The Role of Nutritional Modifications in the Prevention of Macrovascular Complications of Diabetes

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A wide range of dietary changes is likely to reduce the risk of macrovascular complications of diabetes. It is critically important to recommend a balance of macronutrients different from that currently consumed in most Western countries. Saturated fatty acids, especially myristic and palmitic acids, and *trans* fatty acids must be reduced to lower LDL cholesterol. Intake of polyunsaturated fatty acids should not be excessive (less than 10% total energy). Fiber-rich carbohydrate, derived from cereals, vegetables, and fruit with intact cell walls, and *cis* monounsaturated fatty acids should provide the bulk of total energy. These changes are likely to be associated with the most favorable lipoprotein profile and increase intake of dietary antioxidants and so reduce the level of oxidative stress. A reduction of sodium to below 6 g per day will help to reduce blood pressure levels. Optimal glycemic control has not yet been proved to reduce the risk of macrovascular complications, though this is a desirable goal for many other reasons. Ensuring appropriate energy balance (so that BMI is within the desirable range), using low glycemic index foods, and appropriately balancing carbohydrate intake with hypoglycemic drug therapy provide the best nutritional means of achieving satisfactory blood glucose levels. Successful implementation of nutritional recommendations requires the availability of dietitians capable of translating appropriate nutrition into appropriate foods acceptable to people with diabetes and their families. Clear food labeling and the availability of appropriate manufactured foods will further help patients with diabetes to achieve the dietary recommendations. *Diabetes* 46 (Suppl. 2):S125–S130, 1997

Dietary modification and increased physical activity are widely accepted as important aspects of the management of diabetes. However, while all health professionals pay lip service to this aspect of treatment, many remain skeptical about the value of some potential lifestyle modifications. Few would question the need to balance intake of carbohydrate-containing foods with injected insulin and that patients who are overweight or obese should be encouraged to reduce their energy intake. Increased physical activity, altered balance of macronutrients, reduced intake of sodium, use of low glycemic index foods, and increased intake of antioxidant nutrients are recommendations that are often given less attention. Lack of convincing evidence for clinical benefit and the belief that patients will not accept the advice are the most frequently quoted reasons for reduced emphasis on these treatment options. This review summarizes the evidence for benefit of these treatments in reducing the risk of macrovascular complications of diabetes and considers some practical aspects associated with their implementation.

ENERGY BALANCE

Advice to reduce caloric intake and increase energy expenditure is the cornerstone of all recommendations for people with diabetes whose BMI is greater than 25 kg/m^2, especially when excess body fat is centrally distributed (1,2). A wide range of disturbances associated with obesity and increased risk of cardiovascular disease (hypertension, hyperglycemia, dyslipidemia, hyperinsulinemia, insulin insensitivity) improve with weight reduction, but for those who are unable to lose weight, it should be noted that caloric restriction per se is a significant factor in producing these beneficial effects (3). Few data are available to prove that calorie restriction, weight reduction, and increased physical activity can favorably influence clinical events. However, Lean et al. (4) have generated prospective data that suggest that among overweight patients with NIDDM, weight loss over the 1st year from diagnosis is associated with some restoration of life expectancy. On average, each 1 kg of weight loss was associated with 3–4 months increased survival, so that a 10-kg weight loss in an obese person would result in restoration of about one-third of the expected loss in life expectancy. Moy et al. (5) have shown that among those with IDDM, regular physical activity (energy output greater than 2,000 kcal/week) appeared to be associated with a reduction in total mortality as well as diabetes complications. As classic randomized controlled clinical trials cannot be undertaken, it would be helpful to collect further longitudinal observations in an attempt to confirm these findings.

The enormous increase in the prevalence of obesity in the general populations of many countries and the association with reduced levels of energy expenditure (6) emphasize the difficulties involved in achieving the goal of weight reduction in overweight diabetic patients. They also emphasize the need to include advice to increase energy expenditure in attempts to treat and prevent overweight and obesity. While some weight loss programs have been unsuccessful in their

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CHD, coronary heart disease; VLCD, very-low-calorie diet.

attempts to achieve long-term weight reduction, it is clear that others that include both dietary advice and behavioral treatment programs do produce reduction in weight, which might be expected to profoundly influence life expectancy (4,7). The use of very-low-calorie diets (VLCDs) may be associated with rapid improvement in metabolic measurements in NIDDM patients, but long-term benefits have not been established (7). While further research to develop successful approaches to long-term weight reduction should be encouraged, major success is unlikely without population measures aimed at reducing obesity in the population at large.

BALANCE OF MACRONUTRIENTS

The balance of macronutrients that is widely recommended for people with diabetes (Table 1) differs appreciably from that usually consumed by those with diabetes in most European countries and other countries where a Western diet is typically eaten (Fig. 1) (1,8). Indeed, it would appear that at present, nutrient intake resembles that of the general population rather than the recommendations. The key component of the recommendations is the reduction in saturated fatty acids (1,2). This is justified by the high rates of coronary heart disease (CHD) among those with diabetes and the association between saturated fatty acids and total and LDL cholesterol (9). Although it is now clear (principally from research in nondiabetic individuals) that some saturated fatty acids (myristic and palmitic acids) have a more marked elevating effect on total and LDL cholesterol than do others (stearic and lauric acids) and *trans* unsaturated fatty acids (produced during the process of hydrogenation of unsaturated fats) may have a particularly adverse effect on lipids and lipoproteins (10–13), more specific recommendations are not possible because of the lack of detailed information about these nutrients in commonly eaten foods. *Trans* fatty acids are associated with an increase in LDL cholesterol, a decrease in HDL cholesterol, and possibly an increase in lipoprotein(a). Research is underway to determine the effects in people with diabetes, but for the present foods rich in these fat sources should be reduced as much as possible.

There has been a certain amount of controversy regarding the most appropriate nutrients that should be recommended to substitute for the reduction in saturated fatty acids. Under certain circumstances, high-carbohydrate diets may be associated with hypertriglyceridemia and reduced levels of HDL cholesterol, clearly an undesirable state of affairs since this alteration in lipids might further increase cardiovascular risk, especially in patients with NIDDM. High intakes of polyunsaturated fatty acids could similarly have an adverse effect on HDL cholesterol levels, although some increase from current relatively low levels would be expected to facilitate the desired reduction in LDL cholesterol. *Cis* monounsaturated fatty acids appear to be associated with a particularly favorable lipoprotein profile and may have additional benefits in terms of reducing oxidizability of LDL cholesterol (14–16). The major disadvantage of substantially increasing any fat source is that weight loss, an essential goal for many people with diabetes, is made more difficult. There is now fairly convincing evidence for the benefits of recommending a high-carbohydrate, high fiber diet to those needing to lose weight (17), and it is clear that provided the carbohydrate foods eaten are rich in soluble fiber or have a low glycemic index, there is no deleterious effect on lipids and lipoproteins (16). In view of these various observations, the current recommendations seem to provide an excellent compromise with regard to replacement energy for saturated fat: within a wide range of protein intakes (10–20% total energy) and a maximum recommended

TABLE 1
Key aspects of the 1995 European recommendations (modified from Ref. 1)

Dietary energy and body weight	Achieve and/or maintain BMI 19–25 kg/m^2 Diet and exercise important
Components of dietary energy	Saturated fatty acids: <10% total energy n-6 polyunsaturated fatty acids: <10% total energy Protein: 10–20% total energy Carbohydrate and *cis* monounsaturated fatty acids: the remainder
Carbohydrate issues	Low glycemic index foods and those rich in soluble fiber recommended Vegetables, fruits, legumes, and cereal-derived foods preferred Sucrose <10% total energy acceptable in certain circumstances Timing of intake essential for those on insulin
Protein and renal disease	Total protein intake at lower end of normal range (0.7–0.9 g · kg^{-1} · day^{-1}) for those with incipient or established nephropathy
Vitamins and antioxidant nutrients	Increase foods rich in tocopherols, carotenoids, vitamin C, and flavenoids (i.e., a wide range of vegetables and fruits), but supplements not recommended
Minerals	Sodium intake less than 6 g/day Magnesium supplementation may be required in special circumstances
Alcohol	An amount equivalent to 1–2 glasses of wine per day is acceptable for most people with diabetes Special precautions apply to those on insulin or sulfonylureas, those who are overweight, and those with hypertriglyceridemia
Special "diabetic" or "dietetic" foods	Nonalcoholic beverages sweetened with nonnutritive sweeteners are useful Other special foods not encouraged No particular merit of fructose and other "special" nutritive sweeteners over sucrose
Families	Most recommendations suitable for whole family

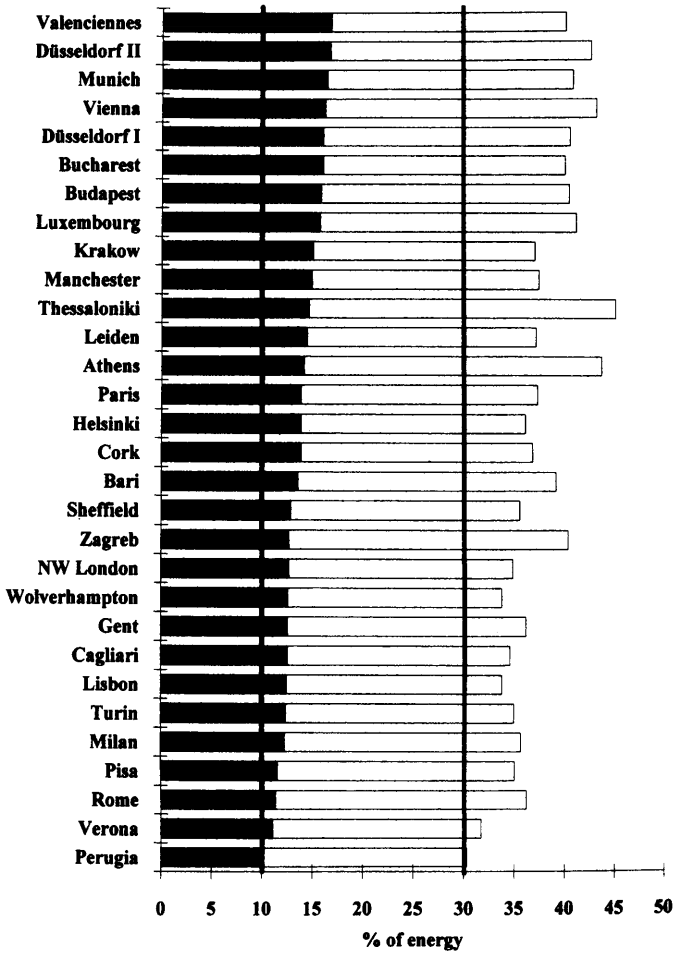

FIG. 1. Intake of total fat (■□) and saturated fatty acids (■) in 2,868 IDDM patients from 30 different European centers. Fat intake calculated from 3-day records. From Toeller et al. (8).

intake of saturated fatty acids and *cis* polyunsaturated fatty acids (no more than 10% each), the bulk of dietary energy should come from a combination of carbohydrates and *cis* monounsaturated fatty acids. There is now evidence to suggest that carbohydrate foods with an intact food structure may be particularly beneficial and, at least in part, explain the benefits previously attributed to soluble fiber or low glycemic index foods (18); and these are especially recommended. Such recommendations will inevitably mean that dietary cholesterol levels are low, and advice concerning precise quantities is usually not necessary. Specific recommendations (to reduce cholesterol intake to below 300 g per day) are offered for those with raised levels of LDL cholesterol. Increased intakes of fish are recommended to facilitate the reduction in saturated fatty acids and because epidemiological studies suggest that fish consumption may reduce cardiovascular risk (19), but insufficient evidence precludes precise recommendations regarding the optimal proportions of n-3 to n-6 polyunsaturated fatty acids. Dietary supplements derived from fish oils are not recommended.

It is conceded that recommendations concerning the balance of nutrients (at least as far as prevention of complications is concerned) were principally based on epidemiological associations and short-term dietary intervention studies (often continuing for 3 months or less) in people with diabetes. It is therefore necessary to consider whether dietary interventions have long-term benefits on risk factors and whether there is any convincing evidence that such changes are likely to be translated into clinical benefit. It must be appreciated that there are no trials in which dietary modifications have been related to morbidity and mortality in people with diabetes. It is therefore necessary to examine data from nondiabetic individuals. On the basis of data from men screened in the Multiple Risk Factor Intervention Trial, Yudkin (20) has argued that modifying the three major risk factors for cardiovascular disease (dyslipidemia, hypertension, and smoking) would do little to rectify the loss of life expectancy of around 10 years for a middle-aged diabetic man. He suggests that several new risk factors for cardiovascular disease—elevated plasminogen activator inhibitor, raised levels of proinsulin-like molecules, and microalbuminuria—could explain much of the excess risk of CHD in diabetes and that fetal and infant growth retardation (along the lines of the Barker hypothesis [21]) might be the underlying cause of the traditional as well as the new cardiovascular risk factors. By implication, ensuring adequate maternal nutrition rather than modifying risk factors later in life provides the key to reducing cardiovascular risk in diabetic and nondiabetic individuals alike. The epidemiological associations between maternal undernutrition and cardiovascular risks are strong, and more recently there has been confirmation from experimental studies. However, the extent to which this factor explains cardiovascular disease in diabetes and the general population is quite unclear. Furthermore, there is evidence to suggest that the gloomy prognostications of Yudkin concerning risk modification in later life are not entirely justified.

Yudkin's computations are based on the 8-year follow-up of the Multiple Risk Factor Intervention Trial participants with an average age of 45 years. It is more appropriate to seek direct evidence from intervention studies. Particularly relevant information comes from the Scandinavian trial, which involved a comparison of Simvastatin and a placebo in patients with established cardiovascular disease (the 4S Study [22,23]). Although the number of diabetic patients involved in the study was relatively small, it is clear from the data in Table 2 that the appreciable beneficial effect in terms of cardiovascular risk and mortality observed in the study population as a whole is also apparent in people with diabetes. Thus, one might expect that cholesterol lowering, however it is achieved, will produce a benefit proportional to the amount of cholesterol lowering that is achieved. In light of this observation, it is of interest to examine the results of the dietary intervention studies in which various dietary manipulations have been used to produce cholesterol lowering. Several meta-analyses have attempted to aggregate the results of the clinical trials, the most comprehensive being that published recently by Truswell (24). From his analysis (Table 3), it is clear that when considering the most satisfactory trials, a reasonable reduction in cholesterol was associated with an appreciable (30%) reduction in cardiovascular risk and mortality and with a smaller but statistically significant reduction in total mortality. Of course, it is possible that diets designed to lower cholesterol levels may also reduce the risk of CHD by other means (e.g., reduced tendency to thrombosis). It is noteworthy, however, that the reduction in CHD risk

TABLE 2
Effect of cholesterol lowering by Simvastatin on mortality in the 4S Study

	Total study group				Diabetic subjects		
	No. of subjects						
	Placebo	Simvastatin	Odds ratio	95% CIs	Placebo	Simvastatin	Odds ratio
n	2,223	2,221	—	—	—	—	—
Total mortality	256	182	0.70	0.58–0.85	24	15	0.56
CHD mortality	189	111	0.58	0.45–0.73	17	12	0.64
Noncardiovascular mortality	49	48	—	—	—	—	—

Data for the group as a whole is contrasted with the findings among patients with diabetes.

appears to be related to the extent of cholesterol lowering achieved. Comparable trials in patients with diabetes are unlikely to be undertaken, but in the light of the 4S Study, these data provide a strong endorsement for dietary recommendations aimed at reducing total and LDL cholesterol.

In view of the potential pathogenetic role of hyperlipidemia in diabetic nephropathy, the results of a recently published study by Lam et al. (25) are also of considerable interest. Lam et al. studied the effects of cholesterol lowering on progression of nephropathy by comparing groups of patients randomly allocated to treatment with the HMG-CoA reductase inhibitor Lovastatin or placebo. Over a 2-year period, the group treated with Lovastatin showed highly significant reductions in total and LDL cholesterol in association with a retardation of progression of nephropathy as evidenced by halting of deterioration of glomerular filtration rate and serum creatinine levels. By contrast, the placebo group showed deterioration in glomerular filtration rate and an increase in serum creatinine. There is no evidence at present to indicate whether additional clinical benefit is likely to accrue should dietary manipulations favorably influence levels of triglyceride and HDL cholesterol.

In light of these observations, it is necessary to consider whether it is possible to achieve long-term cholesterol lowering in people with diabetes. As far as I am aware, only one study has examined this question, and the data are being prepared for publication. We followed patients with diabetes in a study started in the early 1970s to compare the effects of the then-widely-used low-carbohydrate diet (which was relatively high in total and saturated fat) and a high-carbohydrate, modified-fat diet in which saturated fatty acids were appreciably reduced. Total and LDL cholesterol were appreciably lower throughout the follow-up period in those randomized to the modified-fat regimen compared with those following the low-carbohydrate diet. Unfortunately, the number of subjects included in the study was insufficient to establish differences between the two groups with regard to clinical events, though the observed differences in cholesterol would have been expected to produce an appreciable reduction in CHD among those randomized to the modified-fat regime. A more recent study has attempted to determine whether different ways of substituting for energy lost by reducing saturated fat can influence lipids and lipoproteins over a prolonged period (26). The results show that over an 18-month period, there is no lasting difference in lipid and lipoprotein levels between those recommended a high-carbohydrate, high-soluble-fiber diet (relatively low in total fat) and those advised to increase mono- and polyunsaturated fatty acids to replace saturated fatty acids. These data provide strong confirmation of the central importance of recommending a reduction of saturated fat. While the nature of the replacement energy seems to be relevant in short-term, carefully controlled metabolic experiments, this issue appears to be of less relevance in the clinical setting. Considerations other than effects on lipids and lipoproteins may be relevant. For those who are overweight, reducing total fat and energy-dense carbohydrate foods may be particularly relevant. Introducing an element of individual choice may aid compliance, though in this regard it may be important to emphasize to patients that reduction of saturated fat is advised to the reduce CHD risk that is substantially increased in diabetes. Failure to appreciate this fact may account for the reduced degree of compliance to lipid modifying dietary advice in people with diabetes as compared with those with hypercholesterolemia.

Some other recommendations have been made with regard to macronutrients. For those with incipient (as identified by the presence of persistent microalbuminuria) or established nephropathy, protein intake should be at the lower end of the acceptable range of intakes (between 0.7 and 0.9 g/kg body wt/day) since there is some evidence that progression of nephropathy can be delayed (27). A relatively limited amount of information is available, and more research would be helpful. In particular, it should be noted that there are no studies in NIDDM. In those with no evidence of renal disease, a wide range of intakes (10–20% total energy) is regarded as acceptable (1). While moderate intakes of sucrose (<10% total energy) are regarded as acceptable, provided that sucrose and sucrose-containing foods are eaten at meal times and considered within the overall diet prescription (28), it should be noted that in many European populations obesity is a major problem and under these circumstances as much restriction as possible is of considerable importance.

TABLE 3
Odds ratio relating to the effects of cholesterol lowering on total mortality and mortality from CHD in the major dietary trials

	Total no. of participants	All deaths	CHD mortality
All trials	92,623	0.94	0.87
Appreciable cholesterol reduction	7,994	0.89	0.70

Data are shown separately for all trials and for those trials that achieved appreciable cholesterol reduction.

VITAMINS AND ANTIOXIDANT NUTRIENTS

There is no doubt that in diabetes oxidant stress is increased, at least in part, because of generation of oxygen free radicals during protein glycation and glucose oxidation (29). Furthermore, antioxidant defenses such as vitamin C may be reduced in diabetes. These phenomena may be responsible for enhanced oxidation of LDL and in particular the small dense LDL particles that are characteristically observed in NIDDM and have an increased susceptibility to oxidative modification. Oxidized LDL has many biological properties that might promote atherogenesis, including stimulation of adhesion on monocytes to endothelial cells, monocyte chemotaxis, cytotoxicity, uptake of scavenger receptors that results in the formation of macrophage-derived foam cells, and modulation of growth factor and cytokine gene expression. There is evidence from prospective epidemiological studies in nondiabetic individuals that vitamin E (particularly when derived from supplements) is associated with a protective effect against CHD (30). The evidence concerning other antioxidants is less convincing. There is remarkably little information concerning the effects of dietary antioxidants on susceptibility of LDL to oxidation, but a recent study has shown that in NIDDM patients receiving 1,600 IU/day of vitamin E as a supplement, LDL and LDL subfractions become enriched with vitamin E. This is associated with decreased susceptibility of LDL to oxidation in comparison with placebo. Interestingly, the small dense LDL particles, despite a greater percentage increase in vitamin E, remained substantially more susceptible to oxidation than did buoyant LDL (31). The potential for antioxidant nutrients in foods and supplements to influence macrovascular risk is a topic of intense research at present. While these early results appear to be encouraging, the European Association for the Study of Diabetes (EASD) Nutrition Study Group thought that it was too early for specific recommendations beyond suggesting that foods naturally rich in all dietary antioxidants (tocopherols, carotenoids, vitamin C, and possibly flavonoids) should be encouraged (1).

MINERALS

The most important issue regarding intake of minerals concerns dietary sodium. Meta-analyses of the various studies examining the effects of sodium intake and blood pressure suggest that restriction of sodium could have a far more profound effect on blood pressure lowering and consequently on reducing cardiovascular and cerebrovascular risk than had previously been suspected (32). Few studies, however, have been undertaken in people with diabetes. The available data suggest that the effect in them is no different from that in nondiabetic individuals (33). Thus, it would appear that far more emphasis should be given to this aspect of dietary advice than has previously been the case. Current advice is that all people with diabetes should maintain their sodium intake below 6 g/day (1). More marked reductions should be considered in those whose blood pressure shows any degree of persistent elevation. A major problem with regard to the implementation of such advice is that in many countries, a large proportion of dietary sodium is derived from manufactured foods rather than from home cooking or from that added at the table. Thus, national policies and appropriate food labeling provide the best chance of achieving this goal.

OTHER NUTRITIONAL ISSUES

Little has been said thus far about lifestyle measures specifically aimed at helping to achieve optimal glycemic control. While it has not yet been established with certainty that achieving a state of near-normoglycemia will help to reduce cardiovascular risk, there is no longer any doubt that microvascular complications, most especially retinopathy, as well as nephropathy, are reduced in association with improved glycemic control (34). Measures aimed at achieving optimal body weight and the appropriate balance between hypoglycemic therapy, especially insulin, and carbohydrate-containing foods are undoubtedly the best established lifestyle approaches to optimizing glycemic control (1). However, encouraging foods that have an intact structure, are rich in soluble fiber (nonstarch polysaccharide), or have a low glycemic index may further facilitate an overall reduction in blood glucose levels as well as minimize unacceptable fluctuations in levels (35).

In conclusion, it might be noted that a number of conditions are essential for the successful implementation of these dietary recommendations. First, it is necessary that physicians and other health care providers convince their patients that nutrition and lifestyle treatments are as important as any other aspects of treatment. To be able to convince patients, it is clearly necessary for health care providers themselves to be convinced. This is often not the case. Second, it is essential to have the support of a dietitian or nutritionist who is trained to facilitate major lifestyle changes. Physicians usually do not have the necessary training. Finally, it should be emphasized that the nutritional principles that will reduce the risk of macrovascular complications of diabetes are appropriate for the population at large in countries with high CHD rates. Full compliance by people with diabetes will be greatly facilitated by measures that encourage the general population to make lifestyle changes. Widespread availability of appropriate foods at reasonable prices, easily understood nutritional labeling of food, and changes in national patterns of physical activity are of particular importance.

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