Dietary *cis*-monounsaturated fatty acids and metabolic control in type 2 diabetes[1–4]

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ABSTRACT Whether low-fat, high-carbohydrate (CHO) diets or moderately high-fat, high–monounsaturated fatty acid (MUFA) diets are preferable for the treatment and prevention of diabetes has been a matter of debate. High-fat diets based on MUFA-rich oils or whole foods have been compared with high-CHO diets for effects on several cardiovascular risk outcomes in diabetic subjects. Early studies using metabolic diets with wide differences in total fat content (15–25% of energy) generally found a beneficial effect of MUFA diets on glycemic control and serum lipids. Recent studies using prescribed diets with a difference of ≤15% of energy in total fat between low-fat and high-MUFA diets show similar effects on glycemic profiles but still favor MUFA diets for effects on triacylglycerols and HDL cholesterol. It is unclear whether postprandial fat clearance is impaired by CHO diets and improved by MUFA diets, independent of effects on fasting triacylglycerol concentrations. Unless one diet contains abundant antioxidants, the 2 dietary approaches appear to have similar effects on LDL oxidation. Low-fat diets, however, are associated with atherogenic, dense LDL particles, while normal, buoyant LDL predominate with high-fat diets irrespective of fatty acid composition. Limited experimental evidence suggests that MUFA diets favorably influence blood pressure, coagulation, endothelial activation, inflammation, and thermogenic capacity. Energy-controlled high-MUFA diets do not promote weight gain and are more acceptable than low-fat diets for weight loss in obese subjects. Thus, there is good scientific support for MUFA diets as an alternative to low-fat diets for medical nutrition therapy in diabetes. *Am J Clin Nutr* 2003;78(suppl):617S–25S.

KEY WORDS Diabetes, MUFA, olive oil, Mediterranean diet, glycemic control, blood lipids

INTRODUCTION

Lifestyle changes, particularly the modification of dietary habits and physical activity, are the cornerstone of the prevention and treatment of diabetes (1–5). Traditionally, nutrition advice for the treatment of obesity, diabetes, and other cardiovascular risk factors emphasized avoiding animal fat and, preferably, all kinds of dietary fat, and replacing them with carbohydrate (CHO) (6). The central arguments against the consumption of animal fats in particular and of fatty foods in general have been a high content of cholesterol-raising saturated fatty acid (SFA) and excess energy, thought to promote obesity, respectively. In fact, lowering the content of SFA in the diet remains a primary goal of nutrition therapy for health maintenance. *Cis*-monounsaturated fatty acids (MUFA) were considered to be neutral regarding serum cholesterol levels (7), a reason why no specific recommendations about MUFA-rich foods were usually made. However, scientific evidence has accumulated in the past 2 decades about the beneficial role of diets with a relatively high MUFA content on a number of cardiovascular risk outcomes, including diabetes (8). Which, then, is the better nutrient to replace energy sources from SFA in the diet, CHO or MUFA?

There has been a heated debate on whether low-fat, high-CHO diets or moderately low-CHO, high-MUFA diets are preferable for the treatment and prevention of obesity, diabetes, and insulin resistance syndromes (9–13). Nonetheless, in the mid-1990s (14) the American Diabetes Association (ADA) nutrition recommendations shifted the focus from the previous tight limits on energy intake and macronutrient composition (the traditional high-CHO diet with fat ≤30% of energy and ≤10% of energy for the major classes of fatty acids) (6) to a more flexible one that emphasized effects of nutrition therapy on metabolic control and allowed the consumption of more energy from fat in the form of MUFA. In fact, the ADA recommended dividing 60–70% of energy between CHO and MUFA depending on nutritional assessment, desired outcomes, and individual preferences (4, 14).

The principal goals of medical nutrition therapy for diabetic subjects are to attain and maintain optimal metabolic control, including blood glucose, lipid profiles, and blood pressure; to prevent and treat obesity and cardiovascular complications; and to improve general health and well-being through food choices that consider personal and cultural preferences. This paper critically reviews the role of dietary MUFA in reaching such goals. The literature comparing the 2 approaches of low-fat, high-CHO and high-MUFA diets in patients with diabetes was reviewed up to

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TABLE 1
Composition of foods high in MUFA[1]

	Energy	Fat	SFA	MUFA	PUFA
	MJ	*g*	*g*	*g*	*g*
Vegetable oils					
High-oleic-acid sunflower oil, 100 g	3.7	100	9.7	83.6	3.8
High-oleic-acid safflower oil, 100 g	3.7	100	6.2	74.6	14.4
Olive oil, 100 g	3.7	100	13.5	73.7	8.4
Canola oil, 100 g	3.7	100	7.1	58.9	29.6
Nuts					
Macadamia nuts, 100 g	3.0	75.8	12.1	58.9	1.5
Hazelnuts, 100 g	2.6	60.7	4.5	45.7	7.9
Pecans, 100 g	2.9	72.0	6.2	40.8	21.6
Almonds, 100 g	2.4	50.6	3.9	32.2	12.2
Cashews, 100 g	2.4	46.4	9.2	27.3	7.8
Peanuts, 100 g	2.4	49.2	6.8	24.4	15.6
Pistachios, 100 g	2.3	44.4	5.4	23.3	13.4
Fruit					
Avocado, 100 g	0.7	15.3	2.4	9.6	2.0
Olives, 100 g	0.5	10.7	1.4	7.9	0.9
Selected animal products					
Ground beef, regular, 100 g	1.3	26.6	10.8	11.6	1.1
Fried eggs, 2 pieces	0.8	15.0	4.2	6.0	2.8
Regular butter, 25 g	0.8	20.2	12.6	5.9	0.8
Fried bacon, 3 slices	0.5	9.4	3.3	4.5	1.1

[1] Compositional data taken from reference 17. MUFA, monounsaturated fatty acid; SFA, saturated fatty acid; PUFA, polyunsaturated fatty acid.

1996 in the comprehensive meta-analysis of Garg (15). The present review thus is based principally on scientific evidence from the more recent literature and, besides the main outcomes of medical nutrition therapy in diabetes as defined above, considers the effects of CHO and MUFA diets on surrogate cardiovascular risk markers, namely postprandial lipemia, LDL subclasses, LDL oxidation, and endothelial dysfunction. These atherogenic alterations are closely interrelated and cluster in individuals with visceral obesity and associated insulin resistance or frank diabetes (16).

For the purpose of this review, diets compared in feeding trials are designated as high- or low-CHO or MUFA irrespective of the total energy derived from each macronutrient. For the sake of simplicity, only between-diet differences in total fat as a percentage of energy are shown because in the studies reviewed the added or subtracted energy in any given diet is accounted for almost entirely by MUFA, unless otherwise noted.

DIETARY SOURCES OF *CIS*-MONOUNSATURATED FATTY ACIDS

With rare exceptions, oleic acid (*cis* C18:1n−9) comprises more than 90% of MUFA in MUFA-containing foods. As seen in **Table 1** (17), vegetable oils, obtained from either natural or genetically modified oilseed crops, are the richest sources of MUFA, followed by nuts (and spread fats or oils derived from them), and all of these fatty foods have a low SFA content. Two important concepts regarding high-MUFA foods need to be considered for both a correct interpretation of epidemiologic and intervention studies and the design of high-MUFA diets.

The first notion is that many natural or processed animal products are also relevant sources of dietary MUFA (Table 1). This might explain why intakes of MUFA were highly correlated with intakes of SFA in 2 large cohorts of US women in whom MUFA consumption was unrelated to diabetes incidence but polyunsaturated fatty acid (PUFA) intake was shown to have a protective effect (18, 19). Historically, US populations have consumed substantial amounts of PUFA-rich vegetable fats and small amounts of MUFA-rich oils, so a putative protective effect of MUFA from vegetable sources on the development of diabetes would be difficult to detect in US cohorts with baseline nutritional assessments made in the 1980s. No similar studies have been carried out in Mediterranean populations, characterized by a high consumption of MUFA in the form of olive oil and by low intakes of PUFA-rich vegetable fats.

The second concept is that most MUFA-rich foods of vegetable origin contain variable amounts of antioxidant micronutrients and phytochemicals, which may beneficially influence atherogenesis beyond their fatty acid composition. Thus, virgin olive oil, which is obtained directly from pressing ripe olives, retains all the lipophilic components of the fruit, small amounts of α-tocopherol, and sizable amounts of phenolic compounds with strong antioxidant properties, while refined olive oil loses most antioxidants during the refining process (20). Accordingly, refined olive oil was shown to be less efficient than the virgin variety for increasing the resistance of LDL to oxidative stress, both in vitro (21) and ex vivo (22). There is also evidence that heating olive oil at frying temperature in air may destroy phenolic compounds (23). Both MUFA-rich oils from modified seed crops and nuts contain α-tocopherol and phytosterols. Nuts are rich in phenolic compounds as well (24), although they might variably lose them when peeled or roasted. Thus, these foods have the potential to affect cardiovascular outcomes independent of their MUFA content, and it is important to know in which form (virgin or refined olive oil, heated or unheated oils, raw or roasted nuts) they are given in feeding trials or counseled to be consumed in clinical practice.

GLYCEMIC CONTROL

The concern with high-CHO diets for diabetes has been that, in the face of a resistance to insulin-mediated glucose disposal, they prompt additional insulin secretion to maintain glucose homeostasis, furthering insulin resistance and, if β-cell reserve has been exceeded, worsening glycemic control (11). Because diets high in SFA consistently impair both blood lipids (7) and insulin sensitivity (25), and because Western populations do not naturally consume diets with PUFA >15% of energy, MUFA is the ideal fatty acid to enrich the diet when reducing the proportion of CHO. Indeed, high-MUFA diets have been tried since the late 1980s as an alternative to high-CHO diets for diabetic subjects (15).

Garg's meta-analysis of 10 randomized crossover trials comparing isoenergetic high-MUFA and high-CHO diets in patients with type 2 diabetes concluded that consumption of high-MUFA diets improved fasting and postprandial blood glucose and 24-h glucose and insulin profiles while having no effect on fasting insulin and glycated hemoglobin concentrations or insulin sensitivity (15). It should be noted that most of the feeding trials in this meta-analysis used metabolic diets and that in all of them there were wide, unrealistic differences in total fat content between the 2 experimental diets, ranging from 15% to 25% of energy. Since the publication of Garg's review (15), the results of 5 randomized crossover feeding trials comparing the effects of the 2 dietary

TABLE 2
Recent crossover feeding trials comparing the effects of natural diets rich in carbohydrate (CHO) and rich in monounsaturated fatty acid (MUFA) on glycemic control and/or lipoprotein profiles in free-living subjects with and without type 2 diabetes[1]

Study	Time on each diet	Difference in fat content between diets	Source of MUFA in the MUFA diet	MUFA diet compared with CHO diet				
				Glycemic control	Percentage changes in fasting lipids			
					LDL-C	HDL-C	TAG	VLDL-C
	wk	*% of energy*						
Luscombe et al (26; $n = 21$)[2,3]	4	14 (high GI)	Canola fats, almonds	Similar	−3	5[4]	−2	—
		12 (low GI)		Similar	−4	0	20	—
Rodríguez-Villar et al (27; $n = 12$)[3]	6	11	Virgin olive oil	Similar	3	2	−9	−32
Rodríguez-Villar et al (28; $n = 22$)[3]	6	12	Virgin olive oil	Similar	−4	−3	1	−35[4]
Thomsen et al (29; $n = 16$)[5]	4	14	Virgin olive oil	Similar (IS)	4	7[4]	9	—
Pérez-Jiménez et al (30; $n = 59$)[6]	6	10	Olive oil	Similar (IS)	−1	4	−1	—
Kris-Etherton et al (31; $n = 20$)[6,7]	4	9	Olive oil	—	−1	3	−22[4]	—
		9	Peanut oil	—	4	2	−20[4]	—
		11	Peanuts, peanut butter	—	1	2	−22[4]	—

[1] LDL-C, LDL cholesterol; HDL-C, HDL cholesterol; TAG, triacylglycerol; VLDL-C, VLDL cholesterol; GI, glycemic index; IS, insulin sensitivity.
[2] MUFA diet was compared with 2 CHO diets.
[3] Patients with type 2 diabetes.
[4] $P < 0.05$ compared with the CHO diet.
[5] Healthy relatives of patients with type 2 diabetes.
[6] Healthy subjects.
[7] Three MUFA diets were compared with one CHO diet.

approaches on glycemic control in diabetic patients (26–28) and on insulin sensitivity in subjects at high risk of diabetes (29) or healthy individuals (30) have been reported. These studies differ from those analyzed by Garg (15) in some important aspects: they were performed on an outpatient basis with natural foods and mostly prescribed diets, olive oil was the main source of MUFA, and the difference in total fat content between diets was < 15% of daily energy (26–31; **Table 2**).

In the study of Luscombe et al (26), 2 low-fat diets (21% and 23% energy from fat) and a high-MUFA diet (35% energy from fat) provided similar glycemic control, as assessed by fasting glucose and insulin levels, glycated hemoglobin, and 24-h urinary glucose outputs. Similarly, Rodríguez-Villar et al (27) reported no differences in glycated hemoglobin or in fasting and 6-h postprandial glucose and insulin profiles after a diet with 29% energy from fat and a high-MUFA diet (40% energy from fat). Another study from the same group (28) showed similar glycemic control in a larger cohort of diabetic patients prescribed a CHO diet and a diet high in MUFA. No differences in insulin sensitivity were found in healthy relatives of patients with diabetes (29) and in healthy young subjects (30) after a high-CHO diet and a high-MUFA diet.

Recently, Vessby et al (32) performed a parallel-arm feeding trial in 162 healthy subjects who were given diets with 37% energy from fat, either a high-SFA diet (17% SFA, 14% MUFA) or a high-MUFA diet (8% SFA, 23% MUFA). Insulin sensitivity was impaired on the SFA diet but did not change on the MUFA diet, except for subjects whose relative intake of total fat was above the median of 37% energy.

Taken together, these results suggest that, provided the intake of SFA is low, a MUFA diet with a total fat content of up to 40% of energy has effects on glycemic control that are similar to those of the traditional high-CHO diet with fat limited to 25–30% of energy. Thus, the 2 dietary approaches are useful for the prevention and treatment of diabetes.

LIPID AND LIPOPROTEIN PROFILES

Another concern about substituting CHO for fat in the diet is that it may induce an elevation of serum triacylglycerol (TAG) concentration, which is associated with putative atherogenic lipid alterations, including a reduced HDL cholesterol level, exaggerated postprandial lipemia, and small, dense LDL particles that are prone to oxidation (11). Subjects with obesity, insulin resistance, or fasting hypertriacylglycerolemia are overtly sensitive to the TAG-rising effect of high-CHO diets, which may be averted in part by a gradual introduction of CHO into the diet or by a high dietary fiber intake (33). Many feeding trials examining the lipid effects of diets with varying CHO and fat content have been conducted in diabetic individuals, who often share all 3 CHO-sensitivity phenotypes. Only more recent randomized crossover studies in which MUFA and CHO diets were exchanged for effects on lipid outcomes will be discussed.

Fasting lipids and lipoproteins

Garg's meta-analysis of 10 studies (15) showed that the net changes in fasting plasma concentrations of TAG, VLDL cholesterol (reported in 4 studies), HDL cholesterol, and LDL cholesterol (reported in 6 studies) with consumption of a high-MUFA diet were a 19% reduction, a 22.5% reduction, a 4% increase, and a 0% change, respectively. The feeding trials comparing the effects on glucose metabolism of high-CHO versus high-MUFA whole-food diets in outpatients with diabetes (26–28) or healthy subjects (29, 30) that were published thereafter also reported effects on fasting lipoproteins (Table 2). In none of these studies were between-diet differences in serum LDL cholesterol or TAG concentrations observed. The MUFA diet was associated with a substantial reduction of VLDL cholesterol in 1 study (28) and with modest increases in HDL cholesterol in 2 studies (26, 29; Table 2).

Although performed in healthy subjects, a well-designed study by Kris-Etherton et al (31) is illustrative of both the assortment of MUFA-rich foods that can be incorporated into a healthy diet and

TABLE 3
Crossover feeding trials comparing the effects of natural diets rich in carbohydrate (CHO) and rich in monounsaturated fatty acid (MUFA) on postprandial triacylglycerol profiles in subjects with type 2 diabetes

				MUFA diet compared with CHO diet	
Study	Time on each diet	Difference in fat content between diets	Source of MUFA in the MUFA diet	Change in the area under the curve of postprandial triacylglycerols	*P*
	wk	*% of energy*		*%*	
Rodríguez-Villar et al (27; $n = 12$)	6	11	Virgin olive oil	−13[1]	0.099
Campbell et al (39; $n = 10$)	2	14	Assorted nuts	−5[1]	>0.2
Chen et al (40; $n = 9$)	6	15	Not reported	−25	<0.001

[1] Adjusted for fasting triacylglycerol concentrations.

the beneficial effect of MUFA diets on serum TAG when substituted for CHO (Table 2). These investigators compared the average American diet (34% energy from fat, 16% SFA) with 4 cholesterol-lowering diets: the National Cholesterol Education Program (NCEP) Step II diet (25% energy from fat) and 3 different MUFA diets (34–36% energy from fat, 17–21% MUFA). The 4 diets had a similar cholesterol-lowering effect but, compared with those in the average American diet, TAG concentrations were 11% higher with the Step II diet and were 13% lower with the MUFA diets. The HDL cholesterol level was preserved with the high-MUFA regimes, while it was 4% lower with the Step II diet (31). In comparison with low-fat diets, modest TAG reductions and/or HDL cholesterol increases have been observed as well after consumption of diets containing MUFA-rich nuts, such as macadamia nuts (34) and pecans (35). Thus, both in diabetic and in healthy subjects, natural food-based MUFA regimes may be preferable to a low-fat diet because of more favorable effects on TAG-rich lipoproteins and HDL cholesterol, with an attendant decrease of the cardiovascular risk profile. Increasing evidence of the potential for genetic variation among individuals to influence the biological responses to dietary intervention may eventually help to tailor certain diets to those who might benefit most from them (36). As an example, Erkkilä et al (37) recently showed a positive association between dietary sucrose (6–7% of energy) and plasma TAG among patients with coronary heart disease carrying the ε*2* allele of apolipoprotein E, suggesting that they are more vulnerable to the TAG-rising effect of CHO than those carrying the ε*3* or ε*4* alleles.

Postprandial lipemia

Postprandial lipemia, defined by the extent and duration of the rise in plasma TAG after a fatty meal, is a state during which the TAG metabolic capacity is under challenge. Many studies have supported the concept that circulating TAG-rich lipoproteins after meals are significant contributors to the development of atherosclerosis, and this is particularly relevant to the increased cardiovascular risk of individuals with diabetes (38). Because diabetic dyslipidemia is characterized by hypertriacylglycerolemia and this abnormality may be exacerbated by high-CHO diets, interest has also been kindled for studies assessing the magnitude of postprandial lipemia with low-fat diets versus high-MUFA diets in subjects with diabetes. Three studies with a crossover design but with low statistical power have assessed the magnitude of postprandial lipemia after isoenergetic low-fat diets or high-MUFA diets in diabetic subjects (**Table 3**).

Using prescribed CHO and MUFA diets, Rodríguez-Villar et al (27) observed a nonsignificant decrease of the 6-h postprandial TAG profile with the MUFA diet. In the study of Campbell et al (39), 6-h TAG profiles were similar after prescribed CHO and MUFA diets. Chen et al (40) used in-hospital diets high in CHO and high in MUFA and found lower 24-h TAG profiles after the MUFA diet. However, postprandial lipid data were not adjusted for fasting values, which were lower with the MUFA diet.

In a crossover study with metabolic diets in 17 type 1 diabetic subjects, a high-MUFA diet (40% energy from fat) had no effect on fasting TAG but impaired postprandial lipemia when compared with a high-CHO diet (25% energy from fat) (41). On the other hand, using diets with a 20% energy difference in fat and CHO content, Jeppesen et al (42) showed that a high-CHO diet, but not a high-fat diet, magnified postprandial lipemia in healthy women.

Because the magnitude of postprandial TAG increases is directly related to fasting TAG concentrations (38), it is unclear from these studies whether high-MUFA diets are superior to high-CHO diets in improving postprandial lipoprotein metabolism independent of effects on fasting TAG. However, chylomicrons formed after olive oil feeding appear to enter the circulation more rapidly, and to be cleared at a faster rate, than those formed after intake of fats rich in SFA (43, 44) or rich in PUFA, such as safflower oil (44). Accelerated chylomicron metabolism would actually make olive oil less atherogenic even if the overall magnitude of postprandial lipemia was similar to that elicited by other fatty meals.

LDL subfraction profile and oxidation

One of the untoward consequences of a prolonged residence time of TAG-rich lipoproteins in the circulation is enhanced lipid exchange between lipoprotein classes, leading to cholesterol depletion of LDL. These lipoprotein particles (small, dense LDL, as opposed to large, buoyant LDL) are prone to oxidation and enter the arterial wall more readily than larger particles, accelerating the development of atherosclerosis. Indeed, subjects with diabetes or other insulin-resistant states generally have both a predominance of small, dense LDL and lipoproteins that are more susceptible to oxidation (11, 16, 38).

In studies using isoenergetic diets with a varying proportion of CHO and reciprocal changes in the proportion of fat at a fixed MUFA content, a strong linear correlation was observed between decreased fat/increased CHO intakes and prevalence of small, dense LDL in healthy men (45). This is supported by the results of a study in obese women that compared 2 hypocaloric diets, a high-CHO diet (25% energy from fat) and a high-MUFA diet

TABLE 4
Crossover feeding trials comparing the effects of natural diets rich in carbohydrate (CHO) and rich in monounsaturated fatty acid (MUFA) on the resistance of LDL to an in vitro oxidative challenge in free-living subjects with and without type 2 diabetes

Study	Time on each diet	Difference in fat content between diets	Source of MUFA in the MUFA diet	Lag time of conjugated diene formation during LDL oxidation ex vivo (min)[1]		
				CHO diet	MUFA diet	*P*
	wk	*% of energy*				
Rodríguez-Villar et al (27; $n = 22$)[2]	6	12	Virgin olive oil	36	36	>0.2
Gumbiner et al (48; $n = 17$)[2,3]	6	60	High-oleic sunflower oil	152	220	<0.05
Berry et al (49; $n = 17$)[4]	12	12	Olive oil, almonds	11.8[5]	16.1[5]	<0.05
Castro et al (50; $n = 21$)[4,6]	4	10	Olive oil	69	72	>0.2
		10	High-oleic sunflower oil	69	86	<0.001
Hargrove et al (51; $n = 20$)[4,7]	4	9	Olive oil	66	66	>0.2
		9	Peanut oil	66	63	≤0.1
		11	Peanuts, peanut butter	66	66	>0.2

[1] Lag time refers to the time required to initiate formation of conjugated dienes in LDL submitted to an in vitro oxidative challenge, a measurement that reflects the particles' resistance to oxidation. Results depend on assay conditions and are not comparable among different studies.
[2] Patients with type 2 diabetes.
[3] The study had a parallel design and employed formula diets.
[4] Healthy subjects.
[5] Measured as thiobarbituric acid–reactive substances (nmol malondialdehyde/mg LDL protein) in LDL conditioned by incubation with Cu^{++}.
[6] In the study, 2 MUFA diets were compared with a CHO diet.
[7] In the study, 3 MUFA diets were compared with a CHO diet.

(45% energy from fat) based on olive oil, and showed a decrease of the dense LDL fraction in the MUFA group (46). However, in the study of Luscombe et al (26) with diabetic subjects, no differences in LDL size were observed with diets varying in fat content up to 14%.

The inherent susceptibility of LDL to oxidation depends principally on its content of both PUFA, the primary substrate of lipid oxidation, and antioxidants, chiefly vitamin E (47). Many clinical studies have shown that LDL enriched with MUFA of dietary origin is more resistant to an in vitro oxidative challenge than LDL enriched with dietary PUFA (47). Surprisingly, few formal feeding trials have examined the effects of high-CHO versus high-MUFA diets on LDL oxidizability in subjects with or without diabetes (**Table 4**).

In a recent study, Rodriguez-Villar et al (28) found a similar lag time in LDL isolated from well-controlled diabetic subjects after CHO and MUFA diets with a 12% difference in daily energy from fat. On the other hand, using hypocaloric diets with wide differences in fat content, Gumbiner at al (48) found that the LDL particles of obese diabetic subjects were less susceptible to oxidation after a MUFA diet than after a CHO diet. Three studies assessed LDL oxidation in small groups of healthy, free-living individuals who were prescribed natural diets high in CHO and high in MUFA, with ≤12% difference in fat content between diets (49–51). Compared with the CHO diets, the MUFA diets either reduced the susceptibility of LDL to oxidation or had no effect (Table 4). However, an antioxidant effect of α-tocopherol in MUFA-rich foods, such as almonds (49) and high-oleic-acid sunflower oil (50), might have contributed to the increased resistance of LDL to oxidation.

Again, the evidence does not favor high-MUFA diets over high-CHO diets to decrease the susceptibility of LDL to oxidation. Because dietary antioxidants might act synergistically with changes in LDL fatty acids to affect the particles' resistance to oxidation (47), the unknown antioxidant content of the diets is an inherent limitation in the design of even the best-controlled dietary studies with an outcome of LDL oxidation. MUFA-rich oils and nuts contain antioxidant vitamins and phytochemicals (20, 24), but so do many vegetable foods (52), the portions of which are obligatorily reduced when lowering the CHO content of the diet to accommodate more MUFA. For that matter, when dealing with diets rich in low-fat vegetables compared with diets enriched with unsaturated fatty acids from vegetable sources, not only may it be impossible to separate the effects of antioxidants and fatty acids on the susceptibility of LDL to oxidation, but it is most likely irrelevant because both diets are good sources of antioxidants. At any rate, the relevance of LDL oxidizability assessed ex vivo by means of a strong oxidative challenge to atherogenic events taking place in the circulation is still far from clear.

Endothelial dysfunction

Endothelial dysfunction is thought to both precede and accelerate atherosclerosis (53). Accumulating evidence suggests that endothelial dysfunction caused by oxidized lipoproteins may be the link between postprandial lipemia and atherosclerosis (54), and these interrelated events occur frequently in diabetes (55). Furthermore, a close relationship of impaired endothelium-dependent vasodilatation with small, dense LDL has been suggested in diabetes (56, 57). Meal composition is important, because postprandial endothelial dysfunction is aggravated by its content in oxidized fat (ie, thermally stressed PUFA-rich oils) and is attenuated by antioxidant vitamins (58, 59).

If delayed removal of TAG-rich lipoproteins from the circulation induces endothelial dysfunction, this could be improved by maneuvers that reduce serum TAG concentrations. No studies comparing the effects of CHO and MUFA diets on vascular reactivity have been performed in diabetic subjects. Nevertheless, 3 studies illustrate the effects on endothelial function of dietary patterns that include olive oil (60–62). Fuentes et al (60) performed a crossover study in 22 hypercholesterolemic men on a baseline diet high in SFA who were given an NCEP step I diet (28% energy from fat) and an olive oil–rich MUFA diet (38% energy from fat). Both test diets improved endothelial function, but only the increase induced by the MUFA diet was significant. Ryan et al (61) showed that an olive oil diet attenuated the endothelial dys-

function present during consumption of a baseline diet high in PUFA. Finally, Vogel et al (62) showed that a meal with vegetables and olive oil, but not olive oil alone, attenuated the postprandial endothelial dysfunction that follows a fatty meal, implying that improved vascular reactivity was due to antioxidants in vegetables. On the other hand, single fatty meals both rich in MUFA from high-oleic-acid sunflower oil (63) and rich in SFA (64) impaired postprandial endothelial function in comparison with single high-CHO meals. This effect was attenuated in one study by high doses of vitamins E and C in the same meals (64).

Two small feeding trials in healthy subjects (29, 65) assessed changes in fasting concentrations of soluble markers of endothelial function after a high-MUFA diet and a high-CHO diet, with conflicting results: no change in one study (29) and improvement after the MUFA diet in another study (65). Studies of both fasting and postprandial vascular reactivity that are carefully controlled for antioxidant intake are necessary before any meaningful conclusion can be reached on the advantage of meals or diets rich in MUFA over those rich in CHO.

Other antiatherogenic effects

More recent though limited evidence has been presented for a beneficial effect of MUFA on a number of outcomes related to cardiovascular risk, including blood pressure, coagulation factors, endothelial activation, inflammation, and thermogenic capacity (43, 66–76). Most studies have been carried out in experimental models, healthy individuals, or patients with hypertension rather than diabetic subjects.

A small crossover study of a MUFA diet and a PUFA diet in hypertensive patients found significantly lower systolic and diastolic blood pressure and a reduced need for antihypertensive drugs at the end of the MUFA period (66). However, as reviewed by Hermansen (67), the role of MUFA in blood pressure control in normotensive and hypertensive subjects with or without diabetes is uncertain.

The common association of hypertriacylglycerolemia and a prothrombotic status via elevated plasma fibrinogen, factor VII activity, and plasminogen activator inhibitor concentrations suggests that dietary interventions effective for lowering TAG concentrations could have a beneficial effect on coagulation. Indeed, large reductions in TAG through energy restriction and weight loss are accompanied by improved hemostatic variables, but the body weight changes do not allow conclusions to be drawn about an independent effect of TAG lowering (68). Because the coexistence of high TAG and increased factor VII activity is particularly prominent during postprandial lipemia (68), it is noteworthy that healthy subjects following MUFA diets show blunted postprandial factor VII activation in response to a fatty meal by comparison with diets based on fats rich in SFA (43, 69) or PUFA-rich oils (70).

Studies in healthy subjects suggest that diets based on olive oil, as opposed to diets rich in SFA or PUFA, have beneficial effects on atherogenic factors linked to inflammation of the vascular wall, such as monocyte chemotaxis and adhesion to endothelial cells, and expression of adhesion molecules (71–73). In this regard, it is interesting that treatment of endothelial cells with oleic acid protected them against cytokine-induced adhesion molecule overexpression (74). The recent observation that oleic acid exposure of human umbilical vein endothelial cell cultures either had no effect or reduced the expression of the nuclear transcription factor κB and that of other inflammatory genes, as opposed to the stimulatory effect of exposure to PUFA (75), provides a new and conceptually attractive aspect of the putative antiatherogenic effects of MUFA at the molecular level. In a related study, Rodríguez et al (76) recently demonstrated upregulation of uncoupling protein genes—that is, enhanced mitochondrial fatty acid oxidation and thermogenesis—by olive oil feeding in rat adipose tissue and skeletal muscle. This is important, as increased heat production by specific fatty acids provides a mechanism to improve energy balance by decreasing the efficiency of fat deposition, thus targeting the core of the problem in obesity and diabetes.

ENERGY BALANCE

Body fatness is probably the principal modifiable risk factor for the development of diabetes (77). Traditionally, hypocaloric diets intended for weight loss are high in CHO and low in fat. A common perception is that dietary fat of any kind is fattening, while low-fat diets have slimming properties. Thus, in spite of the accumulating evidence of the cardiovascular health benefits of diets high in MUFA, nutrition experts are still reluctant to recommend them as an alternative to low-fat diets (9, 10, 13). However, as reviewed (78, 79), there is no evidence of weight gain with high-fat compared with high-CHO diets under isoenergetic conditions.

This concept is supported by the results of parallel-design studies that compared high-CHO and high-MUFA energy-restricted diets in obese subjects with (80) or without diabetes (46, 81, 82) for outcomes of weight loss and metabolic control. These studies included various sources of MUFA (oleic acid–rich oils and fats, peanuts, and tree nuts) in the high-fat diet groups, with between-diet differences in fat content ranging from 15% to 27% of energy (46, 80–82). All 4 studies showed that it was energy restriction, not diet composition, that determined weight loss, which was similar with the 2 dietary approaches. The study of McManus et al (82) showed superior long-term participation and adherence, with consequent improvements in weight loss, in the high-fat (35% of energy) group than in the low-fat (20% of energy) one. This was due to the higher palatability of a diet containing daily portions of products that are not traditional "diet foods," such as olive oil, peanuts, peanut butter, and mixed nuts (82).

Two meta-analyses (83, 84) compiled data on body weight from randomized, controlled studies that compared ad libitum energy diets high in either total fat or CHO on a number of health outcomes in nonobese, nondiabetic subjects. The results favor low-fat diets for weight maintenance in normal-weight individuals or weight loss in the overweight, but a reduction of SFA, not MUFA intake, was the major component of the CHO-for-fat exchange in the studies reviewed (83, 84). However, the long-term outcome of ad libitum reduced-fat diets for weight control is dismal (85), supporting the notion that attaining a permanent change in eating habits related to obesity is a most difficult task (86). Studies comparing high-MUFA diets and high-CHO diets with ad libitum energy intake are needed to evaluate their efficacy in weight reduction and maintenance of weight loss.

CONCLUSIONS

The main goals of medical nutrition therapy in patients with diabetes are to attain and maintain optimal metabolic control and to prevent and treat cardiovascular risk factors and complications while improving overall health. The traditional approach, reducing fat intake to ≤ 30% of energy, has documented health benefits, but

the constraints of prevailing Western dietary habits make it a difficult goal even for type 1 diabetics, usually a motivated lot (87). As reviewed, there is substantial evidence that in patients with diabetes, diets with a relatively high fat content based on MUFA-rich foods provide a degree of metabolic control that is similar or even better than that obtained with high-CHO diets. There is also limited evidence for a wide spectrum of antiatherosclerotic effects of MUFA diets. Inasmuch as isoenergetic high-MUFA diets and high-CHO diets have similar effects on energy balance, the reasoning behind the much expressed concern of potential weight gain with a fat intake > 30% of energy is no longer scientifically sound. An added advantage of a high-MUFA diet is palatability, so that this approach to medical nutrition therapy may be viewed as unique and enjoyable, thus potentially aiding in compliance, which is so often problematic with low-fat diets.

Present nutritional epidemiology emphasizes the dietary pattern approach to provide practical guidance for nutrition intervention and education at the population level (88, 89). The so-called prudent dietary pattern, characterized by a high intake of vegetables, legumes, fruit, and whole grains and a low intake of red meat, processed meat, high-fat dairy products, and refined grains, is increasingly favored for a beneficial effect on a number of health outcomes (88, 89), including diabetes treatment and prevention (1–4). The prudent diet does not necessarily have to be a low-fat one, because a variety of vegetable foods rich in MUFA that are good sources of antioxidants, such as high-oleic acid oils and nuts (Table 1), can be incorporated into this dietary pattern to increase palatability and compliance, with a good chance of furthering health benefits (90, 91).

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