes contradictory. Factors that are known to contribute to this disease include intake of carbohydrates with high glycemic indexes (for review *see* reference 19), homocysteine (37), C-reactive protein (38, 39), lack of exercise (40), high blood pressure (41), a family history of heart disease (42), oxidative stress (43), smoking (for review *see* reference 44), and obesity and diabetes (45, 46).

Tissue accumulation of fatty acids

In the utilization of fats as fuel, there is selectivity in the partitioning of specific fats between oxidation and storage in adipose tissue. The fatty acid composition of adipose tissue in persons with widely varying dietary intakes is relatively similar. In studies of the influence of dietary composition on adipose fatty acids, dietary intake determined $<25\%$ of the variance in adipose fatty acid composition (47). Nevertheless, diet does influence tissue composition, and recent studies showed that certain fatty acids in adipose tissue are effective biomarkers of specific dietary fatty acid intake (48). For example, 15:0 and 17:0 in adipose reflect dairy intake, and n−3 fatty acids (18:3 and 22:6) reflect fish intake. Dietary and adipose n−6 fatty acids are correlated, and the best indicators of total *trans* fatty acid intake are *cis*,*trans* 18:2n−6 and *trans*,*cis* 18:2n−6, whereas 18:1 and 16:1 *trans* fatty acids are the next best indicators. Although it is commonly believed that saturated fats and dietary cholesterol are the lipids that accumulate in arteries and that this accumulation is a further rationale for decreasing all saturated fatty acids in diets, this is not necessarily true. Excessive n−6 polyunsaturated fatty acid (PUFA) intake from refined vegetable oils has also been implicated as contributing to cancer and heart disease, and arterial plaque is primarily composed of unsaturated fats, particularly polyunsaturated fats, and not saturated fat (49). A recent study found that in healthy persons, the intake of fish oil, which contains long-chain n−3 fatty acids, decreased both fasting and postprandial triacylglycerol concentrations but increased LDL-cholesterol concentrations irrespective of whether the diet was rich in saturated fatty acids or in monounsaturated fatty acids (50). Although evidence suggests that unsaturated fatty acids may protect against atherosclerosis, the replacement of monounsaturated fatty acids with PUFAs in low-fat, high-carbohydrate diets was suggested as being premature on the basis of detrimental effects observed in animal models (51). Other investigators recommend that the daily intake of PUFAs should not be $>10\%$ of total energy (52). If balance and reason are to be applied to intakes of monounsaturated fats and PUFAs, the same cautionary perspectives should be applied to saturated fats.

EVOLUTIONARY PERSPECTIVE ON DIET

A possible consideration in addressing the question of what constitutes the best diet for humans is what they ate during their evolution. Over the past 2.5 million years, humans have evolved as hunter-gatherers and have been carnivorous hunters from the Paleolithic Age. Experts on Paleolithic nutrition say that humans have eaten animal products for most of their existence on earth (53–55). Therefore, humans have consumed saturated fatty acids for their entire existence. Although the genetic profile of humans was programmed with the Paleolithic diet (56), this diet was characterized by lower amounts of total fat, saturated fat, and *trans* fatty acids than those found in the modern Western diet. Animal food provided the dominant (65%) energy source, and plant foods constituted the remainder (35%) (53). Even though hunter-gatherers relied on animal-based foods, the diet consisted of high dietary protein (19–35% of energy) and low dietary carbohydrate (22–40% of energy). These diets had relatively high amounts of monounsaturated fatty acids and PUFAs and a lower ratio of n−6 to n−3 fatty acids. Because Darwinian selection pressure was probably exerted on evolving prehumans and early humans via health issues other than heart disease, it is possible that health issues that are not currently well assessed with respect to fats, such as resistance to infection, have a sensitivity to types of dietary fat that is different from that of heart disease.

MODERN APPROACH TO HUMAN DIETS

Nutrition is a continuously evolving field of study. All the essential nutrients are now known, and recommendations on what constitutes a healthy diet, not for individuals but for the entire human population, have been developed. In 1992, the US Department of Agriculture released *The Food Guide Pyramid*, which was updated in 1996 (57, 58). This guide was developed to educate the American public about dietary choices that would maintain good health. This guide was based in part on the "lipid hypothesis" that there is a direct relation between the amount of saturated fat and cholesterol in the diet and the incidence of CAD (59). However, over the past decade, evidence on the soundness

of this guide has been emerging. This guide promoted the consumption of complex carbohydrates and recommended that everyone, regardless of variations among individuals in the population, limit total fat intake to ≈30% of calories. Although the most recent recommendations are for all adults to limit the intake of saturated fats to ≤10% of calories, the Institute of Medicine (60) summarized the 2002 Food and Nutrition Board recommendations as follows:

> Saturated fatty acids, *trans* fatty acids, and dietary cholesterol have no known beneficial role in preventing chronic disease and are not required at any level in the diet . . . Both types of fat heighten the risk of heart disease in some people by boosting the level of harmful, low-density cholesterol in the bloodstream; this occurs even with very small quantities in the diet. Since there is no intake level of saturated fatty acids, *trans* fatty acids, or dietary cholesterol at which there is no adverse effect, no UL (*sic* upper limit) is set for them; instead, the recommendation is to keep their intake *as low as possible* (emphasis added) while consuming a nutritionally adequate diet, as many of the foods containing these fats also provide valuable nutrients.

These recommendations were made even though the Dietary Guidelines Advisory Committee (2) clearly stated that ". . . no lower limit of saturated fat intake has been identified."

HEALTH EFFECTS OF SATURATED FATTY ACIDS

The approach of many mainstream investigators in studying the effect of consuming saturated fats has been narrowly focused to produce and evaluate evidence in support of the hypothesis that dietary saturated fat elevates LDL cholesterol and thus the risk of CAD. The evidence is not strong, and, overall, dietary intervention by lowering saturated fat intake does not lower the incidence of nonfatal CAD; nor does such dietary intervention lower coronary disease or total mortality (31, 61). Unfortunately, the overwhelming emphasis on the role of saturated fats in the diet and the risk of CAD has distracted investigators from studying any other effects that individual saturated fatty acids may have on the body. If saturated fatty acids were of no value or were harmful to humans, evolution would probably not have established within the mammary gland the means to produce saturated fatty acids—butyric, caproic, caprylic, capric, lauric, myristic, palmitic, and stearic acids—that provide a source of nourishment to ensure the growth, development, and survival of mammalian offspring.

Fatty acids are essential parts of all body tissues, where they are a major part of the phospholipid component of cell membranes. Saturated fatty acids have been suggested to be the preferred fuel for the heart (62). Fatty acids are used as a source of fuel during energy expenditure, and heavy exercise is associated with decreases in the plasma concentrations of all free fatty acids. In light exercise, fat metabolism may be controlled to favor adipose tissue lipolysis and extraction of free fatty acids from the circulation by muscle, whereas in heavy exercise, adipose tissue lipolysis is inhibited and hydrolysis of muscle triacylglycerols may play a more important part (63). In the absence of sufficient dietary fat, the body synthesizes the fatty acids that it needs from carbohydrates. The major fatty acid synthesized de novo via fatty acid synthase is palmitate, which undergoes elongation involving acyl-CoA and malonyl-CoA to form longer-chain saturated fatty acids. Desaturation via fatty acyl-CoA desaturases introduces unsaturation at C4, C5, C6, or C9. The lack of capability to desaturate past C9 makes dietary linoleic acid an essential fatty acid (for review *see* reference 64). Synthesis of palmitic acid is also increased by consumption of very-low-fat diets with a high ratio of sugar to starch (14).

Based on the controversy over the effects of fat in the diet, the question most often addressed is, What are the relative cholesterolemic effects of the major saturated fatty acids in the diet? However, the evidence suggests that caproic, caprylic, and capric acids are neutral with respect to cholesterol-increasing properties and their ability to modulate LDL metabolism; lauric, myristic, and palmitic acids are approximately equivalent in their cholesterol-increasing potential, and stearic acid appears to be neutral in its cholesterol-increasing potential (65; for review *see* reference 66). A limited number of controlled studies suggest that myristic acid is the most potent cholesterolemic dietary saturated fatty acid (for review *see* reference 67). However, there is evidence that the increase in chlolesterol is related to an increase in both LDL and HDL cholesterol (68). Aside from the reported effects on plasma cholesterol concentrations, there are other properties and functions of the individual saturated fatty acids that support beneficial roles in the body. Some of these roles are briefly discussed below.

Butyric acid

Short-chain fatty acids are hydrolyzed preferentially from triacylglycerols and absorbed from the intestine to the portal circulation without resynthesis of triacylglycerols. These fatty acids serve as a ready source of energy, and there is only a low tendency for them to form adipose (69). Butyric acid (4:0) is the shortest saturated fatty acid and is present in ruminant milk fat at 2–5% by weight (70), which on a molar basis is approximately one-third the amount of palmitic acid. Human milk contains a lower percentage (≈0.4%) of butyric acid. No other common food fat contains this fatty acid.

Butyrate is a well-known modulator of genetic regulation (71, 72), and it also may play a role in cancer prevention (73). Published information thus far indicates that butyric acid exhibits contradictory and paradoxical behavior (74). Although butyric acid is an important energy source for the normal colonic epithelium, is an inducer of the growth of colonic mucosa, and is a modulator of the immune response and inflammation, it also functions as an antitumor agent by inhibiting growth and promoting differentiation and apoptosis (75).

Caproic, caprylic, and capric acids

In bovine and human milk, caproic acid (6:0) is present at ≈1% and 0.1% of milk fat, respectively, and caprylic acid (8:0) and capric acid (10:0) are present at ≈0.3% and 1.2% of milk fat, respectively. Goat milk contains the highest percentage of caprylic acid, at 2.7% of milk fat. These 3 fatty acids have similar biological activities. Both caprylic acid and capric acid have antiviral activity, and when formed from capric acid in the animal body, monocaprin has antiviral activity against HIV (76, 77). Caprylic acid has also been reported to have antitumor activity in mice (78). Negative effects of these fatty acids on CAD and cholesterol have not been a dietary issue.

Lauric acid

Lauric acid (12:0) is a medium-chain fatty acid that is present in human and bovine milk at ≈5.8% and 2.2% of milk fat,

respectively. This fatty acid has been recognized for its antiviral (79) and antibacterial (80, 81) functions. Recent results suggest that *Helicobacter pylori* present in stomach contents (but not necessarily within the mucus barrier) should be rapidly killed by the millimolar concentrations of fatty acids and monoacylglycerols that are produced by preintestinal lipases acting on suitable triacylglycerols, such as those present in milk fat (82). Lauric acid is also effective as an anticaries and antiplaque agent (83). Medium-chain saturated fatty acids and their monoacylglycerol derivatives can have adverse effects on various microorganisms, including bacteria, yeast, fungi, and enveloped viruses, by disrupting the lipid membranes of the organisms and thus inactivating them (84, 85). This deactivation process also occurs in human and bovine milk when fatty acids are added to milk (86, 87). The release of monolaurin from milk lipids by human milk lipases may be involved in the resulting antiprotozoal functions (88, 89). One study indicated that one antimicrobial effect against bacteria is related to the interference of monolaurin with signal transduction or toxin formation (90). In addition to disrupting membranes to inactivate viruses, lauric acid has an effect on virus reproduction by interfering with assembly and maturation, ie, cells make the components of the virus, but their assembly is inhibited (79).

Myristic acid

Bovine milk fat contains 8–14% myristic acid (14:0), and in human milk, myristic acid averages 8.6% of milk fat. As stated above, myristic acid is one of the major saturated fatty acids that have been associated with an increased risk of CAD, and human epidemiologic studies have shown that myristic acid and lauric acid are the saturated fatty acids most strongly related to average serum cholesterol concentrations. However, in healthy subjects, although myristic acid is hypercholesterolemic, it increased both LDL- and HDL-cholesterol concentrations compared with oleic acid (68).

Palmitic acid

Palmitic acid (16:0) is present in human and bovine milk at 22.6% and 26.3% of milk fat, respectively. Palmitic acid in triacylglycerols in human milk is predominantly esterified in the *sn*-2 position of the molecule. Feeding human infants a formula containing triacylglycerols similar to those in human milk (16% palmitic acid esterified predominantly in the *sn*-2 position) has significant effects on fatty acid intestinal absorption (91, 92). Myristic, palmitic, and stearic acids are better absorbed from human-like milk than from standard formula, without a change in total fat fecal excretion. Mineral balance is improved in comparison with a conventional formula, as shown by lower fecal calcium excretion, higher urinary calcium, and lower urinary phosphate. The specific distribution of the fatty acids in the triacylglycerol is known to play a key role in lipid digestion and absorption. Because pancreatic lipase selectively hydrolyzes triacylglycerols at the *sn*-1 and *sn*-3 positions, free fatty acids and 2-monoacylglyceriols are produced. Free palmitic acid, but not 2-monopalmitin (which is efficiently absorbed), may be lost as a calcium–fatty acid soap in the feces. A comparison between the effects of dietary laurate-myristate and the effects of palmitic acid in normolipemic humans showed that palmitic acid lowers serum cholesterol (93). In humans, replacement of dietary laurate-myristate with palmitate-oleate has a beneficial effect on an important index of thrombogenesis, ie, the ratio of thromboxane to prostacyclin in plasma (94).

Stearic acid

Dietary stearic acid (18:0) is derived primarily from bovine meat and dairy products. Stearic acid is present in human and bovine milk at 7.7% and 13.2% of milk fat, respectively. In relation to the question of their effects on serum cholesterol, stearic acid and saturated fatty acids with <12 carbon atoms are thought not to increase cholesterol concentrations (95). Dietary stearic acid decreases plasma and liver cholesterol concentrations by reducing intestinal cholesterol absorption. Recent data from studies with hamsters, which have a lipoprotein cholesterol response to dietary saturated fat that is similar to that of humans, suggest that reduced cholesterol absorption by dietary stearic acid is due, at least in part, to reduced cholesterol solubility and further suggest that stearic acid may alter the microflora populations that synthesize secondary bile acids (96).

The absorption of stearic acid from triacylglycerols containing only oleate and stearate depends on the position of esterification. 2-Monstearin is well absorbed if the stearic acid is esterified at the *sn*-2 position of the triacylglycerol. If the triacylglycerol is esterified at the *sn*-1 or the *sn*-3 position, it is released as free stearic acid, and in the presence of calcium and magnesium, it is poorly absorbed (97). In a study of the effects of dietary fat on serum lipid and lipoporoteion concentrations, the absorption of dietary oleic acid, palmitic acid, and stearic acid was similar, which indicates that differential effects of these fatty acids on plasma lipoprotein cholesterol are not due to differential absorption (98). Another study in humans also indicated that, even though stearic acid appears to have different metabolic effects with respect to its effect on the risk of cardiovascular disease than do other saturated fatty acids (95), reduced stearic acid absorption does not appear to be responsible for the differences in plasma lipoprotein responses (99).

Compared with consumption of dietary palmitic acid, consumption of dietary stearic acid (19 g/d) for 4 wk by healthy males produced beneficial effects on thrombogenic and atherogenic risk factors (100). Mean platelet volume, coagulation factor VII activity, and plasma lipid concentrations decreased significantly with consumption of the stearic acid diet, whereas platelet aggregation increased significantly with consumption of the palmitic acid diet. A subsequent study showed no alteration in plasma lipids, platelet aggregation, or platelet activation in short-term (3 wk) feeding trials when stearic acid and palmitic acid were provided in commercially available foods (101). An interesting finding in a study of the association between the composition of serum free fatty acids and the risk of a first myocardial infarction was that the percentage content of both very-long-chain n−3 fatty acids and stearic acid is inversely associated with the risk of myocardial infarction. The investigators speculated that the very-long-chain n−3 fatty acids might reflect diet but also that these 2 free fatty acids might in some way be related to the pathogenetic process and not just reflect their content in adipose tissue (102).

EFFECTS OF SATURATED FATTY ACIDS ON LIPOPROTEIN CHOLESTEROL

A causal relation between total and LDL cholesterol in blood and CAD has long been accepted. However, despite the strength of the relation between circulating concentrations of LDL cholesterol and heart disease, one should not assume that the relation

between saturated fatty acid intake and heart disease is equally strong. Recommendations to decrease the intake of saturated and *trans* unsaturated fat and cholesterol have as a goal the prevention of CAD. However, in the Framingham study, 80% of the subjects who went on to have CAD had the same total cholesterol concentrations as those who did not (103). The metabolic contributor to coronary disease is the atherogenic lipoprotein profile, and there has been widespread use of a coronary risk lipid profile that uses the ratio of total to HDL cholesterol and the ratio of LDL to HDL cholesterol for predicting the risk of vascular disease. Abnormal lipid and lipoprotein cholesterol concentrations are an LDL-cholesterol concentration $\geq$ 4.1 mmol/L, an HDL-cholesterol concentration $<$ 1.0 mmol/L, a triacylglycerol concentration $\geq$ 1.7 mmol/L, and a lipoprotein(a) concentration $\geq$ 3 g/L (104). It has been pointed out that assessment of the effects of diet on CAD should include consideration of the concomitant changes in both HDL and triacylglycerols (105).

Considerable evidence indicates that dietary saturated fats support the enhancement of HDL metabolism. In a study of the effects of reduced dietary intakes of total and saturated fat on HDL subpopulations in a group of multiracial, young and elderly men and women, subjects consumed each of the following 3 diets for 8 wk: an average American diet (34.3% of energy from total fat and 15.0% of energy from saturated fat), the American Heart Association Step I diet (28.6% of energy from total fat and 9.0% of energy from saturated fat), and a diet low in saturated fat (25.3% of energy from total fat and 6.1% of energy from saturated fat) (25). HDL_2-cholesterol concentrations decreased in a stepwise fashion after the reduction of total and saturated fat. A reduction in dietary total and saturated fat decreased both large (HDL_2 and HDL_{2b}) and small, dense HDL subpopulations, although the decreases in HDL_2 and HDL_{2b} were most pronounced. Serum triacylglycerol concentrations were negatively correlated with changes in HDL_2 and HDL_{2b} cholesterol. In children fed a diet in which total fat was substituted with carbohydrate but in which total energy was held constant, total fat and saturated fat were positively associated with total cholesterol and HDL cholesterol (106). Perhaps it is ironic that diets enriched in saturated fat and cholesterol increase LDL-cholesterol concentrations but also increase HDL-cholesterol concentrations. The lack of a scientific, mechanistic understanding of these relations should be a warning that population-wide recommendations for all persons at all ages and circumstances to reduce their intake of saturated fats may be premature. For persons with low LDL and low HDL, is a recommendation to decrease saturated fatty acid intake to the maximum extent possible warranted?

The consumption by humans of a diet low in total fat, saturated fat, and cholesterol (National Cholesterol Education Program Step II diet) decreases both HDL-cholesterol and apo A-I concentrations, which parallels reductions in apo A-I secretion rate (11). An important finding is that persons differ in their response to dietary fat (12). We must recognize not only that individual responses to types of dietary fat vary but also that different fats have markedly different effects on serum lipids and lipoprotein concentrations. Evidence indicates that postprandial triacylglycerol-rich lipoproteins are related to atherogenic risk; however, few investigations of the effects of individual saturated fatty acids on plasma lipoproteins have been conducted. An investigation of the effect of stearic acid and myristic acid on postpranidal and 24-h fasting plasma lipoprotein triacylglycerol and cholesterol concentrations showed that fasting HDL cholesterol was affected within 24 h in healthy young men. HDL-cholesterol concentrations were higher after subjects consumed myristic acid than after they consumed stearic acid. Dietary myristic acid also caused a greater increase in postprandial HDL triacylglycerol than did dietary stearic acid (107). On the basis of the hypothesis that hypertriacylglycerolemia may represent a procoagulant state involving disturbances to the hemostatic system, the effects of individual dietary fatty acids (1 g/kg body wt; 43% from the test fatty acid) on the promotion of factor VII activation were tested (108). The test diets were rich in either stearic acid, palmitic acid, palmitic acid plus myristic acid, oleic acid, *trans* 18:1, or linoleic acid, and the postprandial lipid and hemostatic profiles were measured in young men 2, 4, 6, and 8 h after consumption of the diets. Although all of the diets increased factor VII activation, saturated fatty acids—especially stearic acid—resulted in less of an increase than did the unsaturated fatty acid diets that were tested.

The effects of fatty acids in the diet were examined in another study comparing women who consumed a high–saturated fatty acid diet with those who consumed a diet low in total fat or a diet with a high content of monounsaturated fatty acids and PUFAs (109). This study showed that total and LDL cholesterol and apo B were lowest in the women who consumed the diet high in unsaturated fatty acids. HDL-cholesterol and apo A-I concentrations in the women who consumed the diet high in saturated fatty acids were 15% and 11% higher, respectively, than those in the women who consumed the diet low in saturated fatty acids but were lower than those in the women who consumed the diet with high unsaturated fatty acids. The investigators concluded that to influence the ratio of LDL to HDL cholesterol, changing the proportions of dietary fatty acids may be more important than limiting the percentage of energy from total or saturated fat, at least when the diets contain high amounts of fats derived mainly from lauric and myristic acids, both of which increase HDL cholesterol.

A review was made of 27 controlled studies of the effect of carbohydrate and fatty acid intake on serum lipid and lipoprotein concentrations. When data were analyzed by using multiple regression analysis with isocaloric exchanges of saturated, monounsaturated, and polyunsaturated fatty acids for carbohydrates as the independent variables, all fatty acids elevated HDL cholesterol when they were substituted for carbohydrates, but the effect diminished with increasing unsaturation of the fatty acids (110). A recent meta-analysis of 60 controlled trials of the effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins found that lauric acid greatly increases total cholesterol, but the effect is to decrease the ratio of total to HDL cholesterol. Myristic acid and palmitic acid have little effect on the ratio, whereas stearic acid reduces the ratio slightly (111). Another study (112) showed that plasma phospholipid stearic acid concentrations are strongly positively correlated with plasma total cholesterol, LDL-cholesterol, and triacylglycerol concentrations regardless of the intake of saturated fat (vegan, moderate meat intake, and high meat intake). The author suggested that a reduction in total saturated fatty acid intake would be more appropriate than replacement of other saturated fatty acids with stearic acid, as suggested by the investigators in a study cited above (100). Because the effects of individual fatty acids on the ratio of total to

HDL cholesterol may be different from their effects on LDL, these biomarkers may not directly reflect the risk of CAD.

Although elevated LDL cholesterol is associated with the endpoints of atherosclerotic disease, including heart disease and stroke, this association should not be extrapolated to suggest that there are equally compelling associations between plasma lipoproteins and other phenotypic outcomes. Lipoproteins in plasma are not a simple artifact of a modern Western diet. Lipoproteins play a wide variety of physiologic and pathophysiologic functions, and the multiple roles of lipoproteins in mediating the response to infectious and toxic agents are only now being recognized. Plasma HDL-cholesterol concentrations were recently associated with protection against the risk of infections (113). Acute infections in children seem to be accompanied by enhanced oxidative modification of LDL and by a decrease in HDL cholesterol (114), and circulating HDL protects against endotoxin toxicity (114, 115; for review *see* reference 116).

Lipopolysaccharide (LPS) is the major glycolipid component of the outer membranes of gram-negative bacteria. This endotoxin, which is responsible for pathophysiologic symptoms characteristic of infection, is associated with plasma lipoproteins, which suggests that sequestering of LPS by lipid particles may form an integral part of a humoral detoxification mechanism. The binding of LPS to lipoproteins is highly specific under simulated physiologic conditions, and HDL has the highest binding capacity for LPS (117, 118). Although lipoprotein-binding protein circulates in association with LDL and VLDL in healthy persons (119), chylomicrons, which carry lipids from the intestines into other body tissues, exceed other lipoproteins in LPS-inactivating capacity (120). Thus, lipoprotein-binding protein-lipoprotein complexes may be part of a local defense mechanism of the intestine against translocated bacterial toxin. Because saturated fats enhance HDL concentrations, saturated fats are potentially important in protecting against bacterial LPS toxicity.

CONCLUSIONS

Twenty years ago, government guidelines recommended that all persons consume a low-fat diet, with the advice being to "avoid too much fat, saturated fat, and cholesterol" (121). Consumption of a low-fat diet (defined as one containing 20% of energy from fat) was subsequently shown to induce atherogenic dyslipidemia (122, 123). On the basis of government guidelines, the food industry was obliged to change the formulation of foods to a preponderance of low-fat and nonfat products, with calories from carbohydrates being substituted for fat. It is now known that a high-carbohydrate diet can lead to the lipoprotein pattern (124) that characterizes atherogenic dyslipidemia. At the time the 1980 guidelines were established, there was no solid basis for understanding what the consequences of such overall dietary changes would be for most persons. The recommendation to lower saturated fat intake was based on a single marker of health outcome—a correlation between dietary saturated fat and the incidence of CAD, with blood cholesterol being the indicator of potential disease. Now, the most recent published recommendations are for all persons to reduce the saturated fat content of their diet (10% of total calories), although it was stated in the Dietary Guidelines Advisory Committee report (2) that ". . . no lower limit of saturated fat intake has been identified." The summary report by the Institute of Medicine (60) takes this recommendation one step further by clearly stating that ". . . there is no intake level of saturated fatty acids . . . at which there is no adverse effect." This nutritional rhetoric is driving the food industry to respond to governmental and public demands to decrease the amounts of all saturated fats from the food supply. The agricultural enterprise will continue to lower saturated fatty acids by every means possible.

Public health recommendations for the consumption of total fat and the composition of fat in the diet are being reevaluated, and this reevaluation is projected to be finished in 2004. To meet the body's daily energy and nutritional needs while minimizing the risk of chronic disease, the newest report on recommendations for healthy eating from the National Academies' Institute of Medicine is that adults should get 45–65% of their calories from carbohydrates, 20–35% from fat, and 10–35% from protein. It was recently pointed out that reducing the proportion of energy from fat below 30% is not supported by experimental evidence and that advice to decrease total fat intake has failed to have any effect on the prevalence of obesity, diabetes, and cardiovascular disease (125). The recent conference summary from the Nutrition Committee of the American Heart Association emphasized that studies with cardiovascular endpoints that go beyond the measurements of plasma lipids and lipoproteins are needed to evaluate the effects of individual fatty acids in humans (126).

At this time, research on how specific saturated fatty acids contribute to CAD and on the role each specific saturated fatty acid plays in other health outcomes is not sufficient to make global recommendations for all persons to remove saturated fats from their diet. No randomized clinical trials of low-fat diets (105) or low-saturated fat diets of sufficient duration have been carried out; thus, there is a lack of knowledge of how low saturated fat intake can be without the risk of potentially deleterious health outcomes. Although the removal of particular foods from the diet can be accomplished quickly, the removal of all saturated fats or particular saturated fatty acids from foods cannot be accomplished quickly by the agricultural community. This will require modification of existing foods and changes in policies to improve health, which in turn will require integration of nutrition needs with economic growth and development; agriculture and food production, processing, and marketing; health care and education; and changing of lifestyles and food choices by individual consumers. It requires years to change the course of commodity manipulation and to make drastic changes in the food supply. Before such implementation can be achieved, all food sources of specific saturated fatty acids must be accurately identified and quantified, the core commodities will need to be changed at the level of production, agricultural processes will require new approaches and procedures, and food formulations will need to be changed. The question remains, What is an appropriate amount to which saturated fatty acids in the diet can be lowered for optimal health? Before recommendations are made to further lower the content of these components in the food supply, should we not wait until scientific evidence clearly shows that this is the healthiest direction to take?

Because of the paucity of scientific understanding of the role of specific fatty acids in humans beyond the effects on total and LDL cholesterol, research on the effects of specific fatty acids in a broader health context should be viewed as a clear research priority. Given the varying health status of much of the developed world, it would also be appropriate to explore these effects in a range of human metabolic phenotypes, including persons with various body mass index values, persons with insulin resistance,

and persons with chronic inflammation. Finally, the scientific community not only is recognizing the interindividual variation in dietary response and health but is also building the tools to measure it. Therefore, the influence of varying saturated fatty acid intakes against a background of different individual lifestyles and genetic backgrounds should also be considered.

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