

## Monounsaturated Fatty Acids and Risk of Cardiovascular Disease

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This report summarizes our current understanding of how monounsaturated fatty acids (MUFAs) affect risk for cardiovascular disease (CVD). This is a topic that has attracted considerable scientific interest,<sup>1-3</sup> in large part because of uncertainty regarding whether MUFA or carbohydrate should be substituted for saturated fatty acids (SFAs) and the desirable quantity of MUFA to include in the diet.

### MUFAs in the US Diet

MUFAs are distinguished from the other fatty acid classes on the basis of having only 1 double bond. In contrast, polyunsaturated fatty acids (PUFAs) have 2 or more double bonds, and SFAs have none. The position of the hydrogen atoms around the double bond determines the geometric configuration of the MUFA and hence whether it is a *cis* or *trans* isomer. In a *cis* MUFA, the hydrogen atoms are present on the same side of the double bond, whereas in the *trans* configuration, they are on opposite sides. The American Heart Association Nutrition Committee recently published a scientific statement regarding the relationship of *trans* MUFA to CVD risk,<sup>4</sup> and the present statement, therefore, will be limited to a discussion of dietary *cis* MUFAs, of which oleic acid (*cis* C18:1) comprises ≈92% of *cis* MUFAs. In the United States, average total MUFA intake is 13% to 14% of total energy intake, an amount that is comparable to (or slightly greater than) SFA intake. In contrast, PUFAs contribute less (ie, 7% of energy).

The major emphasis of current dietary guidelines involves replacing SFAs with complex carbohydrates to achieve a total fat intake of ≤30% of calories. There is evidence suggesting that the substitution of MUFA instead of carbohydrate for SFA calories may favorably affect CVD risk.<sup>5-7</sup> The American Heart Association dietary guidelines for healthy American adults recommend a diet that provides <10% of calories from SFA, up to 10% from PUFA, and as much as 15% from MUFA.<sup>8</sup> The recommendation to limit total dietary fat to 30% of calories is intended to facilitate the reduction of SFA and to help control calories to manage weight. At this recommended level of dietary fat, several tablespoons of unsaturated fat can be incorporated in the diet. Depending on SFA and PUFA intake, a high-MUFA diet that provides 15% or more of energy results in a total fat intake >30% of energy. Nonetheless, a high-MUFA diet can be an alternative to the

presently recommended Step 1 diet (≤30% fat, 8% to 10% SFA, and <300 mg of cholesterol per day) to favorably affect CVD risk, provided it does not exceed SFA recommendations and energy needs.

### MUFA Versus Carbohydrate as a Replacement for SFA

The uniqueness of MUFA as a major nutrient in the Mediterranean region's food supply was first identified by Ancel Keys and his colleagues in the landmark Seven Countries Study.<sup>9</sup> Certain Mediterranean populations in that study (Corfu and Crete) had a low prevalence of coronary heart disease (CHD) and low plasma cholesterol levels despite consumption of a diet high in total fat (33% to 40% of calories) and low in SFA (7% to 8% of calories). The typical diet of populations living in Mediterranean countries (eg, Spain, Italy, and Greece) is high in olive oil, which provides 14% to 40% of calories,<sup>10-12</sup> and consequently is high in MUFA (16% to 29% of calories)<sup>9,11,13-16</sup> and oleic acid. Although the Mediterranean diet differs in many respects from the typical American diet, the prevailing view was that these diets protected against CHD because they were low in SFA. A recent study conducted in the United States reported that intake of both MUFA and PUFA was associated with reduced CVD risk. A regression analysis of data from the Nurses' Health Study of 80 082 women followed up for >14 years showed that intake of MUFA was protective against CHD.<sup>17</sup> The statistical model used demonstrated that compared with equivalent energy from dietary carbohydrate, a 5% increment in energy from MUFA resulted in a relative risk of 0.81 (95% confidence interval [CI] 0.65 to 1.00; *P*=0.05). A greater protective effect of PUFA also was reported (relative risk 0.62; 95% CI 0.46 to 0.85; *P*=0.003 for each 5% increment in energy from PUFA). In agreement with the evidence reported by Keys,<sup>9</sup> SFA was shown to increase risk of CHD (relative risk 1.17; 95% CI 0.97 to 1.41; *P*=0.10 for each 5% increment in energy from SFA), as did *trans* fatty acids (relative risk 1.93; 95% CI 1.43 to 2.61; *P*<0.001 for each 2% increment in energy intake from *trans* unsaturated fat). Other epidemiological studies<sup>18,19</sup> that have controlled for a number of potentially confounding variables also have reported protective effects of MUFA against CHD. In contrast, some studies<sup>20-23</sup> have not reported this association,

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perhaps because they did not control for confounding variables.

In the mid-1980s, investigators began to debate the question of the ideal substitute for SFA calories: carbohydrate or unsaturated fatty acids, specifically MUFAs under stable weight conditions. The results of 2 similar studies conducted by Grundy<sup>24</sup> and Mensink and Katan<sup>5</sup> reported a similar total cholesterol-lowering effect of both a high-fat diet ( $\approx 40\%$  of energy) rich in MUFA (24% to 28% of energy) and low in SFA (4% to 10% of energy) and a low-fat/carbohydrate-rich diet ( $\approx 20\%$  of energy from fat and  $\approx 7\%$  of energy from SFA). Although both diets lowered total and low-density lipoprotein (LDL) cholesterol, the high-MUFA diet did not lower high-density lipoprotein (HDL) cholesterol or increase triglycerides, as did the low-fat/carbohydrate-rich diet. The low-fat/carbohydrate-rich diet lowered HDL cholesterol by 14% to 22% and markedly elevated triglycerides (22% to 39%). Since these pioneering studies, a number of subsequent studies have reported similar results.<sup>6,25,26</sup> More recently, the DELTA (Dietary Effects on Lipoproteins and Thrombogenic Activity) Study reported that a Step 1 diet (29% of energy from fat, 8% from SFA, and 292 mg of cholesterol per day) and a high-MUFA diet low in SFA and cholesterol (36% of energy from fat, 21% from MUFA, 9% from SFA, and 293 mg of cholesterol per day) both lowered total and LDL cholesterol levels by 5.5% and 7%, respectively, compared with an average American diet (AAD) in subjects with a low HDL cholesterol level ( $<25$ th percentile), moderately elevated triglycerides ( $>70$ th percentile), or elevated insulin levels ( $>70$ th percentile).<sup>7</sup> Triglycerides increased by 12% and 7% on the Step 1 diet compared with the high-MUFA diet and the AAD, respectively. Interestingly, plasma triglycerides were lower on the high-MUFA diet (by 4%) than on the AAD. Although HDL cholesterol decreased on both blood cholesterol-lowering diets compared with the AAD, the decrease in HDL cholesterol was less on the high-MUFA diet (4.3%) than on the Step 1 diet (7.2%). Thus, HDL cholesterol levels are higher and triglycerides are lower on a high-MUFA than a low-fat/carbohydrate-rich, blood cholesterol-lowering diet.

### MUFA Versus PUFA: Effects on Lipids, Lipoproteins, and LDL Oxidative Susceptibility

Both Keys et al<sup>27</sup> and Hegsted et al<sup>28</sup> analyzed data from controlled feeding studies and developed similar blood cholesterol predictive equations. MUFA did not affect total cholesterol levels, but SFA raised them. PUFA lowered total cholesterol half as much as SFA raised it. More recent analyses confirmed these findings, although there is some suggestion that MUFAs elicit a cholesterol-lowering effect that is less than that observed for PUFAs.<sup>29,30</sup> In support of these findings, Howard et al<sup>31</sup> found greater reductions in total cholesterol levels with PUFAs versus MUFAs ( $P < 0.05$ ) in a controlled-feeding study. However, other controlled-feeding studies, as well as a study with free-living subjects, observed comparable total and LDL cholesterol-lowering effects of these fatty acids<sup>32–36</sup> when  $\approx 4\%$  to 14% of energy of each fatty acid class was substituted for the other. Like-

wise, in a meta-analysis of results of 14 studies published between 1983 and 1994, diets high in oils enriched in MUFA versus PUFA elicited similar effects on total, LDL, and HDL cholesterol, whereas the PUFA-enriched oil had a slight triglyceride-lowering effect.<sup>35</sup> On the basis of existing evidence that compared the relative cholesterolemic effects of MUFA versus PUFA, Grundy<sup>3</sup> concluded that for practical purposes, it seems to matter little which unsaturated fatty acid class replaces SFA in the diet. Thus, the cholesterolemic effects of MUFA versus PUFA substitution for dietary SFA are comparable.

In addition to the quantitative changes in LDL levels that affect the risk of CHD, qualitative changes can affect risk. Oxidized LDLs are readily taken up by monocyte-derived macrophages via scavenger receptors, a process that results in the formation of foam cells, which is an early event in the formation of the atherosclerotic plaque.<sup>37,38</sup> Oxidized LDLs are also cytotoxic and release molecules that are chemotactic for monocytes and T lymphocytes,<sup>39,40</sup> thereby contributing to atherogenesis. By virtue of the presence of double bonds, unsaturated fatty acids are particularly susceptible to oxidative modification, and the extent of this is increased as the degree of unsaturation (ie, number of double bonds) increases. Studies<sup>41–44</sup> have shown that enrichment of the diet with MUFA at the expense of PUFA led to LDLs that were less susceptible to oxidation, as determined by *in vitro* assays. It has not been established, however, whether *in vitro* oxidative susceptibility of LDL is related to atherogenesis or CHD risk.

### Role of MUFA in the Nutritional Management of Diabetes Mellitus

Diets high in carbohydrate (55% to 60% of energy) and low in SFA ( $<10\%$  of energy) and total fat ( $<30\%$  of energy) have been widely recommended as medical nutrition therapy for patients with non-insulin-dependent diabetes mellitus (NIDDM).<sup>45</sup> In recent years, however, studies have provided important new information about the potential beneficial effects for some patients of a diet that is higher in total fat (provided by MUFA) and low in SFA. These findings have resulted in the development of modified guidelines for the nutritional management of NIDDM.<sup>46,47</sup> These recommendations emphasize the importance of individualizing the diet prescription for total fat and, correspondingly, the quantity of dietary carbohydrate. Both the metabolic profile of the patient and a need to lose weight will determine the medical nutrition therapy prescribed (see below). The studies that have formed the basis for these treatment guidelines are discussed below.

Evidence from some studies<sup>48–56</sup> has indicated that a high-carbohydrate diet compared with a high-unsaturated-fat diet (ie, MUFA), both of which are low in SFA and cholesterol, can cause an increase in plasma triglyceride concentrations and a decrease in HDL cholesterol levels. A number of these early studies<sup>51,55,56</sup> were conducted in a metabolic ward setting in which experimental diets very high in total fat (ie, 50% of energy) were fed to participants. More recently, a randomized, crossover, multicenter study<sup>57</sup> was conducted with 42 outpatients with NIDDM who were instructed to follow a high-MUFA diet that provided 45% of

energy from fat and 40% of energy from carbohydrate and a high-carbohydrate diet that provided 55% of energy from carbohydrate and 30% of energy from total fat. Both diets were low in SFA (ie, 10% of energy), and fiber content was comparable. The high-carbohydrate diet increased the level of fasting plasma triglycerides and very-low-density lipoprotein (VLDL) cholesterol concentrations by 24% and 23%, respectively. In addition, plasma glucose and insulin values increased by 12% ( $P < 0.001$ ) and 9% ( $P = 0.02$ ), respectively. Thus, in some individuals, a high-MUFA diet results in a more favorable glycemic profile. Plasma total, LDL, and HDL cholesterol levels were similar on both diets, although HDL cholesterol was 4% lower ( $P = \text{NS}$ ) on the high-carbohydrate diet. On the other hand, studies<sup>50,58</sup> have shown that diabetic patients on high-carbohydrate diets may not have significant increases in triglycerides or glucose if the diets are high in fiber.

A high-MUFA diet can be used instead of a high-carbohydrate diet in patients with NIDDM who present with a distinct metabolic profile. NIDDM patients with hypertriglyceridemia who do not need to lose weight are candidates for a high-MUFA diet. Body weight was maintained in the studies described to control for the confounding effects of weight change. This result is important because weight loss and maintenance of an ideal body weight are associated with favorable effects on plasma triglyceride and HDL cholesterol levels,<sup>59</sup> as well as insulin sensitivity. Thus, calorie control is important for patients with NIDDM. Weight loss or weight maintenance can be achieved either on a high-MUFA or a high complex carbohydrate calorie-controlled diet. In practice, however, the diet prescription will depend on both the metabolic profile and the dietary preferences of the patient.<sup>46,47</sup> Presently, a diet high in MUFA ( $\approx 20\%$  of energy) and low in SFA ( $< 10\%$  of energy) is recommended for some individuals with elevated triglyceride and VLDL cholesterol levels,<sup>46,47</sup> as well as for those who experience HDL cholesterol lowering on a low-fat diet. For individuals who have normal lipid levels and who maintain a reasonable body weight, a Step 1 diet is recommended initially.<sup>46,47</sup> For overweight or obese individuals who need to lose weight, a decrease in dietary fat may be an effective way to reduce calories, and thus, a Step 1 diet is recommended.<sup>46,47</sup> Factors to consider include the dietary habits and preferences of the patient. For some, a high-MUFA diet is difficult to implement, whereas for others, a higher-fat, calorie-controlled diet may promote better dietary adherence and therefore achieve a more favorable weight-loss outcome.<sup>46,47</sup> Thus, diet therapy should be individualized for patients with diabetes mellitus, and close follow-up is advised.

### Effect of MUFA on Other CVD Risk Factors

Presently, there is interest in understanding the role of platelets and hemostatic factors in the development of thrombi leading to clinical manifestations. Changes in platelet function leading to aggregation, an increase in fibrin formation, and a decrease in fibrinolysis favor thrombosis. Limited data suggest that MUFAs may decrease platelet aggregation,<sup>60</sup> increase bleeding time,<sup>61</sup> and increase fibrinolysis,<sup>62</sup> thereby protecting against thrombogenesis. A recent epide-

miological study<sup>63</sup> of participants of the Framingham Heart Study suggested that the risk of ischemic stroke in men declined across increasing quintiles of MUFA (and SFA but not PUFA) intake. Additional studies are needed, however, to gain a better understanding on the effects of MUFA on blood-clotting tendency. Limited evidence suggests that a very-high-MUFA diet (30% of energy from MUFA) significantly decreases systolic ( $-6$  mm Hg) and diastolic ( $-6$  mm Hg) blood pressure in subjects with NIDDM.<sup>64</sup> Collectively, these findings suggest that high-MUFA diets may confer benefits on CVD risk factors beyond those associated with plasma lipids and lipoproteins.

Although there is a substantive body of evidence that has shown cardioprotective effects of diets high in MUFA, paradoxical results from experiments in monkeys show that a diet high in MUFA causes atherosclerosis equivalent to that observed in animals fed a diet high in SFA.<sup>65</sup> This effect appears to result from an increased secretion of cholesteryl oleate-enriched lipoproteins. These results, which are counter to the evidence that shows that MUFAs have beneficial effects, need to be further evaluated to determine whether they are relevant to humans. There is also evidence that a fat load provided by olive oil (versus fats high in either SFA or PUFA) increases the plasma levels of chylomicron remnants,<sup>66,67</sup> which are atherogenic lipoproteins.<sup>68</sup> On balance, however, the preponderance of evidence indicates that dietary MUFAs have favorable effects on CHD risk. Additional inquiry will clarify these disparate findings that are inconsistent with the present database for MUFA.

### High-MUFA Diets and Weight Control

Achievement of calorie control is implicit in the clinical value of a high-MUFA diet. In some instances, this means weight loss, whereas in others, weight maintenance is the goal. There is an ongoing debate concerning whether dietary fat affects obesity, with some researchers<sup>69</sup> contending that a decrease in energy from fat is associated with a reduction in weight; another view is that the relation between dietary fat and obesity is unconvincing or, at best, weak.<sup>70</sup> Controlled clinical trials of free-living subjects are needed to resolve this debate. Nonetheless, any dietary guidance given with regard to MUFA must also instruct that calorie control be achieved by balancing energy intake with regular physical activity to maintain a healthy weight or to lose weight, if needed.

### Planning High-MUFA Diets

Foods that are high in MUFA and low in SFA include certain fats and oils, nuts and nut butters, avocado, olives, sesame seeds, and tahini (Table). In high-MUFA diets, SFA calories are replaced with MUFA calories. The substitution of 9 g of SFA with 9 g of MUFA in a 1500-calorie AAD and 12 g of SFA with 12 g of MUFA in a 2200-calorie diet will increase MUFA from  $\approx 14\%$  to  $\approx 19\%$  of calories and will correspondingly decrease SFA from 13% to 8% of energy. Modest increases in food sources of MUFA that replace food sources of SFA are required to achieve this increase in MUFA.

### Summary

There is epidemiological evidence that dietary MUFAs have a beneficial effect on the risk of CHD. Moreover, evidence

**Fat Composition of Foods High in MUFA (1-oz Portion)**

	Calories	Total Fat, g	SFA, g	MUFA, g	PUFA, g
Vegetable oil					
Canola oil	248	28.0	2.0	16.4	8.2
Olive oil	238	27.0	3.6	20.0	2.2
High oleic (>70%) safflower oil	240	27.2	1.7	20.4	3.8
High oleic (>70%) oil/sunflower oil	248	28.0	2.8	23.4	1.1
Nuts and seeds*					
Mixed nuts	168	14.6	2.0	8.9	3.1
Almonds	166	14.6	1.4	9.5	3.1
Cashews	163	13.1	2.6	7.7	2.2
Hazelnuts	188	18.8	1.4	14.7	1.8
Macadamia nuts	199	20.9	3.1	16.5	0.4
Peanuts	166	14.1	2.0	7.0	4.4
Peanut butter (smooth), 2 Tbsp	190	16.3	3.3	7.8	4.4
Pistachios	172	15.0	1.9	10.1	2.3
Pecans	187	18.3	1.5	11.4	4.5
Sesame butter (tahini) from kernels, 2 Tbsp	169	15.2	2.1	5.8	6.7
Sesame seeds	160	13.9	2.0	5.2	6.1
Walnuts (English)	182	17.5	1.6	4.0	11.1
Walnuts (black)	172	16.0	1.0	3.6	10.6
Fruits					
Avocado, raw	45	4.3	0.7	2.7	0.5
Olives	32	3.0	0.4	2.2	0.3

\*All nuts and seeds are dry roasted.

Source: USDA Nutrient Database for Standard Reference. United States Department of Agriculture Web site. Available at: [http://www.nal.usda.gov/fnic/cgi-bin/nut\\_\\_search.pl](http://www.nal.usda.gov/fnic/cgi-bin/nut__search.pl). Accessed July 13, 1999.

from controlled clinical studies has shown that MUFAs favorably affect a number of risk factors for CHD, including plasma lipids and lipoproteins, factors related to thrombogenesis, in vitro LDL oxidative susceptibility (compared with PUFA), and insulin sensitivity. Compared with SFA, MUFAs lower total and LDL cholesterol levels, and relative to carbohydrate, they increase HDL cholesterol levels and decrease plasma triglyceride levels. Additional research is needed in humans and appropriate animal models to gain a better understanding of the effects of high-MUFA diets on atherogenesis. A diet high in MUFA (versus a high-carbohydrate diet) improves glycemic control in individuals with NIDDM who maintain body weight. Individuals with elevated triglycerides or insulin levels also may benefit from a high-MUFA diet.

A diet that provides as many as 15% of calories from MUFA,  $\approx$ 7% from PUFA, and  $\approx$ 8% from SFA maintains the total fat content of the diet at 30% of calories. This Step 1 diet meets the American Heart Association dietary guidelines for Americans.<sup>8</sup> Diets that are higher in MUFA can be used to manage CVD risk provided they do not exceed the SFA recommendation and compromise weight control. Although a high-MUFA diet that exceeds 30% of calories from fat is not a Step 1 or Step 2 diet because it does not meet the criteria for total fat content, it nonetheless is another viable option for managing risk factors in the prevention and treatment of CHD.

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