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Management of the Metabolic Syndrome and Type 2 Diabetes Through Lifestyle Modification

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Abstract

Sustainable lifestyle modifications in diet and physical activity are the initial, and often the primary, component in the management of diabetes and the metabolic syndrome. An energy-prudent diet, coupled with moderate levels of physical activity, favorably affects several parameters of the metabolic syndrome and delays the onset of diabetic complications. Weight loss, albeit not an absolute prerequisite for improvement, is a major determinant and maximizes effectiveness. Adopting a healthy lifestyle pattern requires a series of long-term behavioral changes, but evidence to date indicates low long-term adherence to diet and physical activity recommendations. This calls for greater research and public health efforts focusing on strategies to facilitate behavior modification.

Keywords

insulin resistance; metabolic syndrome; diabetes; lifestyle modification; diet; exercise; adherence

Introduction

The prevalence of conditions associated with insulin resistance, including the metabolic syndrome and type 2 diabetes, has been increasing over the past few decades. This is mainly due to the increasing prevalence of obesity across all age groups and ethnicities and in both sexes (141). Although pharmacological interventions are available for minimizing or delaying the co-morbidities associated with insulin resistance and the metabolic syndrome, as well as diabetes (103, 120, 196, 214), initial management for the vast majority of the affected population remains focused on lifestyle modification, consisting of sustainable changes in dietary habits and physical activity (25). In this review, we evaluate the existing literature on the effectiveness of lifestyle modification in the management of the metabolic syndrome and type 2 diabetes and discuss the feasibility of incorporating these changes in subjects' everyday routine.

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Metabolic Syndrome

The metabolic syndrome (also known as syndrome X or the insulin resistance syndrome) is a clinical entity characterized by a constellation of metabolically related abnormalities and cardiovascular risk factors, including obesity, insulin resistance/glucose intolerance, dyslipidemia, and hypertension. Based on U.S. adult population data from 1988–1994 and 1999–2000, the age-adjusted prevalence of the metabolic syndrome increased from 24.1% to 27.0% among male and female participants aged ≥20 years, i.e., a relative increase of 12% (72). The metabolic syndrome is associated with a two- to fourfold increase in cardiovascular morbidity and stroke (124). Its increasing prevalence over the past several decades parallels the alarming rise in obesity and increased prevalence of type 2 diabetes. Thus, it is now believed that these conditions are intimately linked via common underlying pathophysiological mechanisms (78, 175).

Despite some controversy surrounding the exact definition of the metabolic syndrome, most established definitions incorporate central (abdominal) obesity, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, hypertension, and elevated fasting glucose concentrations (Table 1). Gerald Reaven was the first to describe the metabolic syndrome or syndrome X in 1988, proposing insulin resistance as the critical underlying factor predisposing patients to hypertension, hyperlipidemia, and type 2 diabetes mellitus (180). Ten years later, the World Health Organization formulated working guidelines for the metabolic syndrome, based on the key feature of insulin resistance (4). Other scientific bodies that have proposed their own set of criteria for diagnosis of the metabolic syndrome (Table 1) include the European Group for the Study of Insulin Resistance (19); the National Cholesterol Education Program, Adult Treatment Panel III (150); the International Diabetes Federation (3); the American Heart Association and the National Heart, Lung, and Blood Institute (85); the American Association of Clinical Endocrinologists and the American College of Endocrinology (65); and the investigators of the Quebec Cardiovascular Study (53). It is conceivable that different criteria for diagnosing the metabolic syndrome, even though concordant for the most part (~90%), may lead to different prevalence rates (39, 41, 71). This discordance may also be responsible for the different estimations of cardiovascular risk and to disagreement on the priority of intervention goals, or differences in the response to the interventions undertaken.

The metabolic syndrome has yet to be ideally defined, because an ideal definition would need to serve the complex needs of both clinicians and researchers (53). In the clinical setting, the goal is to improve the ability of healthcare practitioners to identify individuals at high risk of developing type 2 diabetes and cardiovascular disease. Therefore, the criteria ought to be disseminated via a simple-to-use, accessible, and low-cost diagnostic tool. In research, the goals vary depending on the scientific field. In the context of clinical research, whether studying physiology, lifestyle, or pharmacological interventions to prevent or treat the metabolic syndrome, the definition and methods used should be as detailed and as accurate as possible. Alternatively, epidemiologists require a marker that is easy to detect and that closely tracks the changes in the prevalence of the metabolic syndrome and its relationship with obesity, type 2 diabetes, and cardiovascular disease; thus, the definition

must be simple enough to allow for large numbers of subjects to be investigated at a reasonable cost.

Diet and Exercise as Therapeutic Approaches

The main concern with regard to the metabolic syndrome is the development of diabetes and the associated cardiovascular risk. The National Cholesterol Education Program has recommended that reducing cardiovascular risk should focus on lowering low-density lipoprotein (LDL) cholesterol, as multiple clinical trials have demonstrated the benefits of lowering LDL cholesterol on morbidity and mortality. Secondly, the focus should be on the metabolic syndrome, since this constellation of factors increases risk of cardiovascular disease at any given LDL cholesterol level (150). First-line intervention for the metabolic syndrome involves lifestyle modification, including weight management, diet, and physical activity changes. Long-term adherence to these changes is essential for the successful management of this chronic condition. Results from the Diabetes Prevention Program demonstrate that among participants who met criteria for the metabolic syndrome at baseline, 38% in the lifestyle group, 23% in the metformin group, and 18% in the placebo group no longer had the syndrome a mean 3.2 years of follow-up (164). This illustrates that the metabolic syndrome, contrary to advanced type 2 diabetes, may be a reversible condition if addressed early on, and long-term engagement in lifestyle changes may result in its resolution.

Weight loss—Weight reduction has been the main goal of most intervention studies on patients with the metabolic syndrome because it likely activates one or more underlying mechanisms that lead to improvements in the metabolic syndrome profile. Weight loss is associated with significant improvements in blood glucose control and lipid and nonlipid abnormalities, as well as with metabolic syndrome resolution (40, 169, 222). Even a moderate weight loss (around 7%) has resulted in substantial reductions in blood pressure, glucose, triglyceride, and total cholesterol concentrations within a four-week period, despite the potential persistence of an elevated body mass index (BMI) (even $>38 \text{ kg/m}^2$) (36). Usually, but not invariably, weight reduction is also associated with improvements in inflammation-related markers, namely adiponectin and tumor necrosis factor- α concentrations (239). Obviously, with greater reduction in BMI, improvements are more likely to be observed. In a study with 41 obese (BMI of $\sim 38 \text{ kg/m}^2$) patients with the metabolic syndrome, those losing $>10\%$ of their initial body weight (15 patients with an average weight loss of 18%) experienced greater reductions in the number of metabolic syndrome components, compared to patients losing $<10\%$ (26 patients with an average weight loss of 4%), again despite the high post-treatment BMI levels ($>30 \text{ kg/m}^2$); resolution of the metabolic syndrome occurred in two-thirds of patients in the first group, whereas only in one-fifth in the second group (149). Several dietary approaches have been used for achieving negative energy balance and thus weight loss: a STEP I diet, a diet rich in fruits and vegetables, a low-fat diet focusing on the reduction of saturated fat modeled after the National Cholesterol Education Program, Adult Treatment Panel III dietary guidelines, or even a very-low-calorie diet (12, 36, 40, 149, 202, 225). Several of these diets are discussed in detail in the Type 2 Diabetes Mellitus section.

Dietary changes—Although several studies discuss the association between the metabolic syndrome and diet composition in terms of nutrients, foods, or dietary patterns (24, 48, 54, 133, 210), the data are scarce regarding the effect of macronutrient changes in patients with metabolic syndrome. Muzio et al. (148) compared a diet rich in carbohydrate (65% of energy as carbohydrate and 22% as fat) to a relatively low-carbohydrate diet (45% of energy as carbohydrate and 33% as fat, mainly monounsaturated) with regard to their effect on cardiovascular risk factors in a group of 100 obese (BMI of ~ 37 kg/m²) subjects with the metabolic syndrome over a five-month period. Both diets were hypocaloric (~ 500 kcal/day) and, on average, resulted in the predicted weight loss of ~ 9 kg or 10% of initial body weight (148). Body weight, BMI, waist circumference, systolic and diastolic blood pressure, total cholesterol, serum triglyceride, blood glucose, insulin, and the homeostasis model assessment of insulin resistance score significantly decreased in both diets, whereas HDL cholesterol remained unchanged. The low-carbohydrate diet was more effective in reducing systolic blood pressure and heart rate compared to the high-carbohydrate diet, whereas the latter was more effective in lowering LDL cholesterol (148). Furthermore, it has been shown that weight loss and the reduction in total cholesterol concentration were greater in patients on a low-fat, complex carbohydrate diet, compared to those on a low-fat, simple carbohydrate diet, over a six-month period (171). Thus, as the macronutrient composition of the diet may have specific effects on lipid and nonlipid components of the metabolic syndrome, tailoring the dietary intervention to the specific metabolic syndrome profile may be the most effective approach for reducing cardiovascular disease risk.

Adoption of a Mediterranean-style diet, rich in whole-grain cereals, fruits, vegetables, nuts, and olive oil, compared to a prudent dietary pattern (50%–60% of energy as carbohydrate and $<30\%$ as fat), has been associated with improvements in endothelial function and significant reduction in markers of systemic vascular inflammation in metabolic syndrome patients after two years of follow-up (68). Importantly, after adjusting for changes in body weight, only 40 out of 90 patients in the intervention group were still classified as having the metabolic syndrome at the two-year follow-up visit, compared with 78 out of 90 patients in the control diet group. This reveals a highly significant 42% net reduction in the prevalence rates. Without adjusting for changes in body weight, the overall reduction in the prevalence of the metabolic syndrome was even greater (30 patients in the intervention group and 73 patients in the control group) (68).

The DASH (Dietary Approaches to Stop Hypertension) diet, rich in fruits, vegetables, and low-fat dairy foods and low in saturated and total fat intake (13), has also been shown to exert beneficial effects on metabolic syndrome parameters, and particularly on blood pressure (18). Although the weight reduction may partly explain the favorable outcomes, the significant effect of the DASH diet in reducing the metabolic risks was also seen even after controlling for the confounding effect of body weight changes. Furthermore, the adoption of a DASH diet in the context of a multicomponent lifestyle intervention may be a key feature in achieving a significant decline in blood pressure among patients with metabolic syndrome (126).

Physical activity—Current scientific evidence supports the role of exercise as an effective treatment strategy for the metabolic syndrome. Katzmarzyk et al. (110) reported that 30.5%

of the metabolic syndrome patients were no longer classified as having the syndrome after 20 weeks of supervised aerobic training. In addition, low-intensity exercise training for a two-month period was associated with moderate, but significant, improvements in insulin resistance and adiposity (59). Moderate-intensity exercise, compared to vigorous exercise, may be more effective in improving metabolic syndrome (106), supporting the recommendation for adults to get 30 minutes of moderate-intensity exercise on most days of the week and preferably every day. An exercise dose-response effect has also been recognized, as an increased amount of exercise had greater and more widespread benefits (106).

In the studies mentioned above, exercise refers to supervised sessions, specified in terms of duration and type. However, changes in physical activity were among the principal goals of most lifestyle interventions for metabolic syndrome, mostly in the form of a nonprescribed ad libitum physical activity component, in addition to dietary modifications (36, 68, 149). Although a direct comparison of the separate effects of diet and physical activity on the various components of the metabolic syndrome has not been fully investigated, a combined diet and exercise intervention was significantly more effective than either approach alone for the treatment of metabolic syndrome (11). Furthermore, adding aerobic exercise training to a diet-based weight-reducing program resulted in greater resolution (95% versus 75%) or improvement (adjusted odds ratio 3.68) of the metabolic syndrome compared to diet alone (162), an observation consistent with the well-documented additive effects of diet and exercise interventions on body weight reduction (197). The addition of an exercise component to a dietary intervention led to a significant reduction only in systolic blood pressure compared with the nonexercise, diet-only group (40), whereas adding a weight-reducing behavioral program to an exercise-based intervention had beneficial effects on weight reduction, fasting glucose levels, and diastolic blood pressure, among others (225).

The effect of physical activity has also been examined in relation to the maintenance of metabolic changes. In order to further improve metabolic syndrome parameters or maintain achieved changes (i.e., reductions in body weight, waist-to-hip ratio, systolic and diastolic blood pressure, and plasma LDL cholesterol, glucose, insulin, and apolipoprotein B concentrations) following a very-low-energy diet for two months, adding a structured exercise component to dietary counseling has been found to be as effective as dietary therapy alone; in other words, physical activity did not confer any further benefit(s) to the parameters studied (121). The authors postulated that either the exercise dose was too small or the adherence to the exercise sessions was below the recommended level. Nevertheless, there is accumulating evidence indicating that long-term maintenance of weight loss is facilitated by regular physical activity (101, 105, 192). This is of great value considering that body weight is an important factor affecting metabolic syndrome parameters.

Type 2 Diabetes Mellitus

Type 2 diabetes is a complex metabolic disease that is caused by a variable degree of insulin resistance in target tissues and/or defects in pancreatic insulin secretion (107). Although it has a strong genetic predisposition and despite that susceptibilities to obesity and diabetes do share some common genetic background (100, 128), it is unlikely that the gene pool has

changed appreciably over the short period of time during which the prevalence of these conditions has been increasing rapidly in the western world. During the past several decades, the prevalence of type 2 diabetes has been rising steadily in most parts of the world (143), in parallel with the increase in the prevalence of obesity, suggesting that changes in lifestyle and environmental factors may act in concert with genetics in the causation of diabetes (144, 145, 238). Many epidemiological studies have identified overweight, resulting largely from energy overconsumption and a sedentary lifestyle, as the single most important environmental factor predicting type 2 diabetes, although several other factors may be involved in the development of the disease (38, 42, 73, 98, 147). It has been estimated that approximately 90% of type 2 diabetic patients are overweight or obese (6, 50), though certainly, not all obese individuals develop type 2 diabetes and not all individuals with type 2 diabetes are obese (134). There are many routes via which the metabolic sequelae of obesity may lead to insulin resistance and the development of type 2 diabetes (107, 224), and all of these conditions (i.e., obesity, insulin resistance, and diabetes) are tightly linked to lifestyle.

Diet and Exercise in Diabetes Management

Perhaps the strongest epidemiological evidence supporting an association between lifestyle and type 2 diabetes stems from ecological and migration studies, which indicate a greater risk of developing the disease among people who migrate to westernized countries and those who undergo westernization in their lifestyles (112, 177). Lifestyle modification is therefore considered a cornerstone for the management of type 2 diabetes (43, 216, 235). Early evidence for the long-term effectiveness of lifestyle modification in the prevention and treatment of type 2 diabetes comes from the Malmö study in Sweden (67). In that study, which was not fully randomized, 41 subjects with type 2 diabetes and 181 subjects with impaired glucose tolerance were followed for five years; the intervention consisted of advice to reduce energy intake and increase physical activity. The comparison groups consisted of 79 subjects with impaired glucose tolerance and 114 apparently healthy individuals, who received no specific lifestyle advice. At the five-year follow-up, body weight was reduced by 2%–4% in the treatment groups, whereas it increased by 0.5%–2% in the control groups. Among type 2 diabetics, more than half (~54%) had improved oral glucose tolerance at follow-up and transitioned into remission, i.e., they no longer had glucose concentrations in the diabetes range. Improvement was also observed in ~75% of those with impaired glucose tolerance, with ~52% of them reaching normal glucose tolerance at follow-up. On the contrary, in the control group, oral glucose tolerance at follow-up worsened in 67% of subjects with impaired glucose tolerance. Only 1 out of 9 or 10 patients (10.6%) with impaired glucose tolerance in the intervention group progressed to type 2 diabetes at follow-up, compared with 1 out of approximately 4 patients (28.6%) in the control group; this corresponds to a 63% reduced risk for developing type 2 diabetes. No major changes in glucose tolerance status and no cases of diabetes were observed among the healthy control subjects at follow-up. These data (67) suggest that it may indeed be possible to induce and maintain changes in lifestyle in groups of patients with or at risk for type 2 diabetes, thereby achieving long-term modest weight loss; this seems to be able not only to prevent or postpone progression to diabetes among subjects with impaired glucose tolerance but also to improve the metabolic profile and delay the development of metabolic complications (and thereby the occurrence of symptoms) among diabetic subjects. Since that pivotal study,

several randomized controlled trials have evaluated the efficacy of lifestyle modification in type 2 diabetes prevention and treatment.

Primary Prevention

From the clinical standpoint, diabetes prevention is especially important for people at high risk of developing the disease, such as those with impaired glucose tolerance (64). Several large-scale randomized controlled trials that followed participants of different age, sex, overweight status, and ethnicity for a period of ~2.5 to 20 years have been conducted to evaluate the efficacy of diet and exercise interventions for preventing type 2 diabetes in subjects with impaired glucose tolerance (Table 2) (117, 118, 125, 129, 167, 178, 213). Although lifestyle intervention protocols have been quite variable among studies with respect to physical activity, diet, and behavior counseling strategies, the main goal was to increase the amount of physical activity, decrease energy intake, and adopt healthier eating habits so as to induce and maintain at least modest weight loss. Results from these studies provide strong evidence that lifestyle modification reduces the risk for developing type 2 diabetes among high-risk individuals by approximately 30%–70% (Table 2). In fact, the U.S. Diabetes Prevention Program was prematurely terminated after 2.8 years of follow-up because of the significant benefit observed in the intervention group (179). It is also interesting that lifestyle intervention was at least as effective (178) if not more effective (117) than standard drug treatment (metformin) in preventing type 2 diabetes, whereas the addition of metformin to a lifestyle modification program did not further augment the benefit compared to lifestyle intervention alone (178). Perhaps more importantly, two recent follow-up reports from the Finnish Diabetes Prevention Study (129) and the Da Qing study (125) indicate that the benefits from lifestyle modification persist for many years after cessation of the “active treatment.” These encouraging results for lifestyle modification are corroborated by three independent meta-analyses (83, 165, 240) indicating ~50% lower risk of type 2 diabetes for diet-plus-exercise interventions compared with the control treatment (Figure 1). The scarcity of data on the effects of diet-only and exercise-only interventions precludes drawing conclusions regarding the comparative effects of diet and exercise until more and larger studies become available (83, 156, 165). Evidence from these randomized clinical trials has been successfully implemented into community and routine health care settings, reinforcing the feasibility of preventing type 2 diabetes through lifestyle modification (1, 166, 194).

The reduction in diabetes risk with diet-plus-exercise interventions coincides with significant reductions in body weight, BMI, waist-to-hip ratio, and waist circumference; modest alterations in blood lipid profile (mainly a decrease in triglyceride concentration); and significant blood pressure lowering (165). In the U.S. Diabetes Prevention Program, weight loss was the dominant predictor of reduced diabetes incidence: Among subjects in the lifestyle modification group, every kilogram of weight lost was associated with a 16% reduction in diabetes risk, adjusted for changes in diet and physical activity (89). Older subjects exhibited greater benefit from lifestyle modification than did younger subjects, the difference being largely explained by greater amounts of weight loss among the former (44). Results from a meta-analysis also suggested that the effectiveness of lifestyle modification might be greater among individuals who are more overweight and obese (83). It is important

to point out that major reductions in risk (by ~67%) have been documented even with minor (by ~1.8 kg) decrements in body weight (118), and in fact, modest risk reduction (by ~29%) can be achieved even in the absence of weight loss (178). Other factors, therefore, such as body composition changes and/or a direct effect of exercise may also be responsible for the observed decrease in diabetes risk with lifestyle modification. In this respect, the Finnish Diabetes Prevention Study reported that risk reduction both at the end of the active intervention (213) and after 3–4 years of inactive follow-up (125) was directly related to the success in achieving the lifestyle modification goals of weight loss, reduced intake of total and saturated fat, increased intake of dietary fiber, and increased weekly physical activity and that the more goals achieved, the better the outcome was. This suggests that qualitative aspects of the diet as well as physical fitness, not necessarily related to weight loss, may be involved in mediating the beneficial effect of lifestyle modification in the primary prevention of type 2 diabetes. Further research is needed to fully elucidate the mechanisms leading to diabetes risk reduction independently of weight loss.

Secondary Prevention and Treatment

Importance of weight loss—Medical nutrition therapy in type 2 diabetes primarily focuses on the prevention or the delay in the onset of developing chronic complications, especially cardiovascular disease, which is the major cause of morbidity and mortality among patients with diabetes. Reduction in multiple cardiovascular risk factors in the form of narrow glycemic control, improved dyslipidemia, and blood pressure lowering is a key goal of the interventions (8). Accumulating evidence indicates that moderate weight loss (5%–10% of initial body weight) has many beneficial metabolic effects in type 2 diabetes, including improved glycemic control, lower blood pressure, reduced fasting insulin concentration, increased insulin sensitivity, reduced upper body obesity, reduced serum markers of inflammation, and less atherogenic blood lipid profile consisting of decreased triglyceride concentration, increased HDL cholesterol concentration, and larger and more buoyant (i.e., less dense) LDL particles (28, 134). Moreover, marked weight loss (~30% of initial body weight) following gastric bypass surgery leads to normalization of glycemia in some 65%–85% of extremely obese type 2 diabetic patients and improves glycemic control in almost all of them (55, 172, 173). Importantly, and despite limited available data, a meta-analysis of prospective studies concluded that intentional (but not unintentional) weight loss is associated with a significant reduction in all-cause mortality by some ~25% in overweight and obese type 2 diabetic patients (16); the same appears to hold true for diabetes and cardiovascular disease mortality rates as well (231).

In a recent randomized clinical trial, the effects of weight loss induced by intense lifestyle modification versus bariatric surgery were compared in 60 middle-aged, obese men and women with newly diagnosed type 2 diabetes (56). At the two-year follow-up, the surgical group achieved a mean body weight loss of 20% compared with 1.4% in the lifestyle modification group. Remission of type 2 diabetes was achieved in 43% of the surgically treated subjects and in 13% of the lifestyle-treated subjects, coupled with significant improvement in glycemic control in the former group; greater percentage of weight loss in itself explained almost half of the variance in diabetes remission (56). One very important correlate from this study is that the degree of weight loss, not the method per se, is the

driving factor responsible for glycemic improvement in obese patients with type 2 diabetes. Also, these results do suggest that intensive weight loss should be the fundamental element in the management of diabetes. In fact, out of some 34 patients who achieved a weight loss <10%, which is nevertheless associated with substantial metabolic benefits in this population (see above), only about 12% were in remission at follow-up (56). However, the short duration of the study and the absence of a control group with standard treatment does not allow for solid conclusions. This and several other recent studies on surgically induced weight loss and its metabolic benefits (122, 203) have fuelled interest in the putative clinical utility of bariatric surgery in diabetes treatment (108, 221). At present, however, weight loss through diet and exercise re-mains at the core of scientific recommendations for the management of type 2 diabetes (20, 74, 116). A meta-analysis of 22 weight loss intervention studies in type 2 diabetic patients, including 4659 participants followed for one to five years, concluded that weight loss and control may be difficult to achieve for adults with type 2 diabetes using currently available lifestyle modification strategies (using one or more dietary, physical activity, or behavioral interventions) (160). Still, the observed small reductions in weight (by 2–3 kg) and glycated hemoglobin (by ~0.3%) may be clinically significant (160). Hence targeting body weight could be interpreted in a clinical setting as a means toward targeting diabetic complications themselves (88). There is currently one large-scale randomized controlled trial on the long-term effects of lifestyle modification on diabetes management. The Look AHEAD (Action for Health in Diabetes) trial is a large-scale, multicenter, randomized clinical trial aiming at evaluating the long-term benefits of weight loss among overweight individuals with type 2 diabetes, and especially on the development of cardiovascular disease; 5125 middle-aged (~59 years old), obese (BMI ~36 kg/m²) type 2 diabetic men and women have been recruited and randomized either to a diabetes support and education program (control) or to an intensive lifestyle intervention program (130). The latter aims at a weight loss of 7%–10% of initial body weight during the first year, facilitated by an individualized hypocaloric low-fat diet (<30% of calories from fat and <10% from saturated fat), increased physical activity (targeting 175 minutes of moderate-intensity endurance exercise per week), use of structured dietary intervention strategies including meal replacements, structured menus, and combined fat and calorie counting, as well as behavioral counseling and intensive intervention frequency (combining closed group and individual sessions). Follow-up of Look AHEAD participants is ongoing and is planned to extend for up to 11.5 years. Interim outcomes have not yet been reported in detail, but intermediate weight loss at one year averaged 8.6% in the lifestyle modification group and 0.7% in the control group. This was associated with greater improvements in physical fitness and several cardiovascular risk factors and greater reduction in the use of antidiabetic medications (130), and was accompanied by significant improvements in health-related quality of life in the lifestyle intervention arm (230). Results from this trial in relation to the occurrence of major cardiovascular events such as heart attack, stroke, and cardiovascular-related death are not yet available, but interim changes in cardiovascular risk profile are encouraging and hold great promise.

Dietary approaches for weight loss and metabolic control in diabetes—There are no high-quality data on the comparative efficacy of the dietary treatment of type 2 diabetes. No robust evidence to support any one dietary approach in regard to effects on

body weight and microvascular and macrovascular diabetic complications was found in a recent Cochrane meta-analysis (155) of 36 randomized controlled trials lasting 6 months. The meta-analysis included data from 1467 diabetic participants and evaluated several dietary approaches, including low-fat/high-carbohydrate diets, low-carbohydrate/high-fat diets, low-calorie diets (1000 kcal/day), and very-low-calorie diets (500 kcal/day), as well as fat-modified diets. Short-term randomized controlled trials and observational studies do indicate that nutrition therapy utilizing many different dietary strategies can be successfully implemented in clinical practice and can improve glycemic control among diabetics (75). It is becoming increasingly clear that there is no single optimal diet for type 2 diabetes (26), and this is reflected in the recent guidelines from the American Diabetes Association (20) allowing greater liberalization of dietary approaches and recognizing that a variety of diets may be successful in reducing weight and achieving metabolic control. Limiting carbohydrate intake at a single meal to a reasonable amount with attention to the type and quality of carbohydrate (e.g., whole grains are preferred to simple or refined carbohydrates) is helpful to avoid exacerbating postprandial hyperglycemia. Saturated fatty acids should be limited to less than 7% of total calories and intake of *trans* fatty acids should be minimized. Dietary cholesterol should be limited to less than 200 mg/day (20). The usual amount of protein intake is ~15%–20% of total calories, and there is no evidence indicating that this should be altered in patients with diabetes. Since ingestion of protein could stimulate the secretion of insulin without increasing blood glucose concentration, protein should not be used to treat or prevent acute hypoglycemia (20). The recommendations targeting individual macro- and micronutrients notwithstanding, current dietary guidelines emphasize the importance of weight loss by reducing energy intake as the single most effective measure in the management of diabetes (20).

Several different types of diets have been advocated to promote weight loss, and they vary in their nutritional adequacy as well as in their degree of concordance with guidelines for chronic disease risk reduction (51). The overriding principle in achieving weight loss is the institution of negative energy balance (i.e., energy deficit), achieved both by reducing energy intake and by increasing energy expenditure through exercise. An energy deficit of 500–1000 kcal/day is expected to result in a loss of 0.5–1 kg/week and an average total weight loss of about 8% after six months (153). No adult patient, whether lean, overweight, or obese, who has been studied by direct calorimetry in a metabolic chamber has needed fewer than 1200 kcal/day to maintain body weight (33), which implies that adopting a diet of 1000–1200 kcal should be sufficient to induce weight loss in most patients. More drastic diets, including low- and very-low-calorie diets (<800 kcal/day), induce a rapid weight loss of about 15%–20% within ~4 months and produce substantial improvements in glycemia and dyslipidemia in patients with type 2 diabetes (232). However, their efficacy in long-term weight maintenance is no better than less-severe hypocaloric diets, and their safety is questionable as they carry a higher risk of causing medical complications (92, 123, 151, 232). These diets thus have limited utility in the treatment of type 2 diabetes and should be undertaken only under medical supervision and in conjunction with a structured weight-maintenance program.

Popular diets: Two recent randomized clinical trials with largely similar designs investigated the effectiveness of four popular diets in overweight and obese individuals over a period of one year. The first study (49) evaluated the Atkins (carbohydrate restriction without fat restriction), Zone (macronutrient balance and glycemic load), Weight Watchers (restriction of portion sizes and calories), and Ornish (fat restriction) diets in 160 overweight and obese middle-aged men and women with one or more cardiovascular risk factors; several diabetic patients were included, and ~30% of all subjects had hyperglycemia at baseline (>110 mg/dl). Two months of maximum effort were followed by a self-selected level of dietary adherence. At the one-year follow-up, all diets resulted in modest weight loss (2.1 kg for Atkins, 3.2 kg for Zone, 3.0 kg for Weight Watchers, and 3.3 kg for Ornish) with no statistically significant differences among diets. There was a trend, though not significant, toward a difference in attrition rates between the more extreme diets (48% for Atkins and 50% for Ornish) and the less extreme ones (35% for Zone and 35% for Weight Watchers). The amount of weight loss was not associated with the type of diet, but was curvilinearly related with self-rated dietary adherence, i.e., weight loss occurred only above a certain level of dietary adherence (above 5 on a 10-point scale) and increased proportionally thereafter with increasing adherence. The amount of weight loss per se predicted the improvement in several cardiovascular risk factors (e.g., reduction in ratio of total to HDL cholesterol, reduction in C-reactive protein and fasting insulin concentrations). Unfortunately, dietary adherence progressively decreased over time in a nearly identical manner for all four diets (49). The second study (79) evaluated the Atkins, Zone, LEARN (Lifestyle, Exercise, Attitudes, Relationships, and Nutrition; fat restriction), and Ornish diets, representing a spectrum of varying carbohydrate intake, in 311 overweight and obese nondiabetic, postmenopausal, otherwise healthy women. Attrition rates were much lower in this study (12% for Atkins and 22%–24% for the rest). At two and six months, weight loss was significantly greater for the Atkins group than for all other groups, and this difference was decreased but not completely abolished at the one-year follow-up (4.7 kg for Atkins, 1.6 kg for Zone, 2.6 kg for LEARN, and 2.2 kg for Ornish). Changes in cardiovascular risk factors (blood lipid profile, blood pressure) were in general more favorable in response to the Atkins diet, largely due to the greater amount of weight loss (79). Although the authors interpreted their data as supportive of the low-carbohydrate regimes, differences in weight loss at one year were observed only between the Atkins and the Zone diets, i.e., the two diets at the low end of the carbohydrate-intake spectrum. Moreover, it remains to be seen what the longer-term effects of these diets would be. Thus, there is a need to evaluate the comparative effectiveness of such popular diets among diabetic patients in long-term, large-scale, well-controlled randomized clinical trials.

Low-fat diets: Much debate and substantial press coverage in the popular media have focused on low-fat diets, and several clinical trials have been conducted to determine the importance of the composition of the diet in terms of weight loss. Traditionally, low-fat diets have been promoted as the preferred approach to achieve weight loss, and reduction in dietary fat intake lies at the core of recommended lifestyle interventions for the treatment of type 2 diabetes (184). In this respect, a meta-analysis of 16 short-term trials lasting 2–12 months concluded that nondiabetic subjects assigned to an ad libitum low-fat diet generally lost an average of 3.2 kg more weight than did the respective control groups; however, the

amount of reduction in the dietary fat was not significantly related to the amount of weight loss (14). A meta-analysis of longer-term studies, lasting 1 year, showed that dietary fat consumption within the range of 18%–40% of total energy has little, if any, effect on body weight and fatness among nondiabetics (229). Similarly, results from the Women's Health Initiative Randomized Controlled Dietary Modification Trial, including some 49,000 postmenopausal women (of whom ~5% had prevalent diabetes and ~35% had the metabolic syndrome), indicate that an ad libitum low-fat dietary pattern (~24% of total calories from fat) reduces body weight modestly yet significantly in nondiabetics and diabetics alike (by 0.5–2 kg) (96). When compared with the usual dietary pattern, however, it does not have any significant beneficial effect on the risk of cardiovascular disease over a period of ~8 years (97), nor does it significantly affect the risk of developing diabetes after adjusting for weight loss (209). This could be interpreted as indicating that the dominant factor in diabetes prevention is long-term weight loss in itself, even if modest (< 2 kg), rather than macronutrient composition.

Although the importance of the effects of reduced dietary fat intake on weight loss during the active dieting period remains controversial at best, there is also evidence, particularly from observational studies, to suggest that low-fat diets may promote weight loss maintenance better than other types of dietary approaches, especially when combined with increased physical activity (74). For example, in the National Weight Control Registry (an observational study of individuals who had maintained a weight loss of at least 13.6 kg for at least one year), those who were successful at long-term weight maintenance, among other dietary behaviors, were also consuming a low-energy, low-fat diet (198). Also, in the Women's Health Initiative Randomized Controlled Dietary Modification Trial, there was no evidence of weight gain over the baseline value among women in the low-fat diet group at any time point during follow-up (~8 years), contrary to the control diet group (96). The possibility that low-fat diets are particularly effective in weight maintenance was challenged by a recent randomized controlled trial, where nondiabetic subjects who lost >8% of their initial body weight (~12 kg) through a low-calorie diet (800–1000 kcal/day) for two months were subsequently randomized to three different ad libitum diets: low-fat (25% of total calories), moderate-fat (40% of total calories) rich in monounsaturated fatty acids, and a control diet (58). During the following six months, participants regained ~3 kg with little difference across diets; body fat mass regain was less with both the low-fat and the moderate-fat diets when compared with the control diet (58). Currently, there are no relevant data among patients with diabetes.

Very-low-fat diets, such as vegetarian or vegan diets, have attracted much interest with respect to their potential benefit on diabetes. These plant-based diets contain very small amounts of dietary fat (10%–15% of total calories) and consist mainly of whole-grain or traditionally processed cereals and legumes, nuts (e.g., almonds), viscous fibers (e.g., fibers from oats and barley), soy proteins, and plant sterols. Available data suggest that these diets, especially in conjunction with exercise and concomitant weight loss, may have significant metabolic advantages that are of relevance for the prevention and treatment of diabetes and its complications, such as improved glycemic control, improved blood lipid profile, and beneficial effects on markers of renal function (104). In fact, an early pilot study in type 2 diabetic patients has demonstrated the advantage of an ad libitum low-fat vegan diet over a

traditional low-fat diet in reducing body weight and blood glucose concentration even in the absence of increased exercise (154). Similarly, in a recent clinical trial, 99 middle-aged individuals with type 2 diabetes (61% women; 93% overweight and obese) were randomized to a low-fat, plant-based diet (10% of energy from fat, 15% protein, and 75% carbohydrate) with no energy intake restriction, or an American Diabetes Association hypocaloric diet (15%–20% protein, <7% saturated fat, 60%–70% carbohydrate and monounsaturated fats, and cholesterol <200 mg/day) for 22 weeks (21). Both diets were associated with significant clinical improvements, as indicated by reductions in glycated hemoglobin, body weight, plasma lipid concentrations, and urinary albumin excretion rates, and these improvements were generally greater for the low-fat vegan group than for the traditional low-fat group (21). Interestingly, subjects in the vegan group improved qualitative aspects of their diet (evaluated by using the Alternate Healthy Eating Index) significantly more than did those in the traditional diet group (215). Further research is needed to clarify the long-term impact of low-fat diets in the management of diabetes.

Low-carbohydrate diets: Restriction of carbohydrate intake has been advocated for the dietary treatment of diabetes since the early twentieth century, long before any specific medications were available (227). In recent years, very-low-carbohydrate diets, some with unrestricted fat and protein intake, have attracted much interest. The Atkins diet (15) is the prototype low-carbohydrate diet, and the South Beach diet (2) is an example of a more moderate version of a low-carbohydrate diet. A recent meta-analysis of five clinical trials with 447 participants randomized either to low-carbohydrate (lead-in: <30 g/day; up to 60 g/day) diets with no energy restriction or to low-fat (<30% of total calories) diets with energy restriction found that individuals assigned to low-carbohydrate diets had lost more weight (~3.3 kg) than did individuals randomized to low-fat diets after 6 months, but this difference was no longer significant after 12 months (159). Similar short-term results were reported in a study of 132 severely obese subjects (BMI >35 kg/m²), of whom 39% had type 2 diabetes and 43% had the metabolic syndrome: Weight loss after six months on a low-carbohydrate regime (<30 g/day) averaged 1.6–6.3 kg more than on a low-fat hypocaloric regime (188). The greater initial weight loss observed on low-carbohydrate diets may be related to changes in total body water that occur when glycogen stores are mobilized and increased circulating ketone body concentrations are cleared by the kidney, thereby increasing renal sodium and water loss (52). Triglyceride and HDL cholesterol concentrations changed more favorably in individuals assigned to low-carbohydrate diets, but total cholesterol and LDL cholesterol concentrations changed more favorably in individuals assigned to low-fat diets (159). It is important to point out that the effects of diets with different combinations of carbohydrate and fat on dyslipidemia vary depending on the dietary phase, i.e., weight stabilization, active weight loss, or weight maintenance, but are overall equivalent (119). Also, low-fat and low-carbohydrate diets do not differ with respect to their effect on blood pressure in the short or the long term (32, 159, 188). Retrospective reviews of patient charts have strongly suggested that low-carbohydrate diets are very effective in reducing body weight and in improving glycemic control and lipid profile among diabetics (93, 161, 220). Moreover, in a six-month randomized trial where data were analyzed by diabetes status, it was observed that a low-carbohydrate diet was more effective than a low-fat diet in reducing fasting glucose concentration and glycated hemoglobin in type 2 diabetic patients, but not in those without

diabetes (188). Several studies with different design (including cross-over, single-arm, nonrandomized, and randomized trials) have prospectively evaluated the effects of low-carbohydrate diets exclusively in patients with type 2 diabetes for periods varying in duration from 2 weeks to 22 months. Results from these studies do suggest that these diets are effective in reducing body weight and improving glycemic control (Table 3), with modest beneficial changes in blood lipid profile, predominantly increasing HDL cholesterol and decreasing triglyceride concentrations, and no consistent change in LDL cholesterol concentration (27, 46, 47, 87, 157, 158, 186, 228, 241, 242). Importantly, a reduction or discontinuation of antidiabetic medications (metformin, thiazolidinediones, sulfonylurea, and insulin) has been recorded in most of these studies (61). Attrition rates in dietary intervention studies in people with diabetes have generally ranged from no dropouts for the short-term studies over two to eight weeks to 10%–25% for studies conducted over three months to two years (61), which can be considered at least as good as (79) or better than (49) attrition rates in non-diabetic subjects. There have been reports of many dropouts (45%) in low-carbohydrate trials among diabetics, but attrition rates have not been substantially greater compared with traditional hypocaloric regimes (37%) (228). Until results from large-scale, long-term randomized controlled trials become available, the most useful dietary intervention, by far, remains the initiation of a calorie-restricted diet in patients with type 2 diabetes who are overweight; the major benefits are thought to depend upon the decrease in total calories, not on variations of macronutrient intake (181).

Low-glycemic index diets: It has been suggested that limiting fat consumption may lead to a compensatory increase in carbohydrate consumption, particularly in refined carbohydrates that may have detrimental effects on weight control and metabolic status. Given that carbohydrates differ in their ability to raise plasma glucose concentrations and stimulate pancreatic insulin release, the concept of glycemic index has been developed to quantify this different ability; it is defined as the incremental area under the glucose response curve in response to a standard amount of carbohydrates from a test food relative to that of a control food (white bread or glucose) (132). Glycemic load is the weighted average glycemic index of individual foods multiplied by the percentage of dietary energy as carbohydrate; thus, foods such as potatoes and carrots may have similarly high-glycemic indexes, but those with a greater percentage of carbohydrate (i.e., potatoes) have a higher glycemic load.

A recent 12-week randomized trial of 129 overweight or obese nondiabetic subjects found that individuals assigned to a low-glycemic-index diet were twice as likely to achieve a weight loss of 5% or more as were those on a low-glycemic-index diet, despite that mean body weight loss for the two groups was the same (140). In women in particular, the low-glycemic-index diet was associated with ~80% greater fat mass loss compared to the conventional diet (140). There were no major differences between diets on blood lipid profile and glucose homeostasis, other than a modest reduction in total and LDL cholesterol concentrations after the low-glycemic-index diet (140). In a smaller but longer-term study of 23 nondiabetic obese individuals, those assigned to ad libitum consumption of low-glycemic-index foods over 12 months lost amounts of weight (6%–8% of initial body weight) similar to those lost by a control group receiving an energy- and fat-restricted diet, but exhibited greater decrements in triglyceride and plasminogen activator inhibitor 1

concentrations (63). Using an almost identical study design but an ad libitum approach for both dietary regimes, the same investigators reported similar reductions in weight (~2 kg) and body fat percentage (1%–1.5%) after 18 months of follow-up in 73 nondiabetic obese subjects; plasma HDL cholesterol and triglyceride concentrations improved more on the low-glycemic-load diet, whereas LDL cholesterol concentration improved more on the low-fat diet (62). A significant interaction was observed between the diet and insulin response to oral glucose: The two diets had very similar effects among individuals with low insulin responses, but the low-glycemic-load diet produced a significantly greater decrease in weight and body fat percentage than did the low-fat diet in those with high insulin responses (-5.8 versus -1.2 kg and -2.6% versus -0.9%, respectively) (62). This finding implies that low-glycemic-index diets may be particularly effective in individuals with insulin resistance.

In the Canadian Trial of Carbohydrates in Diabetes, a one-year randomized controlled trial of isocaloric high-carbohydrate/high-glycemic-index, high-carbohydrate/low-glycemic-index, or low-carbohydrate/high-monounsaturated-fat diets in patients with type 2 diabetes, no major differences between diets were found with respect to body weight, blood lipid profile, and blood pressure. However, the low-glycemic-index diet improved oral glucose tolerance and reduced C-reactive protein concentration to a significantly greater extent than did the other two diets, even though glycated hemoglobin was not affected (236). Surrogate estimates of hepatic and skeletal muscle insulin sensitivity (derived from the oral glucose tolerance test) changed in no consistent manner over time and across diets. However, pancreatic beta-cell function (disposition index) improved significantly at one year with the low-glycemic-index diet compared with the low-carbohydrate diet, despite the opposite being true at three months (237). These data stress the importance of long-term observation in order to avoid misleading conclusions; for instance, in one short-term trial lasting six months, an ad libitum low-carbohydrate diet was found to be significantly more effective than a hypocaloric low-glycemic-index diet in reducing body weight and glycated hemoglobin among type 2 diabetics (228). Overall, meta-analyses of available randomized studies lasting up to 12 months conclude that utilizing the concept of glycemic index when selecting carbohydrate-containing foods beneficially influences several aspects of carbohydrate and lipid metabolism in diabetic subjects (i.e., reduction in glycated hemoglobin, fructosamine, total cholesterol, and perhaps also LDL cholesterol) (31, 163), which could be beneficial in the long-term dietary management and metabolic control of diabetes.

Generally, it is believed that glycemic index should not be used in isolation, but instead should be interpreted in relation to other relevant dietary parameters, such as energy content, relative amount of macronutrients, available carbohydrates, and dietary fiber (183). After all, it is important to note that the window of glycemic index variability in a free-living population is quite narrow (170). Provided all qualities of the food are taken into account, available evidence supports the use of glycemic index as a helpful additional marker indicating which carbohydrate-containing foods to preferentially include in the diet; this is particularly relevant for diabetic patients in whom postprandial glucose regulation is impaired (183). This premise, stemming mainly from the results of small, relatively short-term dietary intervention and mechanistic studies, needs to be rigorously tested in larger and

longer-term randomized trials to determine the efficacy of diets based on low-glycemic-index foods on weight loss and other metabolic parameters in type 2 diabetes.

Mediterranean diet: The Mediterranean diet has long been touted for its health benefits and has been associated with reportedly greater longevity and better quality of life (138); recent data from prospective studies suggest that greater adherence to a Mediterranean diet is indeed associated with significant improvements in health status, as evidenced by lower incidence of and mortality from chronic diseases (204). This diet encourages the moderate consumption of fat (~40% of calories), mainly from foods high in monounsaturated fatty acids, fruits, vegetables, nuts, legumes, whole-grain cereals, fish, and moderate amounts of alcohol (138). Although Mediterranean dietary patterns typically contain higher amounts of fat than do traditional low-fat diets (mostly in the form of unsaturated fatty acids), results from randomized studies are encouraging. In one study with 101 overweight and obese nondiabetic subjects (139), those assigned to a moderate-fat, Mediterranean-style diet lost more weight over 1.5 years than did those randomized to a traditional low-fat diet and exhibited much lower attrition rates. And, in another shorter-term study with 722 subjects at risk for cardiovascular disease, of whom 50%–60% had type 2 diabetes (70), those following Mediterranean-style diets for three months lost amounts of body weight similar to those of subjects assigned to a conventional low-fat diet, but those following the Mediterranean diet exhibited greater improvements in cardiovascular disease risk factors (blood glucose, C-reactive protein, ratio of total to HDL cholesterol, and blood pressure).

In a more recent two-year trial (195), 322 middle-aged, moderately obese nondiabetic and type 2 diabetic subjects were randomized to a low-fat calorie-restricted diet, a Mediterranean calorie-restricted diet, or a low-carbohydrate diet without caloric restriction. Frequent meetings with dietitians and motivational telephone calls throughout the study resulted in very low attrition rates, ~5% at one year and ~15% at two years. There were significant differences between groups, with two-year attrition rates of 9.6% for the low-fat diet, 14.7% for the Mediterranean diet, and 22.0% for the low-carbohydrate diet. All three diets resulted in reduction in body weight after two years (3–5 kg), with the greatest weight loss achieved by the low-carbohydrate and the Mediterranean diet groups. Interestingly, a very different pattern of body weight change over time was observed among the three diets, with weight loss during the first 6 months being greater for the low-carbohydrate diet group, and weight regain during the remaining 18 months being minimal for the Mediterranean diet group. The Mediterranean diet was particularly effective in women (who were underrepresented in this study), resulting in 2–3 times greater weight loss compared with the low-carbohydrate and the low-fat diets; differences between diets among men were less pronounced. Reductions in blood pressure were similar between diet groups, regardless of sex. Changes in blood lipid profile (reduced triglyceride and increased HDL cholesterol concentrations) generally favored the low-carbohydrate over the low-fat group, whereas C-reactive protein concentration decreased significantly in the low-carbohydrate and the Mediterranean diet groups. In diabetics, fasting plasma insulin concentration decreased significantly in all diet groups, but fasting plasma glucose and the homeostasis model assessment of insulin resistance score decreased significantly only in the Mediterranean diet group. The proportion of glycated hemoglobin decreased non-significantly by ~0.5% in the low-fat and the

Mediterranean diet groups, and significantly by ~1% in the low-carbohydrate group. Results from this study (195) strongly suggest that both the Mediterranean and the low-carbohydrate diets are effective alternatives to the low-fat diet for weight loss and appear to be just as safe; moreover, they may have greater beneficial metabolic effects and should thus be considered in the medical nutrition management of diabetes.

Exercise for inducing weight loss and “treating” diabetes—Although exercise is considered a critical component of a successful weight loss program for overweight and obese subjects, in addition to having cardiovascular benefits, the amount of weight loss achieved through exercise alone (i.e., without caloric restriction) is very modest (80, 233). In fact, in type 2 diabetic subjects, two independent meta-analyses of data from several studies concluded that exercise training (without dietary intervention) lasting from 8 to 52 weeks has no significant effect on body weight compared with no exercise (29, 208). However, addition of regular exercise to an energy-restricted diet produces a 20% greater initial weight loss (13 kg versus 9.9 kg) and a 20% greater sustained weight loss (6.7 kg versus 4.5 kg) at one year compared with diet alone, based on the results of another meta-analysis of six studies lasting from 10 to 52 weeks and including some 407 overweight and obese participants (45). Importantly, increased physical activity may have beneficial effects in terms of mortality at all levels of adiposity, although it does not eliminate the increased risk of death associated with obesity (99).

Even though exercise has only a small effect on weight loss in real life [despite that under carefully controlled conditions, exercise and hypocaloric diet alike result in predictable weight loss (205)], it may still offer several other important benefits for patients with type 2 diabetes (Table 4) (5, 218). For example, many studies have shown that exercise training, whether endurance (aerobic) or resistance (strength), increases insulin sensitivity and improves glucose tolerance in both healthy and insulin-resistant subjects; in fact, the benefits of exercise appear to be greater for the latter group of people (82, 135). Much of the beneficial effect of exercise is already evident after just a single bout of exercise (135), i.e., before any changes in body weight and/or composition occur. Aerobic exercise (29) and resistance exercise (37, 60) training also produce a significant reduction in glycated hemoglobin (by 0.6%–1.1%) in type 2 diabetic patients independently of changes in body weight. Improvements in insulin sensitivity and glycated hemoglobin have been observed following a wide range of exercise types and intensities (135, 208), but greater effects of higher-intensity exercise (30) and/or higher energy expenditure (94, 136) cannot be ruled out. Adoption of regular exercise within the context of a dietary program has been proven to be a more efficient means for improving glycemic control in type 2 diabetics compared with diet alone (155). These observations reinforce the role of regular physical activity in diabetes management even in the absence of weight loss.

Furthermore, increases in fat-free mass and resting metabolic rate in the long-term can provide an advantage in maintaining weight loss. In fact, a major rationale for incorporating exercise into a weight-loss program is that a high level of physical activity is an important predictor for successful long-term maintenance of lost weight; in this respect, the effects of exercise appear to be dose dependent (102). Again, data from the National Weight Control Registry indicate that individuals who were successful in long-term maintenance of weight

loss reported expending ~2800 kcal/week (i.e., approximately 60 minutes of moderate-intensity exercise per day) (95). Others have shown that maintaining a daily physical activity level equivalent to ~80 minutes of moderate-intensity exercise (e.g., brisk walking) or ~35 minutes of vigorous exercise (e.g., jogging) decreases the risk of weight regain (192, 226). Based on these and several other studies, there is good consensus that energy expenditure of ~2500–2800 kcal/week (equivalent to 60–90 minutes of moderate-intensity physical activity per day) is necessary to prevent weight regain (190). Still, this amount of exercise may be overwhelming for most sedentary individuals, especially since, until recently, ~70% of the U.S. adult population failed to meet the recommended 30-minute goal of regular exercise and ~40% did not engage in any kind of physical activity (193). Although it may be difficult and impractical for the typical overweight or obese person who follows a sedentary lifestyle to achieve this level of activity right away, a reasonable recommendation is to start with 30 to 45 minutes of moderate-intensity physical activity 3–5 days per week and to encourage the establishment of a regular exercise routine. Ideally, this can ultimately be increased to at least 60 minutes of physical activity per day in most if not all days of the week.

The amount and type of exercise recommended by the American Diabetes Association for patients with type 2 diabetes varies according to goals (201). To improve glycemic control, assist with weight maintenance, and reduce risk of cardiovascular disease, at least 150 minutes per week of moderate-intensity aerobic physical activity or at least 90 minutes per week of vigorous aerobic exercise are recommended. Exercise should be distributed over at least three days per week, with no more than two consecutive days without physical activity. Also, performing 4 hours per week of moderate to vigorous aerobic and/or resistance exercise is associated with greater cardiovascular disease risk reduction compared with lower volumes of activity. For long-term maintenance of major weight loss, larger volumes of exercise (seven hours per week of moderate or vigorous aerobic physical activity) are required. Furthermore, in the absence of contraindications, people with type 2 diabetes should be encouraged to perform resistance exercise three times per week, targeting all major muscle groups, progressing to three sets of 8–10 repetitions at a weight that cannot be lifted more than 8–10 times. To maximize health benefits and minimize the risk of injury from strength exercises, initial supervision and periodic reassessments by a qualified exercise specialist is recommended. Before any vigorous exercise regime is instituted, however, patients should be evaluated for potential contraindications (e.g., active cardiovascular disease, uncontrolled hypertension, proliferative or severe nonproliferative retinopathy) or factors that may predispose them to injury (such as peripheral or autonomic neuropathy, arthritis) (218). Care should also be taken to prevent exercise-induced hypoglycemia, whether during or after exercise, by monitoring capillary blood glucose concentration (201). A useful clinical approach together with typical exercise programs for different type 2 diabetes subpopulations, based on disease duration, physical fitness level, and number of cardiovascular risk factors, has recently been proposed and can be used as a rule of thumb in diabetes management (176). Diabetics can benefit from regular physical activity, but the suitability of routine exercise regimes should be thoroughly evaluated and individualized by the treating physician so that the advantageous effects of regular exercise surpass any potential risks (245).

Patient Adherence To Lifestyle Recommendations and Behavior Modification

Because unhealthy eating habits and a sedentary lifestyle are among the strongest risk factors for obesity, metabolic syndrome, and type 2 diabetes, modification of eating habits and physical activity constitutes an important component of any successful management program (76, 77). Adopting a healthy, balanced diet and a physically active lifestyle requires a series of behavioral changes as well as appropriate responses to overcome challenges. Changes should be consistent, and long-term adherence to them is of paramount importance; however, neither is easy to accomplish, requiring concerted efforts at an individual level as well as multiple social and/or economic transformations. Therefore, despite the fact that diabetic people are routinely advised to adopt a healthy lifestyle, a significant proportion of them (20%–50%) remain poorly controlled (17, 90, 137, 146, 187), they exhibit low adherence to diet and physical activity recommendations (152, 185, 199, 207, 223, 244), and they are less successful in maintaining long-term weight loss compared to people without diabetes (86). On the other hand, even if their diets are not consistent with the guidelines, people with diabetes do report efforts to modify their habits (81). Their efforts may be futile, however, for several reasons, including the possibility that the changes may not be toward the most relevant direction. Also hampering efforts is the fact that patients often receive confusing and contradictory advice from a variety of sources and encounter several barriers (81, 243). More specifically, patients report difficulties in maintaining a diet away from home and an active lifestyle irrespective of the weather and their physical limitations, a preference for foods not included in the meal plan, a constant need for food planning and self-care, a lack of appropriate social support, and time constraints (34, 66, 191, 200, 211). Patients often feel a loss of eating pleasure and autonomy (189, 191), and they express their willingness to adopt revised dietary strategies that would incorporate appropriate education on how to make healthy food choices (66).

Lifestyle interventions should take these issues into account in order to promote better adherence and improve effectiveness. Under this perspective, assessing readiness and facilitating behavior change may contribute to a successful program. Patients' readiness, defined as the probability that a person will enter into, continue, and adhere to a specific change strategy (142), has been recognized as one of the hurdles in the clinical setting (57). Interventions should evaluate readiness and motivate patients to increase their likelihood of following the recommended course of action; failure to do so may increase dropout rates and non-adherence, resulting in low success rates (243). Stages of change may be a good predictor of attendance at diabetes prevention intervention sessions (91). Patients at earlier readiness stages had lower glycated hemoglobin levels than did those at later stages (212), and among patients participating in a diabetes educational intervention, those in preparation and action stages achieved a significantly larger reduction in glycated hemoglobin levels in a shorter period than did patients in precontemplation and contemplation stages (168). However, patients' stages of change may vary greatly in different dietary and physical activity areas; in addition, these could refer to the overall dietary and physical activity behaviors or some minor aspects of them (109). Although determining patients' stages of

change occasionally may be difficult, several simple clinical tools are available (115, 168, 217).

Beyond readiness and motivation, facilitating behavior change involves a series of strategies, with the aim of empowering patients and enabling them to assume increasing control of their condition. The most commonly used or proposed strategies are self-monitoring (keeping track of food ingested and activity performed), controlling stimulus (mainly modification of the physical environment, e.g., keeping healthy foods at home and avoiding tempting circumstances), setting clear, specific, attainable, and personally relevant goals, improving self-efficacy, reinforcing social support, and preventing relapse (7, 22, 23, 69, 111, 113, 114, 182, 235).

Research conducted thus far to evaluate the effects of various behavioral modification techniques on the lifestyle habits of diabetic patients is heterogeneous in nature with respect to study design and outcome measures, thus making comparisons between studies extremely difficult (174). A multifaceted approach is considered necessary, especially since the treatment regime for individuals with diabetes is complex: it includes both lifestyle components (i.e., diet and physical activity) and, most commonly, pharmacological components (i.e., oral medications and insulin). To date, little research has examined how best to combine lifestyle and pharmacological treatments in order to maximize compliance to both treatment regimes and to increase overall effectiveness (234). A recent meta-analysis concluded that instruction delivered by a team of trained educators, with reinforcement made at additional points of contact, may provide the best opportunity for outcome improvements in patients with diabetes (131). For example, in the absence of post-treatment booster sessions, subjects tend to maintain only part of the changes achieved or may even return to their initial status (127); in contrast, when active follow-up is included in treatment, a further improvement in clinical parameters may be achieved (149).

Although education is the cornerstone of diabetes management, great uncertainty exists about the key determinants for better adherence, including the combination of components, and the duration of treatment needed to optimize outcomes in the short and long term (219). Thus, the question of whether any specific intervention may effectively enhance adherence to treatment recommendations in patients with type 2 diabetes remains to be conclusively answered. However, there is a tendency to change the nature of the treatment modalities: Patients are expected to explore and discover their personal responsibilities and capabilities, while health professionals are encouraged to shift from the concepts of compliance and adherence to those of collaboration, concordance, and therapeutic alliance (9, 10). Greater research attention should be directed at issues related to the promotion of healthful eating and physical activity habits and strategies for modifying unhealthy behaviors in patients with diabetes and the metabolic syndrome.

Conclusion

Unhealthy diets and sedentary lifestyle are directly implicated in the increasing prevalence of obesity and insulin resistance/metabolic syndrome leading to type 2 diabetes. It is conceivable that slowing, let alone reversing, these trends requires lifestyle changes,

particularly changes in diet and physical activity. Results from studies on diet and exercise interventions provide promising data for the effective management of the metabolic syndrome and type 2 diabetes, although much more remains to be learned. An energy-prudent diet coupled with at least moderate levels of physical activity may favorably affect parameters of the metabolic syndrome, reduce the risk for developing type 2 diabetes, and minimize or delay the occurrence of diabetic complications. Weight loss per se, although not likely an absolute prerequisite, is certainly the major determinant and maximizes effectiveness. This is clearly highlighted in recent dietary and physical activity guidelines (20, 116, 201). There is also no single optimal diet or exercise prescription for the management of the metabolic syndrome and type 2 diabetes; a variety of approaches may be useful in inducing weight loss and promoting metabolic control. Furthermore, lifestyle modification does not merely consist of changes in diet and exercise habits, but should also target alcohol consumption (74), smoking (85), and sleep disorders (206); as yet there are insufficient data to make any suggestions regarding coffee consumption (35, 84). Finally, what appears to be of paramount importance and thus should be the focus of future investigation is the means by which patients can not only effect desirable changes, i.e., the adoption of a healthy, balanced diet and a physically active lifestyle, but also adhere to and maintain them in the long term.

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Relative risk for type 2 diabetes

Figure 1.

The effectiveness of lifestyle modification in primary prevention of type 2 diabetes. Relative risks and 95% confidence intervals are shown for diet-plus-exercise interventions versus control interventions (values lower than 1 indicate protection). Data are derived from three independent meta-analyses (83, 165, 240).

Table 1

Criteria for diagnosing the metabolic syndrome

Scientific body	Required criteria	Central obesity	Lipid profile	Blood pressure	Other
WHO ^a (4)	Glucose intolerance, impaired glucose tolerance, or diabetes and/or insulin resistance (defined from insulin clamp), plus two or more of the criteria in the following columns:	Waist-to-hip ratio >0.90 (males) or >0.85 (females) kg/m ²	Triglyceride 150 mg/dl and/or HDL-cholesterol < 35 mg/dl (males) or <39 mg/dl (females)	140/90 mm Hg	Microalbuminuria (urinary albumin excretion rate 20 g/min or albumin/creatinine ratio 30 mg/g)
EGIR ^a (19)	Insulin resistance (defined as fasting hyperinsulinemia; top 25% of nondiabetic population), plus two or more of the criteria in the following columns:	Waist circumference 94 cm (males) or 80 cm (females)	Triglyceride 180 mg/dl and/or HDL-cholesterol <39 mg/dl or treated for dyslipidemia	140/90 mm Hg or treated for hypertension	Fasting glucose 110 but < 126 mg/dl and/or 2-hour glucose (after standard oral load) 140 but < 200 mg/dl
NCEP ATPIII ^b (150)	Three or more of the criteria in the following columns:	Waist circumference > 102 cm (males) or >88 cm (females)	Triglyceride 150 mg/dl HDL-cholesterol <40 mg/dl (males) or < 50 mg/dl (females)	130/85 mm Hg	Fasting glucose 110 mg/dl
IDF ^b (3)	Increased waist circumference (ethnicity specific) plus two or more of the criteria in the following columns:	Europeids (and eastern Mediterranean, sub-Saharan Africans, and Middle East/Arab populations): 94 cm (males) or 80 cm (females); South Asians and Chinese (and edinic South and Central Americans): 90 cm (males) or 80 cm (females); Japanese: 85 cm (males) or 90 cm (females)	Triglyceride > 150 mg/dl and/or HDL-cholesterol <40 mg/dl (males) or < 50 mg/dl (females) or treated for dyslipidemia	130/85 mm Hg or treated for hypertension	Fasting glucose 100 mg/dl
AHA/NHLBI ^b (85)	Three or more of the criteria in the following columns:	Waist circumference > 102 cm (males) or >88 cm (females)	Triglyceride 150 mg/dl and/or HDL-cholesterol <40 mg/dl (males) or < 50 mg/dl (females)	130/85 mm Hg	Fasting glucose 100 mg/dl
AACE/ACE ^a (65)	Any of the following, but other risk factors should also be considered:	–	Triglyceride >150 mg/dl and/or HDL-cholesterol <40 mg/dl (males) or <50 mg/dl (females) or treated for dyslipidemia	130/85 mm Hg	Fasting glucose 110 but <126 mg/dl and/or 2-hour glucose (after standard oral load) 140 but <200 mg/dl
QCS ^b “hypertriglyceridemic waist” (53)	Both of the following:	Waist circumference 90 cm	Triglyceride 180 mg/dl	–	–

^aDefinition targets primarily individuals at risk of type 2 diabetes^bdefinition targets primarily individuals at risk of coronary heart disease.

WHO, World Health Organization; EGIR, European Group for study of Insulin Resistance; NCEP ATPIII, National Cholesterol Education Program, Adult Treatment Panel III; IDF, International Diabetes Federation; AHA/NHLBI, American Heart Association and the National Heart, Lung, and Blood Institute; AACE/ACE, American Association of Clinical Endocrinologists and American College of Endocrinology; QCS, Quebec Cardiovascular Study.

Table 2
Lifestyle intervention for the prevention of type 2 diabetes in subjects with impaired glucose tolerance

Study	Participants	Interventions	Follow-up	Outcome
Da Qing, China (125, 167)	577 47% women Age: 45 ± 9 years BMI: 26 ± 4 kg/m ²	Four arms: (a) diet-only group received counseling sessions on reducing energy intake, and those with BMI >25 were encouraged to lose 0.5–1 kg of weight per month until a BMI of 23, (b) exercise-only group encouraged to increase daily exercise, (c) diet-plus-exercise group received both of the above interventions, and (d) control group received general instructions.	6 years (167)	The cumulative incidence of diabetes was 68% in the control group, 44% in the diet group, 41% in the exercise group, and 46% in the diet-plus-exercise group, corresponding to reduced risk for developing diabetes by 31 % in the diet group, 46% in the exercise group, and 42 % in the diet-plus-exercise group.
		Active intervention ceased at 6 years.	20 years (125)	The cumulative incidence of diabetes was 93 % in the control group and 80% in the intervention groups (all three combined), corresponding to reduced risk for developing diabetes by 43 % in the lifestyle intervention group (by 42% in the diet group, 49% in the exercise group, and 34% in the diet-plus-exercise group).
Diabetes Prevention Study, Finland (129,213)	522 67% women Age: 55 ± 7 years BML 31 ± 5 kg/m ²	Two arms: (a) lifestyle intervention group received individualized advice on diet, physical activity (endurance and strength exercise), and weight loss, along with behavior counseling, (b) control group received general information for diabetes prevention.	3.2 years (213)	The cumulative incidence of diabetes was 24% in the control group and 11 % in the lifestyle intervention group, corresponding to reduced risk for developing diabetes by 58% in the lifestyle intervention group.
		Active intervention ceased at 3.2 years.	6 years (129)	The cumulative incidence of diabetes was 38% in the control group and 23 % in the lifestyle intervention group, corresponding to reduced risk for developing diabetes by 43 % in the lifestyle intervention group.
Diabetes Prevention Program, USA (117)	3234 68% women Age: 51 ± 11 years BMI: 34 ± 7 kg/m ²	Four arms: (a) lifestyle intervention group received advice on diet and physical activity emphasizing weight loss, along with behavior counseling, (b) control group received general information on healthy lifestyle, (c) metformin group (see text), and (d) troglitazone (discontinued).	2.8 years	The cumulative incidence of diabetes was 29% in the control group and 14% in the lifestyle intervention group, corresponding to reduced risk for developing diabetes by 58% in the lifestyle intervention group.
Japan (118)	484 0% women Age: 52 years BMI: 24±2 kg/m ²	Two arms: (a) lifestyle intervention group received advice on diet and physical activity emphasizing weight loss if BMI ≥ 22, along with behavior counseling, and (b) control group received less-frequent advice on diet and exercise and was encouraged to lose weight if BMI ≥ 24.	4 years	The cumulative incidence of diabetes was 9% in the control group and 3% in the lifestyle intervention group, corresponding to reduced risk for developing diabetes by 67% in the lifestyle intervention group.
Diabetes Prevention Program, India (178)	531 21% women Age: 46±6 years BMI: 26±4 kg/m ²	Four arms: (a) lifestyle intervention group received advice on reducing dietary intake and increasing physical activity, along with behavior counseling, (b) control group received standard advice, (c) metformin-only group (see text), and (d) metformin-plus-lifestyle modification group (see text).	2.5 years	The cumulative incidence of diabetes was 55% in the control group and 39% in the lifestyle intervention group, corresponding to reduced risk for developing diabetes by 29% in the lifestyle intervention group.

Table 3
Low-carbohydrate diets in type 2 diabetic patients

Study	Subjects and design	Changes from baseline	
		Body weight (kg)	Glycated hemoglobin (%)
Gutierrez et al. 1998 (87)	19 treated, BMI 27.9 kg/m ² ; cross-over: carbohydrate 25% of total energy, 8 weeks vs usual diet (carbohydrate 55% of total energy), 12 weeks	-1.4 ^a	-1.8 ^a
Gutierrez et al. 1998 (87)	9 not treated, BMI 29.6 kg/m ² ; cross-over: carbohydrate 25% of total energy, 8 weeks vs usual diet (carbohydrate 55% of total energy), 12 weeks	-0.8	-1.4 ^a
Robertson et al. 2002 (186)	88, BMI 38.6 kg/m ² ; single arm: carbohydrate 40 g/day, 12 months	-4.9 (1 mo) ^b -7.8 (3 mo) ^b -9.5 (6 mo) ^b -7.2 (12 mo) ^b	-1.4 (3 mo) ^b -0.9 (6 mo) ^b -0.8 (12 mo) ^b
Boden et al. 2005 (27)	10, BMI 40.3 kg/m ² ; cross-over: carbohydrate 21 g/day, 14 days vs usual diet (carbohydrate 309 g/day), 7 days	-2.0 ^a	-0.5 ^a
Yancy et al. 2005 (241, 242)	28; BMI 42.2 kg/m ² ; single arm, carbohydrate 20 g/day, 4 months	-8.7 ^a	-1.2 ^a
Nielsen & Joensson 2006 (157), Nielsen et al. 2005 (158)	16, 100.6 kg; nonrandomized: hypocaloric diet with carbohydrate 20% of total energy, 6 months with follow-up at 22 months (control: 15, 101.5 kg; hypocaloric diet with carbohydrate 60% of total energy, 6 months without follow-up)	-8.7 (3 mo) ^{a,c} -11.4 (6 mo) ^{a,c} -8.6 (22 mo) ^a	-2.1 (3 mo) ^{a,c} -1.4 (6 mo) ^{a,c} -1.1 (22 mo) ^a
Daly et al. 2006 (46, 47)	51, BMI 35.4 kg/m ² ; randomized: carbohydrate 70 g/day, 3 months with follow-up at 6 months (control: 51, BMI 36.7 kg/m ² ; low-fat diet)	-3.6 (3 mo) ^{a,c} -3.8 (6 mo) ^{a,c}	-0.6 ^a -0.5 ^a
Westman et al. 2008 (228)	21, BMI 37.8 kg/m ² ; randomized: carbohydrate 20 g/day, 6 months (control: 29, BMI 37.9 kg/m ² ; low-glycemic-index diet)	-11.1 ^{a,c}	-1.5 ^{a,c}

BMI, body mass index.

^aSignificant change from baseline ($P \leq 0.05$).

^bSignificance not reported.

^cSignificant versus respective change in control diet group ($P \leq 0.05$).

Table 4
Beneficial effects of exercise in patients with type 2 diabetes

Cardiovascular	Increases aerobic capacity and fitness level
	Decreases resting pulse rate and rate-pressure product
	Decreases or does not affect blood pressure at rest and during exercise
	Decreases resting and submaximal heart rate
	Increases stroke volume, cardiac output, and oxygen extraction
Lipid profile	Increases high-density lipoprotein cholesterol concentration
	Does not affect or reduces low-density lipoprotein cholesterol concentration
	Does not affect total cholesterol concentration
	Reduces ratio of total to high-density lipoprotein cholesterol
Body composition	Does not affect or slightly reduces body weight
	Reduces fat mass and visceral adipose tissue, especially in obese patients
	Does not affect or increases fat-free mass
Metabolic parameters	Increases insulin sensitivity and glucose tolerance
	Reduces glycated hemoglobin
	Increases resting metabolic rate and postprandial thermogenesis
Psychological effects	Improves self-concept and self-esteem
	Reduces depression and anxiety
	Reduces stress response to psychological stimuli

Derived from Albright et al. (5) and Verity (218).