Influence of stearic acid on cholesterol metabolism relative to other long-chain fatty acids[1-3]

Scott M Grundy

ABSTRACT Stearic acid is a long-chain saturated fatty acid. However, in contrast with other saturated fatty acids, stearic acid apparently does not raise serum cholesterol concentrations. Studies carried out three decades ago provided strong suggestive evidence that this was the case. More recent investigations that specifically compared stearic acid with other fatty acids in human studies have confirmed that stearic acid is not hypercholesterolemic. Stearic acid was shown not to raise low-density-lipoprotein cholesterol relative to oleic acid, which is known to be neutral in its effects on cholesterol concentrations. In contrast, palmitic acid, another long-chain saturated fatty acid, definitely raises cholesterol concentrations. For this reason, fats rich in stearic acid might be used in place of those high in palmitic acid in cholesterol-lowering diets. *Am J Clin Nutr* 1994;60(suppl): 986S-90S.

KEY WORDS Stearic acid, cholesterol, low-density lipoprotein, oleic acid, palmitic acid

Introduction

Stearic acid constitutes 7-10% of total fatty acids in the American diet. This is about one-fourth of dietary saturated fatty acids. Many health organizations have recommended that intakes of saturated fatty acids be decreased in an effort to reduce serum cholesterol concentrations and thereby decrease the risk for coronary heart disease (CHD). Because stearic acid is a saturated fatty acid, it has followed in the minds of many people that intakes of stearic acid should be decreased. However, there is growing evidence that the various saturated fatty acids have differing effects on serum cholesterol concentrations. Thus, it is possible that the general recommendation to reduce intakes of saturated fatty acids as a class will have to be reconsidered.

The reconsideration of recommendations about saturated fatty acids may have to be extended to other dietary fatty acids as well. Recent research has revealed some inconsistencies in effects of different fatty acids on serum total cholesterol concentrations. In addition, new information is available on effects of different fatty acids on the various lipoprotein fractions. Some of this information has come from investigations carried out in our laboratory, but several other laboratories have been involved as well. In this article, our current understanding of the influence of different fatty acids on serum cholesterol and lipoprotein concentrations will be considered. Attention will be given first to saturated fatty acids and then to unsaturated fatty acids. Stearic acid will be considered last and its relation to the other fatty acids will be taken into account.

Palmitic acid

The major saturated fatty acid in the diet is palmitic acid (16:0). In the American diet, palmitic acid constitutes ≈60% of total saturated fatty acids. It is present in both animal and plant products. It is the predominant saturated fatty acid in most meat and dairy fats, but a substantial fraction of palmitic acid in the diet comes from plant products. It makes up ≈45% of fatty acids in palm oil, ≈25% in cottonseed oil, and lesser amounts in other plant oils. However, a major reduction in palmitic acid intake could be achieved by specifically curtailing intakes of animal fats.

The evidence is very strong that palmitic acid raises the serum total cholesterol concentration, compared with unsaturated fatty acids or carbohydrate. This evidence comes primarily from metabolic-ward studies (1-5) but it is bolstered by epidemiologic evidence (6). The increase in total cholesterol concentrations induced by palmitic acid occurs predominantly in the low-density-lipoprotein (LDL) fraction. Slight increases also may occur in high-density lipoproteins (HDLs) and very-low-density lipoproteins (VLDLs). The mechanisms whereby palmitic acid raises LDL-cholesterol concentrations is not fully understood, but there is growing evidence that it acts to suppress the expression of LDL receptors (7, 8). Still, the possibility that it may promote the secretion of lipoproteins containing apolipoprotein B-100 (apo B) has not been ruled out with certainty.

In recent years some investigators have questioned whether palmitic acid actually raises serum LDL-cholesterol concentrations. This view is based on at least two considerations. First, in some animal species, including some primates, diets rich in palmitic acid seemingly have only small cholesterol-raising effects, much smaller than has been reported in humans. Second, in several previous human studies in which the experimental design was not rigorous, little cholesterol-raising action of diets high in

[1] From the Center for Human Nutrition, Departments of Internal Medicine, Biochemistry, and Clinical Nutrition, University of Texas Southwestern Medical Center, Dallas.

[2] Presented at *Metabolic Consequences of Stearic Acid Relative to Other Long-Chain Fatty Acids.*

[3] Address correspondence to SM Grundy, Center for Human Nutrition, 5323 Harry Hines Boulevard, Health Science Center, G4-100, Dallas, TX 75235.

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palmitate could be detected. Nonetheless, some studies investigating the effects of palmitic acid in humans had dietary intakes rigorously controlled and monitored (3–5). The results of these studies show clearly that palmitic acid raises LDL-cholesterol concentrations relative to unsaturated fatty acids (or carbohydrate). These studies leave little doubt that dietary palmitic acid is hypercholesterolemic. Furthermore, this fatty acid accounts for most of the cholesterol-raising action of most diets rich in saturated fatty acids.

Myristic acid

Myristic acid (14:0), another dietary saturated fatty acid, is found in butter fat and in certain tropical oils (coconut oil and palm-kernel oil). Although there is strong circumstantial evidence that myristic acid is hypercholesterolemic, direct data are less strong than for palmitic acid. According to Keys et al (1), myristic acid raises serum cholesterol concentrations about as much as does palmitic acid. However, Hegsted et al (2) presented evidence that myristic acid is even more hypercholesterolemic than palmitic acid. Which of these two views is correct has not been determined. The practical importance of myristic acid as a cholesterol-raising fatty acid for most diets is much less than for palmitic acid because myristic acid is present in much smaller amounts. We must await future studies to learn more precisely how much myristic acid raises cholesterol concentrations. At the very least, on the basis of previous studies, myristic acid must be considered to be at least as hypercholesterolemic as palmitic acid and it must be added to the list of cholesterol-raising fatty acids.

Lauric acid

Saturated fatty acids are divided into two groups: long chain and medium chain. The long-chain group includes stearic acid (18:0), palmitic acid (16:0), and myristic acid (14:0). Saturates having 8 and 10 carbon atoms belong to the medium-chain group. An intermediate-length saturated fatty acid is lauric acid (12:0). Long-chain fatty acids are absorbed as triglycerides that are incorporated into chylomicrons. The medium-chain fatty acids are absorbed directly into the portal circulation as free fatty acids. Lauric acid in contrast seems to enter the circulation partly as a component of chylomicron triglycerides and partly as a free fatty acid.

Previously it was thought that medium-chain saturates do not raise cholesterol concentrations, and some researchers have suggested that lauric acid belongs in the medium-chain category. On the other hand, Keys et al (1) reported on the basis of limited data that lauric acid is just as hypercholesterolemic as are palmitic and myristic acids. Hegsted et al (2) in contrast claimed that lauric acid increases cholesterol concentrations much less than do the other long-chain fatty acids. If the latter is true, lauric acid might be increased in the diet as a substitute for the cholesterol-raising saturated fatty acids.

To resolve the uncertainly about the effects of lauric acid, we recently carried out a study in which lauric acid was incorporated into a synthetic fat (9). This fat was used to test the effects of lauric acid on cholesterol concentrations. Essentially the only fatty acids in this triglyceride preparation were lauric acid and oleic acid, which were present in about equal proportions. This lauric acid–enriched fat was compared with palm oil (which differed in composition only by having palmitic acid in the place of lauric acid). It also was compared with safflower oil, in which most of the fatty acids consisted of oleic acid. Palm oil markedly raised LDL-cholesterol concentrations compared with safflower oil, which is high in oleic acid; this confirms the hypercholesterolemic action of palmitic acid. At the same time, oil enriched in lauric acid also raised LDL-cholesterol concentrations compared with the unsaturated oil. However, the extent of the rise was less than that for palm oil. Lauric acid appeared to increase LDL concentrations only about two-thirds as much as did palmitic acid. Even so, lauric acid does raise LDL-cholesterol concentrations compared with oleic acid; for this reason, lauric acid must be listed as a cholesterol-raising fatty acid and, as such, is not a candidate to be a substitute for other long-chain fatty acids.

Medium-chain fatty acids

The effects of medium-chain fatty acids (8:0 and 10:0) on serum cholesterol concentrations surprisingly have not been determined with certainty. Ahrens et al (10) postulated that these fatty acids are markedly hypercholesterolemic. They argued that because butter is especially hypercholesterolemic compared with other saturate-rich fats and because butter fat is rich in medium-chain fatty acids, the medium-chain fatty acids must raise cholesterol concentrations. However, later investigations failed to demonstrate a hypercholesterolemic effect of these fatty acids (11, 12). Thus, most current investigators think that medium-chain fatty acids do not raise cholesterol concentrations; rather they are thought to have an action on cholesterol concentrations similar to that of carbohydrates. In our view, however, this question is not resolved. Better studies than those previously carried out are needed to define with certainty whether medium-chain fatty acids do or do not raise cholesterol concentrations.

Monounsaturated fatty acids

There are two types of monounsaturated fatty acids in the diet. The predominant form is 9-*cis* 18:1 (oleic acid). This fatty acid is found in both animal and vegetable products and it is the major fatty acid in the American diet. Oleic acid makes up ≈45% of total fatty acids. The other type consists of *trans* 18:1 fatty acids. *Trans* monounsaturated fatty acids are produced by hydrogenation of polyunsaturated oils. The most common *trans* 18:1 fatty acid is the ω9 form, elaidic acid. However, other *trans* unsaturated isomers are produced during hydrogenation of polyunsaturates. The effects of *cis* and *trans* monounsaturates on serum lipids must be considered separately.

Oleic acid

Available evidence indicates that most saturated fatty acids raise serum cholesterol concentrations relative to oleic acid (1, 2, 4, 5). As indicated before, oleic acid generally has been considered to be a neutral fatty acid, neither raising nor lowering cholesterol concentrations. In fact, this neutrality appears to extend to all of the lipoprotein fractions: VLDL, LDL, and HDL. For practical purposes, it is convenient to evoke the concept of the neutrality of oleic acid as a baseline with which to judge the responses of other nutrients (both fatty acids and carbohydrates). The fact that the body synthesizes a large quantity of oleic acid

suggests that it has a variety of biological advantages, and to this extent the concept of the neutrality of oleic acid can be extended to imply its safety. Indeed, in a variety of studies on the relative carcinogenicity of fatty acids or their ability to suppress the immune system, oleic acid emerges as one of the most benign fatty acids.

One reason why oleic acid may not raise serum LDL-cholesterol concentrations is because it is the favored substrate for acyl CoA: cholesterol acyltransferase (ACAT) in the liver. When the liver contains an excess of oleic acid, unesterified cholesterol appears to be readily esterified. The resulting decrease in amount of unesterified cholesterol in the liver cell may release the suppressive effects of the unesterified form on LDL-receptor synthesis (13). Whether this is the only mechanism whereby dietary oleic acid maintains a relatively low serum LDL-cholesterol concentration is not known. For example, enrichment of cell membranes with unsaturated fatty acids might enhance receptor uptake of LDL, or the synthesis of lipoproteins by the liver might be decreased. Although these latter mechanisms have not been ruled out, neither have they been proven. Further, the effect of high intakes of oleic acid to allow for normal LDL-receptor expression appears to be the major action of this fatty acid. Because dietary oleic acid does not lower serum VLDL concentrations relative to saturated fatty acids, it is unlikely that the synthesis of VLDL by the liver is curtailed with diets high in oleic acid. Finally, diets high in oleic acid have little if any HDL-lowering action compared with saturated fatty acids (3, 14).

Trans *monounsaturates*

Although for many years there has been uncertainty about the effects of *trans* monounsaturates on cholesterol concentrations in humans, recent data suggest that in contrast with oleic acid they are not neutral. In fact, dietary *trans* monounsaturates appear to raise LDL-cholesterol concentrations compared with oleic acid (15). In addition, they may have a mild HDL-lowering action (15). To what extent *trans* fatty acids raise LDL concentrations is uncertain because available data are limited. The rise may be less than that produced by palmitic acid. Nonetheless, *trans* monounsaturates now appear to be LDL-cholesterol-raising fatty acids. This fact probably will necessitate some rethinking of dietary recommendations in the future. Thus, not all monounsaturates can be lumped together as neutral fatty acids. *Cis* and *trans* fatty acids must be considered separately.

The mechanisms whereby *trans* fatty acids increase LDL concentrations, compared with oleic acid, have not been determined. Certainly the two fatty acids have a different steric configuration. The *cis* double bond in oleic acid makes it a flexible molecule. This accounts for the liquid state of high-oleic oils, such as olive oil. *Trans* monounsaturated fatty acids in contrast are more rigid molecules and oils high in *trans* fatty acids tend to be solids. Indeed there is a similarity in functional structure between *trans* monounsaturates and saturated fatty acids. The rigidity of both types of molecules may contribute to their LDL-raising properties. This property could be expressed at the level of ACAT in the liver. Perhaps *trans* unsaturates, like saturated fatty acids, are a poor substrate for ACAT. If so, both may inhibit cholesterol esterification in the liver. The resulting increase in unesterified cholesterol could suppress LDL-receptor activity, which in turn would raise serum LDL-cholesterol concentrations.

Polyunsaturated fatty acids

Polyunsaturated fatty acids belong to two categories. One type consists of $\omega 6$ fatty acids. The major fatty acid in this category is linoleic acid (18:2ω6). The other group includes the $\omega 3$ fatty acids. The primary $\omega 3$ fatty acid in plant products is linolenic acid (18:3ω3). In addition, fish oils are high in longer-chain $\omega 3$ fatty acids, notably eicosapentaenoic acid (EPA; 20:5ω3) and docosahexaenoic acid (DHA; 22:6ω3). EPA and DHA constitute 26% of the total fatty acids of fish oils.

Linoleic acid

For many years linoleic acid was thought to be the preferable fatty acid for the diet because it was considered to be the most effective cholesterol-lowering fatty acid. Early studies suggested that linoleic acid was more potent than oleic acid in lowering cholesterol concentrations when they were compared with saturated fatty acids (1, 2). This belief led to widespread promotion of vegetable oils high in linoleic acid for lowering cholesterol. As a result, over the past 30 y, intakes of linoleic acid have increased in the American diet because of increased consumption of vegetable oils. About 40 y ago, intakes averaged $\approx$4% of total energy; today, linoleic-acid uptake has increased to $\approx$7% of total energy.

Despite an increase in linoleic acid intake, there has been simultaneously a growing reservation about the wisdom of recommending an increased consumption of linoleic acid. One reason for this is that no large population has ever consumed large quantities of linoleic acid with proven long-term safety. In addition, in experimental animals, high intakes of linoleic acid promote chemical carcinogenesis (16, 17) and tend to suppress the immune system (18). In humans, high intakes of this fatty acid can lower HDL-cholesterol concentrations (3, 19–21) and may increase the risk for cholesterol gallstones (22, 23). Finally, the presence of linoleic acid in LDL lipids makes them more prone to oxidation, which could promote the development of atherosclerosis (24). Because of these potential detrimental effects, current recommendations have been moderated and now caution that intakes of linoleic acid should not exceed current concentrations, ie, $\approx$7% of total energy (25).

In addition, several studies (3, 14, 26, 27) indicate that linoleic acid has little if any cholesterol-lowering effect compared with oleic acid. This is particularly the case for LDL cholesterol (3, 24, 26). Because linoleic acid often lowers HDL cholesterol and VLDL cholesterol relative to oleic acid, the total cholesterol concentration declines somewhat more than with oleic acid. However, the difference, if any, is not substantial. A recent meta-analysis of all available metabolic studies (28) indicates that the difference in effect is considerably less than reported previously (1, 2). Thus, if linoleic acid produces a more favorable effect on the overall lipoprotein profile relative to oleic acid, this advantage does not appear to outweigh the potential adverse effects outlined above. This marginal benefit-to-risk ratio provides adequate reason not to raise linoleic acid intakes above current concentrations.

Omega-3 fatty acids

In recent years there has been a great interest in the possible benefits of fish-oil fatty acids, particularly EPA and DHA. Various claims have been made for the beneficial actions of fish oils, including improving the lipoprotein profile, preventing thrombosis, and retarding the development of atherosclerosis. The pri-

mary effect of ω3 fatty acids on plasma lipids is to lower VLDL-triglyceride concentrations (29, 30). This occurs through inhibiting secretion of VLDL triglycerides and not from increasing triglyceride lipolysis (31). Apart from inhibiting VLDL-triglyceride secretion, fish-oil fatty acids have few other effects on lipoprotein metabolism. In patients with elevated triglycerides, a lowering of triglyceride concentrations often results in an increase in LDL-cholesterol concentrations (32); the same is true with other triglyceride-lowering therapies. Omega-3 fatty acids do not have a unique LDL-cholesterol lowering action; however, when they are substituted for saturated fatty acids, LDL-cholesterol concentrations fall just as they do when other types of unsaturated fatty acids are substituted. Omega-3 fatty acids likewise do not have any unique actions on HDL metabolism.

Carbohydrates

Any discussion of effects of fatty acids on lipoprotein metabolism is not complete without a comparison with carbohydrates. For many years, carbohydrates have been said to be neutral with respect to cholesterol concentrations (1, 2). Generally, they have effects similar to those of oleic acid, which also is said to be neutral. In fact, the two nutrients do have similar effects on total cholesterol concentrations. In addition they affect LDL-cholesterol concentrations similarly (33–36), but here the similarity ends. Compared with dietary oleic acid, carbohydrates tend to raise VLDL-triglyceride concentrations and to lower HDL-cholesterol concentrations (33–36). Both of these changes are more striking when total fat intake falls below 30% of total energy, but in some patients these actions are manifest when total fat intake decreases from 40% to 30% of total energy. An important but unresolved question is as follows: What is the clinical significance of the triglyceride-raising and HDL-lowering actions of carbohydrates? Do these apparently adverse effects truly increase the risk for CHD? These questions have not been answered.

Stearic acid

The early studies of Ahrens et al (37), Keys et al (1), and Hegsted et al (2) suggested that stearic acid, in contrast with other saturated fatty acids, does not raise serum cholesterol concentrations. This finding was confirmed in investigations in our laboratory (5, 38). In particular, stearic acid does not raise LDL-cholesterol concentrations. Although one study (39) suggested a mild increase in LDL-cholesterol concentrations relative to linoleic acid, most of the available data suggest that stearic acid is neutral in its action on LDL-cholesterol concentrations. Stearic acid does not raise triglycerides and it is possible that it may have a very mild HDL-lowering effect (39), but this is uncertain (5, 38). For practical purposes it can be said that stearic acid is essentially neutral in its effects on lipoproteins, similar to oleic acid.

The reason why stearic acid does not raise LDL-cholesterol concentrations whereas other long-chain fatty acids do is not entirely clear. Although early investigations suggested that stearic acid is not well absorbed, recent investigations indicate that $> 90\%$ of the stearic acid normally available in the diet is absorbed (5). Another possible reason for lack of LDL lowering is that stearic acid is converted rapidly into oleic acid. Studies in laboratory animals (40, 41) and in humans (5) suggest that much of stearic acid is converted into oleic acid. This conversion appears to be relatively rapid; it requires only desaturation at the ω9 position. In contrast, palmitic acid, which raises LDL concentrations, must be elongated into stearic acid before being desaturated into oleic acid. This slower process may allow it to exert its LDL-raising action for a longer time period, and this would make it more active as a saturated fatty acid. Whether stearic acid is degraded more rapidly than palmitic acid is not known, but there is no good reason to believe that it is. In our view, a more rapid conversion to oleic acid is the most likely mechanism for stearic acid's lack of LDL-raising potential (5, 40, 41).

Some investigators have speculated that stearic acid may be particularly thrombogenic. If so, this could be one reason to limit its intake. Normally, free acids circulate in serum bound to albumin. If they come unbound from albumin, they can activate the coagulation system and promote thrombosis. Among the various fatty acids, the saturates, particularly stearic acid, bind less tightly to albumin than do saturated fatty acids. Thus, should high intakes of stearic acid lead to the presence of unbound fatty acids in the circulation, the result could be an increased risk for developing thrombosis. Studies in laboratory animals indicate that infusions of large quantities of unbound free fatty acids promote thrombogenesis, and among these, stearic acid is the most thrombogenic (42). Of course, this does not mean that ingestion of stearic acid leads to the presence of unbound stearic acid in the circulation. Thus, the possibility that dietary stearic acid increases the risk for thrombosis in humans has by no means been proven. Until more definitive evidence is obtained, this possible effect hardly justifies a general recommendation to restrict stearic acid intakes.

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