The Prevention and Treatment of Obesity

Application to type 2 diabetes

CAROL A. MAGGIO, PHD
F. XAVIER PI-SUNYER, MD

Type 2 diabetes, or non-insulin-dependent diabetes mellitus (NIDDM), accounts for 90–95% of the 16 million cases of diabetes in the U.S. today (1). As many as 90% of individuals with type 2 diabetes are overweight or obese (2). However, not all individuals with type 2 diabetes are obese and not all obese individuals develop type 2 diabetes (1,3). The major purpose of this technical review is to assess the effectiveness of existing strategies for the prevention and treatment of obesity as applied to people with type 2 diabetes. This review is designed to address the following questions:

1. What is the association between obesity and type 2 diabetes?
2. What are the benefits of weight loss in type 2 diabetes?
3. Have effective strategies for the prevention of obesity been identified? If so, what is the impact of such strategies on the prevention of type 2 diabetes?
4. How effective are current treatment strategies in promoting weight loss in obese individuals with type 2 diabetes? In addition, what are the effects of these strategies on glycemic control?

OBESITY AND TYPE 2 DIABETES — According to a 1985 National Institutes of Health Consensus Development Conference (4), obesity is defined as a BMI (weight in kilograms divided by height in meters squared) ≥27.8 in men and ≥27.3 in women. Both obesity and type 2 diabetes (1,3) are considered heterogeneous disorders that involve multiple etiologies. While the mechanism(s) underlying the relationship between obesity and type 2 diabetes in susceptible individuals remains to be identified (3), there is nevertheless a strong association between the presence of obesity and the development of type 2 diabetes. For example, early cross-sectional studies showed that the largest environmental influence on the prevalence of diabetes in a population was its degree of obesity (5,6). Data from the second National Health and Nutrition Examination Survey indicated that the prevalence of diabetes is 3.8 times higher in overweight (defined as the 85th percentile values of BMI for men and women aged 20–29 years) compared with normal-weight individuals aged 45–75 years (7). In a Scandinavian prospective study, the risk of developing diabetes was ten times greater in men whose body weight exceeded the standard by 35–45% (8).

An increased risk of diabetes with increasing weight has been shown by prospective studies in Norway (8), the U.S. (9), Sweden (10), and Israel (11). More recently, the Nurses' Health Study found that the risk of developing diabetes increases as BMI increases from a level as low as 22 (12). An association between diabetes and increasing relative weight is also observed in populations at high risk for obesity and diabetes, such as the Pima Indians (13).

The development of type 2 diabetes is also positively associated with the duration of obesity (14,15) and weight gain after 18 years of age (16). Finally, several studies have shown increased intra-abdominal fat in individuals with type 2 diabetes (17–19), and it is now apparent that an upper-body or central distribution of body fat is a major risk factor for type 2 diabetes, independent of the absolute level of obesity (20–22).

Impact of obesity on type 2 diabetes

Obesity not only increases the risk of developing type 2 diabetes but also complicates its management. The presence of obesity exacerbates metabolic abnormalities of type 2 diabetes, including hyperglycemia, hyperinsulinemia, and dyslipidemia (2,23–25). Obesity also increases insulin resistance and glucose intolerance (26–28). This makes type 2 diabetes in obese patients more difficult to treat pharmacologically (29,30).

Obesity may contribute to excessive morbidity and mortality in type 2 diabetes (31). While obesity is an independent risk factor for hypertension (32) and cardiovascular disease (33), the coexistence of obesity and type 2 diabetes makes the risk of developing these associated disorders even greater and significantly increases morbidity and mortality (9). In general, the mortality ratio for individuals with diabetes whose body weights are 20–30% above ideal is 2.5–3.3 times higher than for those of normal weight (34). For individuals with diabetes whose body weights are more than 40% above ideal, the mortality ratio becomes 5.2–7.9 times higher (34). Clearly, the presence of obesity further complicates the health risks associated with type 2 diabetes.

Regional fat distribution

An upper-body or central distribution of body fat, independent of the absolute level of obesity, increases the risk not only for type 2 diabetes but also for hypertension, coronary heart disease, and stroke and shows a strong positive association with overall mortality rate (35–38). In people with type 2 diabetes, excess abdominal fat has been associated, even in the absence of overall obesity, with poor metabolic control, atherogenic blood lipid levels, and cardiovascular complications (39). Insulin resistance, which increases with abdominal

From the Division of Endocrinology, Diabetes, and Nutrition, St. Luke's-Roosevelt Hospital Center, Columbia University College of Physicians and Surgeons, New York, New York.

Address correspondence and reprint requests to Xavier Pi-Sunyer, MD, Division of Endocrinology, Diabetes, and Nutrition, St. Luke's-Roosevelt Hospital Center, Columbia University College of Physicians and Surgeons, 1111 Amsterdam Ave., New York, NY 10025. E-mail: xps1@columbia.edu.

This paper was peer reviewed, modified, and approved by the Professional Practice Committee, 14 May 1997.

Abbreviations: FDA, Food and Drug Administration; IGT, impaired glucose tolerance; MUFA, monounsaturated fatty acid; SOS, Swedish Obese Subjects; VLCD, very-low-calorie diet.

or visceral obesity (40–42), is one possible factor underlying the increased health risks of upper-body obesity (43,44).

EFFECTS OF WEIGHT LOSS IN TYPE 2 DIABETES — The health benefits of weight loss in type 2 diabetes have long been recognized (45). Inpatient studies of intensive dieting have repeatedly shown that fasting hyperglycemia rapidly declines, largely within the 1st week of the diet and thus before significant weight loss (46–53). This implies that most of the early reduction in fasting glucose results from caloric restriction rather than from weight loss per se. Underlying the early reduction in fasting glycemia is a parallel reduction in hepatic glucose output (48,49,52,53). Urinary glucose excretion also declines (51). In the longer term, as weight loss progresses and is maintained, an enduring improvement of glycemia may be evidenced by a reduction in glycosylated hemoglobin (46,50,51).

As shown by the U.K. Prospective Diabetes Study of 3,044 patients with newly diagnosed type 2 diabetes, the reduction in fasting hyperglycemia is usually greatest in the patients who lose the most weight (54). However, several studies have documented improvement in metabolic control with even modest weight loss (55–58). Indeed, hyperglycemia can be reduced (as shown by a 0.6% reduction in HbA_{1c}) with even a 5% weight loss (56). However, not all patients show an improvement of glycemic control with weight loss (59). For example, patients whose glycemia fails to improve with weight loss may be at an advanced stage of insulin deficiency.

Weight loss improves the insulin resistance that is characteristic of both obesity and type 2 diabetes (46,48,49,52,55, 60–63). With weight loss, enhanced insulin action is reflected in both an increase in the ability of insulin to suppress hepatic glucose output and an improvement in insulin-mediated glucose uptake into peripheral tissues (49). Virtually all aspects of peripheral glucose uptake have shown improvement with weight loss (23,25,64). However, the precise mechanisms underlying this improvement have not yet been defined (23,25).

It is generally agreed that weight loss decreases fasting insulin levels (23,25). The effect of weight loss on insulin secretion has been inconsistent, with some studies reporting an increase (52,60,62,65) and others reporting no change (48,49,53,55, 61,66). The insulin secretory capacity of type 2 diabetes patients as a group is highly variable (67,68); effects with weight loss may thus depend on the prediet capacity (64). Nevertheless, even the absence of a change in insulin secretion may reflect an improvement in diabetes control when it is accompanied by reductions in glycemia and insulin resistance (23,25).

In type 2 diabetes, weight loss not only improves glycemic control but also ameliorates coexisting disorders such as dyslipidemia and hypertension. Many patients with type 2 diabetes, particularly those who are obese, exhibit a mixed dyslipidemia consisting of elevated triglyceride and reduced HDL cholesterol levels (69). Each of these lipid abnormalities has been shown to increase the risk for coronary artery disease in patients with type 2 diabetes (70,71). With dieting, the elevated triglyceride levels of obese patients with type 2 diabetes rapidly decline (46–48,50–52,56, 72–75). This improvement is usually seen within the initial weeks of caloric restriction. More variable effects have been reported on HDL levels, which appear to be influenced by the amount of weight loss and the duration of weight maintenance (75,76). Significant increases in HDL levels have been reported in studies that have been of sufficient duration (46,75,77). For example, in one study, there was no change in HDL levels after 2 weeks of intensive dieting, but a significant increase was observed after 3 months of weight maintenance (75). In addition, several studies have reported that weight loss may promote a beneficial change in the ratio of total to HDL cholesterol (50,75).

In people with type 2 diabetes, total and LDL cholesterol levels are generally quite similar to those of the general population (78). However, individuals with type 2 diabetes appear to have a higher prevalence of small, dense LDL particles, which are highly atherogenic (79). Weight loss reduces LDL levels in obese individuals with type 2 diabetes (80) and may also, through a reduction of triglyceride levels, promote a reduction in the frequency of small, dense LDL particles (81).

The coexistence of hypertension accelerates the progression of microvascular and macrovascular complications of type 2 diabetes (25). Furthermore, when both hypertension and obesity coexist, the risk of cardiovascular morbidity and mortality in type 2 diabetes becomes especially high because the independent risk associated with each condition is multiplied (4). Numerous studies have documented that weight loss decreases both systolic and diastolic blood pressures in obese patients with type 2 diabetes (51,57,74,75,80). An improvement in blood pressure may be observed as early as the 1st week of caloric restriction (51). In type 2 diabetes, the mechanism by which diet promotes a reduction of blood pressure is complex, but may involve concomitant improvements in insulin resistance and hyperinsulinemia (25,64).

An upper-body distribution of adipose tissue, which is found in many patients with type 2 diabetes (17–19), increases cardiovascular health risks and mortality, independent of the overall level of obesity per se (35–38). There are currently few data available on the impact of weight loss on the body fat distribution of patients with type 2 diabetes. In one study of obese patients with type 2 diabetes who participated in a year-long weight-control intervention, weight loss was associated with significant reductions in the waist-to-hip circumference ratio, an index of upper-body obesity, at both 6 months and 1 year (82). Reductions in waist-to-hip ratio were generally greatest in patients with a higher initial waist-to-hip ratio. However, improvements in glycemic control were not independently associated with changes in waist-to-hip ratio but rather with overall weight loss. In a 3-month study (83), men with type 2 diabetes showed a significant reduction in abdominal adipose tissue area, as measured by magnetic resonance imaging, a more precise indicator of adipose tissue distribution. These patients also showed an increase in insulin sensitivity and reductions in fasting cholesterol and triglyceride levels. The limited data that are available thus show that weight loss in type 2 diabetes is associated with a reduction in the upper distribution of body fat. These data also suggest that a reduction in upper-body fat in patients with type 2 diabetes promotes improvements in insulin resistance and lipid profile.

Effect of weight loss on medication costs in type 2 diabetes

Almost all studies report that weight loss in type 2 diabetes is accompanied by a reduction in or elimination of the need for glucose-lowering agents and medications for associated disorders such as hypertension (23,25). The pharmacy expenses of individuals with diabetes are three to eight

times higher than those of individuals without diabetes (84). A recent study compared the medication costs of obese patients with type 2 diabetes before and 1 year after an intensive weight-loss program (85). Before the program, monthly expenses for antidiabetes and antihypertensive medications and diabetes supplies averaged $63.30. At the end of the 12-week program, weight loss averaged 15.3 kg and monthly medication cost decreased to $20.40. At the 1-year follow up, there was an average weight regain of 6.3 kg and the average monthly medication cost was $32.40. Over the year, the estimated average savings in medication costs was $442.80.

Effects of weight loss on mortality in type 2 diabetes

While the previous discussion implies that weight loss may improve morbidity in type 2 diabetes and ease its economic burden, there have been few studies on the direct impact of weight loss on mortality. This is largely because many patients with type 2 diabetes experience involuntary weight loss as the severity of their disease progresses and complications such as kidney failure and heart disease ensue (64). The available data, reviewed below, appear to indicate that weight loss that is not associated with the complications of diabetes improves mortality.

Lean et al. (86) performed a retrospective study of 263 elderly type 2 diabetes patients in an Aberdeen, Scotland, clinic who died between 1985 and 1986. In this group of patients, age-adjusted life expectancy was 35% lower than published figures for the general population. Nevertheless, multiple regression analysis showed that each kilogram of weight loss from the year of initial diagnosis was associated with a 3- to 4-month increase in survival. With a 10-kg weight loss, life expectancy was restored to that of the general population.

The World Health Organization Multinational Study of Vascular Disease in Diabetes was a prospective cohort study performed between 1975 and 1988 (87). For the European cohort (n = 992), weight loss in the subjects who were initially leanest (BMI <26) was associated with a mortality risk three times greater than that in subjects in the same initial weight category who maintained their weight (relative risk 3.05). In general, these leanest subjects had type 2 diabetes longer, were more likely to be receiving insulin therapy, and had a higher prevalence of retinopathy. Their weight loss was thus more likely due to the severity of their illness than to voluntary dieting. In such individuals, greater mortality with weight loss would be expected. In contrast, a reduction of mortality risk with weight loss (relative risk 0.84) was observed in the subjects who were initially most obese (BMI ≥29), who would be more likely to have experienced voluntary weight loss.

It must be emphasized that the two studies described above did not distinguish between voluntary and involuntary weight loss. A prospective intervention study conducted in Malmö, Sweden, investigated the effect of voluntary weight loss early in the progression of type 2 diabetes on subsequent mortality (88). In the Malmö study, overweight and sedentary middle-aged men with early-stage type 2 diabetes (n = 41) or impaired glucose tolerance (IGT; n = 181) were treated with diet and exercise and followed for 5 years. The average mortality of subjects who sustained a 2.0- to 3.3-kg weight loss dropped to a level lower than that of the general population (3.2 vs. 3.7%). In contrast, the mortality of subjects who did not lose weight increased to 11.9%.

Although research in this area is sparse, there are data that suggest that voluntary weight loss improves mortality in individuals with type 2 diabetes who are overweight or obese.

PREVENTION OF OBESITY —

According to recent national statistics, the prevalence of obesity in adults has increased by 30% over the past decade (89). Over the past 2–3 decades, the prevalence of overweight and obesity in children and adolescents has doubled, and this secular trend appears to be accelerating (90,91). Since obesity is an established risk factor for type 2 diabetes, this increase in the prevalence of obesity may also increase future rates of type 2 diabetes (1). Nevertheless, few controlled clinical trials have investigated the prevention of obesity as it relates to type 2 diabetes. According to the National Task Force on Prevention and Treatment of Obesity (92), this paucity of research is the result of the difficulty in identifying suitable at-risk individuals or groups as well as the lack of effective prevention strategies. The results of two well-known prevention trials are discussed below. One trial is considered unsuccessful because weight loss was not sustained; the other trial is considered successful because there was long-term maintenance of weight loss. Also described are the designs and outcomes of prevention strategies implemented within specific groups currently considered at high risk for obesity (92).

The Minnesota Heart Health Program was a research study that investigated the impact of a multifaceted education campaign on cardiovascular risk factors in three matched pairs of communities in Minnesota, North Dakota, and South Dakota (93). One member of each of the three community pairs was provided with 5–6 years of intensive health-promotion education; the other member of each community pair served as a nonintervention control. Although obesity was not the primary focus of intervention, weight control was encouraged for all participants. In addition, several of the component programs targeted obesity; these included adult education classes, a worksite weight-control program, a weight-loss home correspondence course, and a weight-gain prevention program. The 1,700 individuals who participated in these obesity programs experienced generally modest, short-term weight loss. The average degree of weight loss ranged from 1 kg for the weight-gain prevention program to 3 kg for the worksite and home correspondence programs. None of the programs were effective in sustaining weight loss for more than 1 year. Moreover, overall rates of weight gain remained similar in the three intervention and the three control communities, and at the end of the intervention, the average adult weight in the six communities increased by ~1 BMI unit, or 3.2 kg. This multidimensional education intervention was thus largely ineffective in implementing weight control. The inherent weakness of an educational approach in inducing the behavioral change necessary for obesity prevention, especially in an environment already heavily exposed to the promotion of weight loss, has been among the factors cited in the failure of this program.

The Malmö study (88), which involved a lifestyle intervention program that emphasized a reduced-calorie diet and physical training, was cited in an earlier section of this review on the impact of weight loss on mortality in type 2 diabetes. This section will describe the effectiveness of the Malmö study intervention in promoting and sustaining weight loss and delaying progression to type 2 diabetes. A total of 181 overweight, sedentary men with IGT were enrolled in this lifestyle intervention program. Participants were selected from a large-scale screening survey and thus did not represent

a sample of volunteers. During the 5-year intervention, the dropout rate was only 10%. At the 5-year follow-up, participants showed a mean weight reduction of 2.3 kg. In contrast, 79 nonintervention subjects with IGT showed a mean weight gain of 0.5 kg. In the intervention group, 75.8% showed an improvement in glucose tolerance and only 10.6% progressed to type 2 diabetes. In the nonintervention group, 67.1% showed a deterioration of glucose tolerance and 28.6% progressed to type 2 diabetes. Thus, weight changes in the groups were associated with a significant difference in the relative risk of developing type 2 diabetes. In contrast to the Minnesota Heart Health Program, which failed to sustain weight loss over 1 year, the Malmö study illustrates the feasibility of a diet and exercise intervention program in sustaining weight loss over 5 years and reducing progression to type 2 diabetes. The specific factors underlying the success of this program have not been identified. It has also not been possible to distinguish the specific roles of the diet and exercise components of the program. The success of the Malmö study promotes optimism that effective strategies for the prevention of obesity and type 2 diabetes may be implemented. Further analysis of factors underlying the success of this study is clearly warranted.

In recent years, the prevalences of both obesity and type 2 diabetes have become especially high in minority groups (1,3,94,95), including certain tribes of Native Americans (1,3,96). For example, rates of obesity (97) and type 2 diabetes (13) in the Pima Indian tribe are among the highest in the world. The factors that underlie the increased prevalences of obesity and type 2 diabetes in Native Americans are incompletely understood (3,98). However, both disorders occur far less frequently in Native Americans living a "traditional" lifestyle, characterized by a low-fat, high–complex-carbohydrate diet and physical labor, than in those living in an "affluent" environment, characterized by a high-fat diet and little physical activity (99). Community-based interventions to modify diet and activity levels could thus be an appropriate preventive strategy in Native American communities (98).

The Zuni Diabetes Project is a community-based exercise and weight-control program to reduce rates of obesity and provide primary and secondary prevention of type 2 diabetes (100). A study of the exercise aspect of the program, which involves aerobic exercise sessions, was performed in 30 individuals with type 2 diabetes. Mean program attendance was 1.7 sessions per week for 37 weeks, and mean length of follow-up was 50 weeks. Weight loss averaged 4 kg in participants vs. 0.9 kg in 56 nonparticipants matched for age, health care provider, and duration of type 2 diabetes. In participants, fasting glucose decreased from 13.2 to 10.8 mmol/l. By contrast, fasting glucose in nonparticipants only changed from 12.6 to 12.4 mmol/l. In addition, participants were more than two times as likely as nonparticipants to have decreased their diabetes medication.

The weight-control aspect of the program included a weight-loss competition. Participants received an educational packet every 2 weeks. A team approach was emphasized, and incentives were awarded for different levels of participation and achievement. Of the 271 participants, 92% completed the 10-week program, and a target weight loss of 2.3 kg or more was achieved in 49% of program-completers. The results of these studies illustrate that community-based diet and exercise programs may be a feasible means of promoting at least moderate weight loss in Native American communities. School-based interventions involving diet and exercise are currently being investigated as a means of preventing weight gain in Native American children (98).

The growing rate of obesity among children and adolescents may increase future rates of obesity in adults, since many obese children are likely to remain obese as adults (101). Thus, interventions in childhood obesity may provide an important means of preventing adult obesity (92). A prospective randomized study performed by Epstein et al. (102) with family-based behavioral therapy provides evidence that the effects of treating childhood obesity may persist at least until young adulthood. Seventy-six obese 6- to 12-year-old children and their parents were randomized into three groups that received 8 months of similar diet, exercise, and behavioral training but differed in the focus of reinforcement. In two groups, either the child and the parent or the child alone were reinforced for weight loss; in the third group, the family was reinforced for attendance. At both 5- and 10-year follow-up, children in the child-plus-parent group showed decreases in percentage overweight (−11.2 and −7.5%, respectively). In contrast, increases in percentage overweight at 5 and 10 years were seen in children in the child-only (2.7 and 4.5%) and attendance (7.9 and 14.3%) groups. These differences in percentage overweight were the result of differential weight gain in the three groups. Although children in the child-plus-parent group remained highly overweight, these results indicate that strategies that reinforce weight change in the family may have a long-term impact on attenuating weight gain during childhood and adolescence.

Menopause has been identified as a high-risk period for weight gain (92). The Women's Healthy Lifestyle Program focuses on the prevention of weight gain during the perimenopausal period (103). Five hundred women ages 42–50 years will be randomly assigned to either a lifestyle-intervention program or an assessment-only control group. The 20-week intervention involves a group program designed to reduce intakes of total and saturated fat and cholesterol and to increase physical activity. All participants will be assessed annually. Initial results in 60 women indicate better weight loss in the intervention (−4.8 kg) than in the control (−0.09 kg) group. In addition, 50% of women with BMI >25 have met their weight-loss goal of 4.5–6.8 kg, and 75% of women with BMI <24 have met their weight-loss goal of 2.3 kg. Of course, the long-term maintenance of this weight loss and its impact on health risks remain to be determined.

At present, there is little knowledge concerning the prevention of obesity in individuals or in populations (92). The programs described above serve to illustrate the effectiveness of different prevention strategies. Community-based education programs, such as the Minnesota Heart Health Study, are often ineffective (92,93), but nevertheless, engage a significant number of individuals at relatively low cost (104). Interventions involving diet and exercise are difficult and expensive to implement and maintain and sometimes have high rates of recidivism (105). Moreover, the increasing prevalence of obesity and type 2 diabetes in minority populations has focused attention on the need to develop strategies that are culturally sensitive (95,105). As concluded by the National Task Force on Obesity, the most compelling need in obesity research today is for well-designed studies on the prevention of obesity (92).

TREATMENT OF OBESITY — As discussed, little is known about the pre-

Table 1—*Weight-loss interventions in type 2 diabetes*

Diet
Moderate caloric restriction
Macronutrient alterations
VLCDs
Behavioral therapy
Exercise
Pharmacological therapy
Bariatric surgery

vention of obesity and its impact on comorbid conditions such as type 2 diabetes. In contrast, numerous studies have investigated the treatment of established obesity. As reviewed in an earlier section of this document, these studies generally show that weight loss has beneficial effects on type 2 diabetes. However, many of these studies have been conducted in optimal settings such as inpatient metabolic wards or outpatient multidisciplinary weight-loss clinics (23). Many of the subjects involved were volunteers who may have been selected for motivation or compliance and thus may not be representative of the general obese type 2 diabetes population. As shown in a recent meta-analysis of weight-loss interventions in type 2 diabetes (106), the majority of studies have used a one-group pretest-posttest design, which tends to inflate effect sizes. Moreover, few studies have included follow-up.

The next section of this review addresses the effectiveness of existing weight-loss strategies in type 2 diabetes (Table 1) and focuses, where possible, on controlled experimental studies that include a period of follow-up. Diet therapy and the composition of weight-loss diets are considered first. Next, very-low-calorie diets (VLCDs), behavioral therapy, and exercise are evaluated as alternative strategies to improve weight management in type 2 diabetes. Studies involving combinations of these strategies are also included. Finally, effects on type 2 diabetes of pharmacological therapy to induce weight loss and bariatric surgery are reviewed.

Diet

Diet and weight loss have traditionally been the cornerstone of therapy in obese patients with type 2 diabetes. However, as concluded in a recent American Diabetes Association position statement (107), current dietary strategies are usually not effective in achieving long-term weight loss. As early as 1973, a review by West (108) acknowledged that less than 15% of individuals achieve long-term weight reduction and that the majority of individuals fail to follow dietary recommendations. A recent study analyzed the food intake records of patients attending a diabetes clinic in the U.K. (109). Few of the 67 type 2 diabetes patients evaluated had reduced their caloric intake to lose weight or adjusted their carbohydrate and fat intakes to recommended levels. In an 18-month study that compared the use of three sets of dietary guidelines for type 2 diabetes (110), no significant changes in body weight were observed and almost none of the 70 subjects achieved recommended intakes of carbohydrate or unsaturated fat. While dietary nonadherence may, in a large part, underlie the poor success of such interventions, it must be emphasized that weight loss may also be opposed by physiological adaptations that occur with dieting, such as increased activity/responsiveness of the fat-storage enzyme lipoprotein lipase (111) and decreased energy expenditure (112).

The difficulty of promoting successful weight loss with diet is illustrated on a larger scale by the Diabetes Intervention Study conducted in the former East Germany (113) (Table 2). A group of 1,139 newly diagnosed type 2 diabetes patients (average BMI 29.2) were randomly assigned to either a standard diabetes clinic or an intensive health-modification program including a low-calorie diet. After 5 years, neither group lost weight and energy intakes were 400 kcal/day higher than recommended for the general population.

In the U.K. Prospective Study, 2,597 newly presenting type 2 diabetes patients were treated with diet alone for 3 months before randomization for pharmacological therapy (54). The average caloric prescription was 1,361 kcal/day, with calories restricted according to level of obesity and activity. The average weight loss over 3 months was 5 kg, and body weight decreased from 130 to 123% of ideal. Weight loss was greatest in the heaviest patients, who were prescribed the most restrictive diets. By study criteria, only 16% of the group achieved satisfactory fasting plasma glucose levels (6 mmol/l or less). These individuals had an average weight loss of 8 kg, and their body weight decreased from 132 to 121% of ideal. Not surprisingly, the rate of weight loss achieved in the initial 3 months was not sustained.

A multicenter randomized clinical trial by Franz et al. (114) investigated the effects of two levels of dietitian-provided nutrition intervention. Although the primary outcome measure was metabolic control, strategies to promote weight loss were also implemented. A total of 247 subjects with type 2 diabetes (average BMI 33) were randomized to receive either basic care consisting of one dietitian session or practice-guidelines care consisting of up to three sessions within 6 weeks. At 6-month follow-up, weight loss in the groups was statistically significant but modest (overall average loss, 1.4 kg). Between-group differences in weight loss were not statistically significant. In the basic-care group, weight loss averaged 1.7 kg and 16% achieved a successful weight loss of 4.5 kg or more, while in the practice-guidelines group, weight loss averaged 1.4 kg and 19% achieved successful weight loss. HbA_{1c} (initial level of 8.3%) was significantly reduced in both groups (−0.7% with basic vs. −0.9% with practice-guidelines care). Over the same period, a nonrandom comparison group of 62 subjects who had no contact with a dietitian showed no change in HbA_{1c}.

A Finnish study performed by Laitinen et al. (115) involved 86 obese patients with recently diagnosed type 2 diabetes. After 3 months of basic diabetes education, patients lost an average of 3.4 kg. They were then randomly allocated to receive intensive dietary therapy or conventional diabetes treatment. The intensive intervention lasted 12 months and involved six bimonthly visits with a physician, a nurse, and a clinical nutritionist. At the end of the 12-month experimental period, the intervention group lost an additional 1.8 kg, and the control group gained 1.0 kg. Although this difference in weight change was statistically significant, it is not large given the difference in the intensity of the treatments imposed.

In a study by Heller et al. (116), 75 obese (average BMI 31.4) patients with newly diagnosed type 2 diabetes were randomized to receive either routine clinic care or group education by diabetes specialist nurses and a dietitian in a British university hospital. There was no standard diet prescription. The education program consisted of three weekly sessions and follow-up visits at 3 and 6 months. At 6 months, patients receiving group education lost significantly more weight than did patients receiving routine care (median losses of 7 vs. 2 kg, respectively) and showed significantly bet-

Table 2—*Dietary interventions and weight loss in type 2 diabetes*

Reference	Study design	Patients	Outcome
Hanefeld et al. (113)	Randomized; treatment in standard diabetes clinic vs. 5-year health modification program including low-calorie (800–1,500 kcal/day) diet.	1,139 newly diagnosed patients (average BMI = 29.2)	At 5 years, no overall weight loss in either group.
UKPDS Group (54)	Single group; 3-month trial of diet alone (average of 1,361 kcal/day, based on level of obesity and activity) before drug therapy.	2,597 newly diagnosed patients (130% of ideal body weight)	Reduction to 123% of ideal body weight (5-kg weight loss)
Franz et al. (114)	Randomized; dietitian-provided medical nutrition therapy according to basic (1 session) vs. practice-guidelines (3 sessions in 6 weeks) care.	247 patients (average BMI = 33)	At 6-month follow-up, weight loss of 1.7 kg with basic care vs. 1.4 kg with practice-guidelines care. Successful weight loss of ≥4.5 kg in 16% of basic care vs. 19% of practice-guidelines care group.
Laitinen et al. (115)	3 months of basic diabetes education, followed by randomization to conventional treatment vs. intensive dietary therapy (6 bimonthly visits with physician, nurse, and nutritionist).	86 newly diagnosed patients (average BMI = 33.5)	At 3 months, overall weight loss of 3.4 kg. At end of 12-month experimental period, weight gain of 1.0 kg with conventional treatment vs. additional weight loss of 1.8 kg with intensive treatment.
Heller et al. (116)	Randomized; routine clinic care vs. group education by nurses and dietitian (3 weekly sessions, follow-up at 3 and 6 months).	75 newly diagnosed patients (average BMI = 31.4)	At 6 months, median weight loss of 2 kg with routine care vs. 7 kg with group education. At 1 year, median weight losses were 3 and 5.5 kg, respectively.
Hadden et al. (117)	Single group; 1,450 kcal/day diet and monthly visits with physician and dietitian for 6 months; 2,000 kcal/day diet and visits every 3 months for up to 72 months.	223 newly diagnosed patients (32% above ideal weight for age).	Weight loss at 6 months of 9 kg, which was maintained over 6-year study period.

ter glycemic control (median HbA_1 of 7.5 vs. 9.5%). At 1 year, however, the difference in weight loss became smaller (−5.5 vs. −3 kg) and a difference in glycemic control was no longer observed.

One of the few reports of successful long-term weight loss with diet comes from the Diabetes Treatment Study (117), which provided long-term access to therapeutic contact. In this uncontrolled prospective trial conducted in Northern Ireland, 223 patients with recently diagnosed type 2 diabetes (32% above desirable weight for age) were placed on a 1,450-kcal diet for 6 months and seen monthly by physicians and a dietitian. Caloric intake was then increased to 2,000 kcal, and patients were seen at 3-month intervals for up to 72 months. Average weight loss at 6 months was 9 kg, and this was maintained for the 6-year study period. Moreover, NIDDM could be managed by diet alone in 87% of the patients at 1 year and in 71% at 6 years.

The six studies reviewed above involved middle-aged patients with a recent diagnosis of type 2 diabetes who were generally treated with diet alone. Thus, patient variables, such as age, severity of diabetes, and its treatment, were not likely to have contributed to the observed differences in treatment outcome. Other patient variables, such as motivation, cannot be excluded but are difficult to assess. The studies were performed in different countries, thus introducing differences in health care systems and dietary habits. Most importantly, the studies differed in the type of treatment provided, its frequency, and its length. One major factor that characterized the Diabetes Treatment Study, where major weight loss was sustained, was the initial use of frequent medical and dietary counseling, which was then implemented at intervals over a number of years.

In patients with type 2 diabetes, as in the general population, the available data seem to show that the implementation of successful weight loss with diet is often difficult to achieve and even more difficult to maintain. With moderate caloric restriction, individuals generally lose ~10% of initial body weight (118). However, an average of one-third of the lost weight is usually regained in the year after treatment, and almost all of the lost weight may be regained within 5 years (119). This alarming degree of recidivism has promoted the recognition that obesity, like type 2 diabetes, is a chronic condition that requires continuing care and major lifestyle changes (119–121). Although not a controlled study, the Diabetes Treatment Study (117) does illustrate that maintenance of significant weight loss may be achieved when weight-loss therapy is provided on a long-term basis. Furthermore, as shown in controlled studies involving nondiabetic individuals (121,122), maintenance of weight loss is improved when some form of follow-up contact is provided.

Diet composition

Prescription of a weight-loss diet in type 2 diabetes requires attention to the effects of that diet on both glycemic control and the associated risk factor of dyslipidemia. There has been controversy concerning the optimal nutrient composition of diets for weight loss in type 2 diabetes, as well as for type 2 diabetes in general (123–126). Nevertheless, few controlled studies have investigated the effects of diet composition on weight loss in type 2 diabetes. The few available studies have been of short duration and have involved a limited number of subjects.

Low-fat diets. In nondiabetic subjects of normal weight, several well-controlled lab-

oratory investigations have shown that consumption of a low-fat diet promotes weight loss (127–129). However, in overweight and obese subjects, low-fat diets have not consistently been associated with better weight loss (130).

Until recently, dietary recommendations for patients with diabetes have emphasized the reduction of calories from total and saturated fat and their replacement with calories from starches (131). The rationale underlying this approach has been that lower-fat diets will reduce the risk of coronary artery disease by reducing total and LDL cholesterol levels. However, in patients with type 2 diabetes, there has been some concern that the substitution of carbohydrate for fat in the diet may impair glucose tolerance, increase hypertriglyceridemia, and reduce HDL cholesterol (123,126,132). Deleterious effects of a high-carbohydrate diet were not observed in a recent randomized 10-center study that compared a prepared meal plan designed to meet national cardiovascular risk reduction guidelines with a similarly designed self-selected diet in 560 subjects with type 2 diabetes, hypertension, or dyslipidemia (133). The macronutrient composition of the diets, which were followed for 10 weeks, was (by calories) ~62% carbohydrate, 21% protein, and 17% fat. On both diet plans, subjects with diabetes showed significant decreases of plasma glucose, insulin, fructosamine, and HbA_{1c}, and the cohort as a whole showed significant improvement of lipid parameters.

Few studies have specifically varied the fat contents of weight-loss diets in type 2 diabetes. Pascale et al. (134) studied 44 obese women with type 2 diabetes who were enrolled in an intensive behavioral weight-control program. The women were randomized to consume a 1,000–1,500 kcal/day diet containing either <30% or <20% fat. The group on the 20% fat diet had lost significantly more weight at the end of the 16-week program (−7.7 vs. −4.6 kg). Even after adjusting for differences in weight loss, improvements in fasting glucose, glycosylated hemoglobin, and total cholesterol levels were similar in the two diet groups at 16 weeks. Although at 1-year follow-up the 20% fat group maintained significantly better average weight loss (−5.2 vs. −1.0 kg), only 33% of this group maintained a weight loss of 5 kg or more. With weight regain, none of the initial 16-week metabolic improvements were maintained in either diet group.

Advantages of a hypocaloric, lower-fat diet were not observed in a study of weight loss in 25 obese women, 13 of whom had a history of gestational diabetes (135). This blinded, randomized, crossover study compared 6 weeks of treatment with 1,500 kcal/day diets containing either 40 or 55% carbohydrate. The diets were provided largely in the form of nutritional supplement bars. Weight losses on the diets were comparable. During the first phase of treatment, most women lost 2.3–4.5 kg. During the second phase, there was reduced adherence to the diets and weight losses declined. In general, triglyceride levels became higher during treatment with the lower-fat, 55% carbohydrate diet. This study differed from the Pascale et al. (134) study both in the length of treatment and in the form of the diet. In addition, the Pascale et al. (134) study was implemented within a more comprehensive weight-control program, which included training in diet, behavioral modification, and exercise.

High–monounsaturated-fat diets. Potential deleterious effects of high-carbohydrate diets in some patients with type 2 diabetes have prompted the investigation of diets enriched with monounsaturated fatty acids (MUFAs) (126). Several short-term studies have in fact shown that such diets are associated with better glycemic control and lower triglyceride levels than high-carbohydrate diets (136–138). However, these improvements, in some cases, neither were of sufficient magnitude to be considered clinically significant nor were associated with more important measures of glycemic control such as glycosylated hemoglobin. There is some concern that in the longer term, the increased fat content of such diets may promote weight gain and thus impair glycemic control through increased insulin resistance (124).

A recent short-term study compared the weight-loss effects of hypocaloric (50% of maintenance calories) formula diets enriched with MUFAs (49% of calories, 70% calories from fat) or carbohydrates (70% of calories, 10% calories from fat) (139). Seventeen obese patients with type 2 diabetes were matched for fasting glucose level and BMI; nine of the patients consumed the MUFA diet and eight consumed the high-carbohydrate diet for 6 weeks. Weight losses were similar in the two groups, but the MUFA group showed significantly greater decreases in fasting and 24-h glycemia. After 4 weeks of refeeding on the diets to achieve weight maintenance, postprandial glycemia deteriorated in the high-carbohydrate group but not in the MUFA group.

There is clearly a need for longer, larger-scale studies to investigate the optimal diet compositions to promote weight loss in type 2 diabetes and the effects of such diets on metabolic control. However, note that several reviews of the dietary treatment of obesity have concluded that weight loss cannot be achieved or maintained without a reduction of caloric intake, regardless of diet composition (118,130,132).

VLCDs. VLCDs were developed as a means of achieving larger and more rapid weight losses than are attainable with standard low-calorie diets, but without the dangers of total starvation (140). Current VLCDs are consumed over a 12- to 16-week period and contain 400–800 kcal/day, with at least 70 g of high-quality protein to conserve lean body mass (23,25,140). VLCDs are now administered in the form of either liquid formulas or solid foods. Food-based VLCDs are called protein-sparing modified fasts and consist of lean meat, fish, and fowl (141). The use of VLCDs including both a liquid formula and solid foods has also been evaluated (80).

Individuals treated with VLCDs generally lose more weight more rapidly and have higher short-term success in achieving weight loss than do individuals treated with more moderate caloric restriction (23). VLCDs have produced weight losses of 15–20 kg in 12 weeks, which is more than twice the average weight loss of 8.5 kg in 20–24 weeks produced by standard low-calorie diets of 1,000–1,500 kcal/day (142). With VLCDs, 90% of patients may lose 10 kg or more, whereas with standard low-calorie diets, only 60% of patients lose this amount (140).

Current VLCDs are generally recognized as safe when administered under proper medical supervision (140). Common side effects, which are generally well tolerated, include fatigue or weakness, dizziness, constipation, diarrhea, nausea, headache, and cold intolerance (23,25, 140). More serious side effects have included gallstones, acute cholecystitis, and gout. According to the National Task Force on the Prevention and Treatment of Obesity (140), use of a VLCD is generally indicated only in well-motivated individuals with BMI >30 who have failed at more moderate approaches to weight loss. Use of a VLCD may also be indicated in individuals with BMI of 27–30 who have likewise

Table 3—*Controlled studies of VLCDs in type 2 diabetes*

Reference	Study design	Number of patients	Outcome
Wing et al. (147)	Behavioral program with standard 1,000 kcal/day diet throughout vs. 400 kcal/day VLCD for 12 weeks followed by gradual increase of intake to 1,000 kcal/day from week 16 onward.	93 (≥30% above ideal body weight)	Target 11% weight loss achieved in 35% of standard diet group in 12.7 weeks vs. 80% of VLCD group in 9.1 weeks. 15 weeks later, weight losses from study entry of 18.1 kg in the standard diet vs. 19.2 kg in the initial VLCD group.
Wing et al. (148)	20-week behavioral program with standard 1,000–1,500 kcal/day diet throughout or inclusion of an 8-week 400 kcal/day VLCD.	36 (average BMI = 37.7)	At 20 weeks, greater weight loss in VLCD (−18.6 kg), than in standard diet (−10.1 kg) group. At 1 year, weight-loss maintenance similar (−8.6 and −6.8 kg, respectively).
Wing et al. (77)	50-week behavioral program with standard 1,000–1,200 kcal/day diet throughout or inclusion of two 12-week periods of 400–500 kcal/day VLCD.	93 (average BMI = 37.9), 74 in 2-year follow-up.	Difference in weight loss maximum at end of first VLCD (12 weeks): 11.1 kg in standard diet vs. 16.0 kg in VLCD group. At 50 weeks, losses were 10.5 and 14.2 kg, respectively. At 2 years, weight loss from study entry similar: 5.7 and 7.2 kg, respectively.
Anderson et al. (80)	12-week behavioral program with 800 kcal/day diet as liquid formula alone vs. liquid formula plus evening meal of solid food.	40 (BMI = 30–40)	No effect of form of diet. Average weight loss of 15.7 kg at 12 weeks, 8.8 kg at 1-year follow-up.

failed to lose weight and who have a comorbid condition such as type 2 diabetes that may improve with rapid weight loss.

A major concern regarding the use of VLCDs in obese patients in general is that long-term maintenance of this weight loss is often poor (119,140,142,143). For example, Wadden and Stunkard (144) observed that patients regained 64% of their weight loss within 1 year, and Sikand et al. (145) found that patients regained almost their entire weight loss within 2 years. At 5-year follow-up, Wadden et al. (146) found regain up to or beyond pretreatment weight in 61% of patients treated with a VLCD.

Controlled clinical trials have shown that VLCDs generally result in greater weight loss and slower weight regain when combined with behavior therapy and in better maintenance of weight loss when combined with exercise (140). As a result, VLCDs are now often administered within the framework of multifaceted weight-control programs that also include behavior therapy, nutritional education, and exercise. A drawback of VLCDs is their high cost, which has been estimated at $3,000 for 26 weeks of treatment (140). VLCDs are considered more expensive to administer than low-calorie diets and, although considered safe when administered under proper medical supervision (140), present more risks than standard low-calorie diets (119). Moreover, when the high rates of weight regain following VLCDs are considered, the cost per kilogram of weight loss with VLCDs becomes significantly higher than the cost of conventional diets (140).

As shown in a recent meta-analysis (106), VLCDs have been the dietary intervention studied most often with regard to weight loss in type 2 diabetes. Many of these studies have been short-term and have been conducted in small numbers of hospitalized patients to analyze the metabolic improvements associated with weight loss (23). Several studies indicate that obese patients with type 2 diabetes may lose slightly less weight than nondiabetic patients (50,51) but that they do not exhibit greater loss of lean body mass (50). A review of VLCD therapies lasting from 23 days to 6 months concluded that average weight loss attained in patients with type 2 diabetes is generally in the range of 1–3 kg per week (23).

In obese patients with type 2 diabetes, treatment with VLCDs has generally been associated with large, statistically significant improvements in body weight and in most major metabolic control variables (106). Numerous studies have shown a rapid improvement in metabolic control within the first 1–2 weeks of treatment and before significant weight loss (46–53). For example, in a study performed by Henry et al. (48) of 30 obese type 2 diabetes patients treated with a 330 kcal/day diet for 40 days, 87% of the reduction in fasting plasma glucose levels (−139 mg/dl, or −7.7 mmol/l) occurred within the first 10 days of the diet, when only 4.6 kg was lost. By day 40, fasting plasma glucose levels decreased by only an additional 20 mg/dl (1.1 mmol/l) as total weight loss increased to 10.5 kg. With refeeding to maintain weight loss, much of the initial glycemic improvement was lost; fasting plasma glucose levels increased by 80% during 40 days of isocaloric feeding. Such findings support the concept that caloric restriction, rather than weight loss, is the major factor underlying the glucose-lowering effects observed with VLCDs.

The above findings imply that a large part of the superior metabolic improvement associated with VLCDs may endure only as long as severe caloric restriction is maintained. This possibility is supported by the results of a study by Wing et al. (147) that compared the metabolic effects of comparable (11%) weight loss in patients who were randomized to treatment with either a 400 or a 1,000 kcal/day diet (Table 3). This study also permits some comparison of the effects on weight loss of a VLCD versus more moderate caloric restriction in type 2

diabetes patients. Only 53 of the 93 patients studied managed to achieve an 11% weight loss in 20 weeks. A significantly greater percentage of patients achieved this goal in the 400-kcal compared with the 1,000-kcal condition (80 vs. 35%, respectively). In addition, the target weight loss required fewer weeks of dieting in the 400-kcal condition (9.1 vs. 12.7 weeks, respectively). On achievement of the target weight loss, patients in the 400-kcal condition had significantly lower fasting glucose levels and greater insulin sensitivity than did patients in the 1,000-kcal condition.

Intake in the 400-kcal group was then increased to 1,000 kcal/day and both groups were studied for an additional 15 weeks. Weight loss from entry to end of study was comparable (−19.2 kg in the initial 400-kcal group vs. −18.1 kg in the 1,000-kcal group). The group initially treated with the 400-kcal diet showed a modest increase in fasting glucose and no further change in insulin sensitivity, while the group treated with the 1,000-kcal diet throughout showed a further decrease in fasting glucose and a trend toward further improvement in insulin sensitivity. As a result, the groups no longer differed in either fasting glucose level or insulin sensitivity at the end of the 15-week period.

The above short-term study does confirm that in patients with type 2 diabetes, a VLCD is initially associated with superior weight loss and improvements in glycemic control, but it also implies that these superior initial effects of a VLCD may be lost when caloric intake is increased only to the level of a conventional weight-loss diet. In obese patients with type 2 diabetes, it is thus important to know whether the increased costs of VLCDs are justified in terms of their effects on the long-term maintenance of weight loss and glycemic control. Numerous noncomparative metabolic ward studies have documented that VLCDs may induce excellent short-term weight loss and improvements in metabolic control. However, few comparative studies have evaluated the long-term effects of VLCDs in obese patients with type 2 diabetes.

In another study by Wing et al. (148), 36 obese patients with type 2 diabetes were treated in an intensive 20-week behavioral weight-loss program that either used a 1,000–1500 kcal/day diet or included an 8-week period of a 400 kcal/day VLCD. At the end of the program, the VLCD group showed greater weight loss (−18.6 vs. −10.1 kg) and reductions in fasting glucose (−6.5 vs. −3.5 mmol/l) and HbA_1 (−3.1 vs. −1.8%). At follow-up 1 year later, the groups maintained similar weight losses (−8.6 vs. −6.8 kg). Nevertheless, the VLCD group continued to show small but significant decreases in fasting glucose (−3.8 mmol/l) and glycosylated hemoglobin (−1.2%). In the conventional diet group, both of these measures had increased to beyond prestudy levels. Thus, despite maintenance of similar weight loss, only the VLCD group maintained some long-term improvement of glycemic control.

A more recent study by Wing et al. (77) in 93 patients evaluated a 50-week behavioral program that included two 12-week periods of a 400–500 kcal/day VLCD. At the end of the first VLCD (12 weeks), maximum differences were observed between the VLCD group and the group treated throughout with 1,000–1,200 kcal/day in both weight loss (−16.0 vs. −11.1 kg, respectively) and improvement in HbA_1. At the end of the program, the VLCD group still showed slightly more weight loss than the standard diet group (−14.2 vs. −10.5 kg). However, reductions in HbA_1 from study entry to 1 year were statistically similar in the VLCD (−2.3%) and standard diet (−1.4%) groups, as were reductions in fasting glucose and insulin levels. In addition, the groups showed a similar significant decrease in waist-to-hip circumference ratio, an index of upper-body distribution of body fat that is associated with both type 2 diabetes and cardiovascular disease (82). This improvement in body fat distribution was related to overall weight loss rather than to glycemic control.

Of the patients studied by Wing et al. (77), 74 attended a 2-year follow-up assessment. Weight loss from prestudy was similar in the VLCD (−7.2 kg) and standard (−5.7 kg) diet groups. Despite this 2-year maintenance of an average 6-kg weight loss, all laboratory measures of glycemic control had reverted to prestudy levels in both groups. Significantly more patients in the VLCD than in the standard diet group (55 vs. 31%) were able to remain off diabetes medication. Nevertheless, the authors concluded that the extent of the long-term differences between the VLCD and standard diet conditions was quite modest and thus of questionable clinical significance.

In nondiabetic obese patients treated with VLCDs, a controlled trial found no additional benefit of restricting intake to <800 kcal/day (149). The studies in obese patients with type 2 diabetes described above used diets of only 330–500 kcal/day. A recent study by Anderson et al. (80) in 40 obese patients with type 2 diabetes suggests that similar weight loss may be obtained through the use of an 800 kcal/day VLCD within an intensive behavioral program. Patients were randomized to consume the diet either as a liquid formula alone or in combination with an evening meal of solid food, but results were not influenced by the form of the diet. At the end of 12 weeks, patients lost an average of 15.7 kg. Metabolic improvements included a 27.8% reduction in serum glucose and a 20.8% reduction in glycosylated hemoglobin. At 1-year follow-up, an 8.8-kg weight loss was maintained. Long-term effects on glycemic control are not reported, although it is mentioned that blood pressures remained significantly reduced despite less use of antihypertensive medication. Similarly, an inpatient study by Bauman et al. (73) found that treatment with a 900 kcal/day diet for 23 days resulted in an average weight loss of 1.8 kg/week. In the 62 patients evaluated, fasting plasma glucose fell from 221 to 122 mg/dl (12.3 to 6.8 mmol/l). As a result of such findings, more moderate diets of 800 or more kcal/day are now often used in place of more severe VLCDs of <800 kcal/day (25).

Obese patients with type 2 diabetes may benefit from VLCDs because these diets generally produce large initial improvements in glycemic control (23,25,140,143). In patients with type 2 diabetes, use of these diets requires careful blood glucose monitoring and adjustment of diabetes medication. Not all patients with type 2 diabetes who experience weight loss on a VLCD show significant improvements in glycemic control. According to a retrospective study (59), 60% of 135 patients who lost at least 9.1 kg after 3–7 days of fasting followed by 2 weeks of a 500 kcal/day VLCD maintained a random plasma glucose level of >10 mmol/l. These nonresponders were considered to suffer from insulin deficiency and, with weight loss, were farther from ideal body weight than responders, who were considered to suffer largely from insulin resistance. In a smaller study of a 500 kcal/day diet (150), patients who had had type 2 diabetes for >5 years (n = 8) showed less improvement in fasting glucose and oral glucose tolerance than did patients who had had type 2 diabetes for <2 years (n = 10). This difference was observed even though the groups

Table 4—*Behavioral therapy and weight loss in type 2 diabetes*

Reference	Study objective	Number of patients	Outcome
Guare et al. (153)	To compare weight losses of women with or without type 2 diabetes in a 16-week program.	20 nondiabetic, 23 with type 2 diabetes matched for age and weight (average BMI = 34)	At 16 weeks, weight loss of 6.4 kg in nondiabetic vs. 7.4 kg in women with type 2 diabetes. At 1 year, regain of 1.0 and 5.4 kg, respectively.
Wing et al. (56)	To assess long-term effects of participation in behavioral programs that met weekly for 10–16 weeks, monthly for next 6 months, and then at 9 and 12 months (data compiled from three separate studies).	114 (59% above ideal weight)	At end of weekly treatment, weight loss averaged 5.6 kg. At 1 year, maintenance of 4.5-kg loss.
Wing et al. (154)	To examine outcome predictors of treatment in 12- to 20-week programs with 1 year of monthly follow-up.	178 (average BMI = 36.5)	Average weight loss of 7.3 kg at end of weekly treatment, 4.8 kg at 1 year. Men had greater weight loss than women; weight loss was not related to diabetes treatment modality.
Wing et al. (156)	To compare weight losses of black patients and white patients in a 1-year program.	16 black, 59 white (average BMI = 37.7)	Average weight loss of 7.1 kg in black patients vs. 13.9 kg in white patients.
McNabb et al. (160)	To assess weight loss in an 18-week program designed for inner-city black women.	13 (average BMI = 35.6)	At 1 year, maintenance of 4 kg weight loss. Retrospective control group gained 1.4 kg.

had similar initial degrees of obesity and fasting and oral glucose tolerance and incurred similar weight loss.

In summary, the available data indicate that in obese patients with type 2 diabetes, treatment with a VLCD generally results in a large initial weight loss and improvement in glycemic control but that these effects are seldom maintained on a chronic basis. Current VLCD programs are costly, and it is unclear whether these additional costs are justified in terms of the long-term improvements in weight loss and glycemic control that have been maintained. In addition, some data suggest that not all obese patients with type 2 diabetes show the same degree of glycemic improvement when treated with a VLCD. The use of VLCDs in obese patients with type 2 diabetes clearly requires further studies to investigate strategies to help maintain the superior short-term effects of such diets on both weight loss and diabetes control and to identify the patients most likely to attain these improvements.

Behavioral therapy

Behavioral weight-control therapies are based on the premise that weight loss can be achieved by altering eating and/or exercise behaviors (142,151). Behavioral therapy is usually provided in weekly sessions to groups of 6–20 individuals, which is more cost-effective than individual treatment. Careful self-monitoring of food intake and exercise is one of the most important components of behavioral treatment. Other aspects include training in problem solving, nutrition education, self-reinforcement, and stimulus control techniques to limit exposure to food. Many programs now also include cognitive therapy to help the individual overcome self-defeating thoughts.

In general, the rate of weight loss obtained with behavioral programs is only 0.4 to 0.5 kg per week (142). However, the majority of data on behavioral weight-loss treatments is derived from university-based studies and may thus overestimate the amount of weight loss achieved under normal clinical practice (152).

According to a recent meta-analysis of weight-loss interventions in type 2 diabetes (106), behavioral therapy alone was associated with the smallest overall mean change of body weight except for that observed with exercise alone. In a controlled study of patients matched for age and weight (153), the weight loss of 20 obese women with type 2 diabetes enrolled in a 16-week behavioral program was comparable to that of 23 nondiabetic women (−7.4 and −6.4 kg, respectively; Table 4). However, at 1-year follow-up, the type 2 diabetes group showed poorer weight maintenance and regained 5.4 kg, compared with only 1.0 kg in the nondiabetic group.

The majority of controlled studies on the behavioral treatment of obesity in type 2 diabetes have been conducted by Wing and colleagues at the University of Pittsburgh and thus involve a fairly homogenous group of patients. In a review of these studies, Wing (151) concluded that the degree of weight loss achieved and maintained in behavioral programs has increased as programs have increased in length and have included additional components such as diet modification and exercise. For example, the initial 16-week behavioral program resulted in a 6.3-kg weight loss, which was statistically superior to the 3.9-kg weight loss attained in a standard 16-week nutrition education program. At 1-year follow-up, weight-loss maintenance was poorer in the behavioral program (−1.8 kg) than in the nutrition education program (−3.8 kg), although this difference was not statistically significant. In contrast, weight loss in a more recent 1-year behavioral program that included the use of VLCDs was 12.3 kg at 6 months, and 10.5 kg of this weight loss was maintained at the end of the year.

Behavioral programs have generally promoted only modest weight loss. However, an analysis of data compiled from 114 type 2 diabetes patients participating in three studies of behavioral treatments at the University of Pittsburgh demonstrated that in some patients, the amount of weight lost may be large enough to have a long-term effect on glycemic control (56). On study entry, patients were 59% above ideal body weight. At the end of 10–16 weeks of treatment, patients lost an average of 5.6 kg. Treatment was conducted monthly for the next 6 months and then at 9 months

and 1 year. At 1 year, an average weight loss of 4.5 kg was maintained. Patients who lost >6.9 kg (n = 26) or 5% or more of initial body weight (n = 44) showed significant improvement of glycosylated hemoglobin at the end of 1 year. This improvement was attained despite the fact that these patients remained 42% above ideal body weight.

In the above study, the majority of patients did not achieve weight loss sufficient to improve long-term glycemic control. Patient variables associated with successful outcome were analyzed in an additional study of 178 obese patients with type 2 diabetes who participated in behavioral weight-control programs that met weekly for 12–20 weeks and included monthly follow-up for 1 year (154). Weight loss averaged 7.3 kg at the end of weekly treatment and 4.8 kg at 1 year. Sex was the only variable significantly related to weight loss: men lost more weight than women at end of treatment (−9.5 vs. −6.3 kg, respectively) and maintained greater weight loss at 1 year (−6.9 vs. −3.8 kg). Weight loss was not related to type of diabetes treatment: patients treated with diet alone, oral agents, or insulin did not differ in weight loss at either time point. The variable that had the largest effect on improvement in glycemic control, as assessed by fasting blood glucose or HbA_{1c}, was the initial level of fasting blood glucose. Thus, patients whose initial blood glucose level exceeded 200 mg/dl (11.1 mmol/l) showed the greatest improvements in glycemic control.

In the U.S., blacks have a higher prevalence of type 2 diabetes than whites and exhibit higher rates of diabetes-related complications and death (1,3,94,95). In black women, the prevalences of type 2 diabetes and obesity are especially high (155). A recent study compared the effectiveness of a year-long behavioral weight-control program in obese black and white patients with type 2 diabetes (156). Overall weight losses averaged only 7.1 kg in black patients compared with 13.9 kg in white patients. The poorer outcome in black patients resulted from greater weight regain during the second 6 months of the program, when their attendance declined. Although only 16 of the 75 patients were black, these results are consistent with other reports showing that blacks are often less successful at weight loss than whites (157–159).

A preliminary report has appeared concerning PATHWAYS, a behavior-oriented program designed for inner-city black women with type 2 diabetes (160). Ten of the 13 women who completed the 18-week program showed an average weight loss of ~4 kg, which was maintained at 1-year follow-up. In contrast, a retrospective control group showed a 1.4-kg weight gain over the same period. Despite maintenance of weight loss, program participants showed an increase of glycosylated hemoglobin to prestudy level.

To summarize, in obese patients with type 2 diabetes, the available data indicate that behavioral treatments have resulted in only modest weight losses, which in some cases have been associated with long-term effects on glycemic control. Behavioral treatment programs have become more costly as they have increased in length. For example, the cost per kilogram of weight loss of a 26-week behavioral treatment program has become similar to the cost of a VLCD (140). However, as recent reviews have indicated (151,161), the amount of weight loss attainable in behavioral programs and its long-term maintenance may be improved when such programs use a combination treatment approach based on diet modification and exercise. The available data on the effects of exercise on the treatment of obesity in individuals with type 2 diabetes are reviewed in the following section.

Exercise

In obese individuals, exercise may improve blood pressure, lipid and insulin levels, and cardiopulmonary function even in the absence of weight loss (162). Exercise improves insulin sensitivity and acutely lowers blood glucose (132,163). Exercise may also increase psychological well-being and self-esteem (162). However, the effects of exercise on weight loss are generally modest: controlled studies of exercise training have generally found weight losses of only 2–3 kg in exercised groups compared with sedentary control groups (164). When exercise is combined with diet, the average additional weight loss is only 1.8 kg beyond that observed with diet alone. Exercise is nevertheless considered a major determinant of the long-term maintenance of weight loss (142,151,161,162,165). Several correlational studies have shown that individuals who exercise maintain their weight losses better than those who do not (166–169). A recent report of the National Weight Control Registry Study of individuals who have maintained a weight loss of at least 13.6 kg for at least 1 year shows that the majority of the 784 individuals enrolled modified both diet and physical activity during both initial weight loss (89%) and weight-loss maintenance (88%) (169). As a randomized clinical trial has shown, moderately obese men who exercised continued to maintain most of their weight loss as long as 18–36 months after treatment with a standard low-calorie diet or a VLCD (170).

In patients with type 2 diabetes, a recent meta-analysis showed that exercise alone was associated with the poorest effects on weight loss of all interventions evaluated (106). For example, in an uncontrolled study of a 3-month exercise-based diabetes program (57), 111 moderately obese patients with type 2 diabetes showed an average body weight reduction of only 2.4 kg. Nonetheless, this weight loss was accompanied by significant improvements in fasting plasma glucose, serum triglyceride, and glycosylated hemoglobin levels. A modest reduction of blood pressure also occurred. Both the specific contributions of the exercise and diet aspects of this program and whether this degree of weight loss and metabolic improvement could be sustained in the longer term are unknown. However, note that adherence to this exercise program was poor, with only 50% of participants continuing at 3 months and only 10% continuing at 1 year.

Controlled studies evaluating the comparative effects of exercise on weight loss in type 2 diabetes have yielded conflicting results (Table 5), but these studies have varied greatly in methodology, including the type of exercise intervention used. Three short-term, comparative studies that included no follow-up will be considered first. Two of these studies (171,172) showed no advantage of exercise alone or in combination with diet. The third study (173) showed that the combination of diet and exercise was superior to diet alone.

In a study by Kaplan et al. (171), 65 individuals with type 2 diabetes were randomly assigned to behavioral treatment programs involving exercise alone, diet alone, or their combination or to a standard program of diabetes education. Each program lasted 10 weeks; the combination program included 5 weeks of diet followed by 5 weeks of exercise. The exercise program involved stretching and walking. Two weeks after completion of treatment, weight loss was greatest in the diet-alone (−3.3 kg) versus the exercise-alone (−0.6 kg), combination (−0.3 kg), and education-control (+0.05 kg) groups. The diet-alone group also experienced a significant

Table 5—*Controlled studies of exercise and weight loss in type 2 diabetes*

Reference	Treatment condition	Treatment length	Number of patients	Weight loss (kg)
Short-term studies				
Kaplan et al. (171)	Diabetes education	10 weeks	65	+0.05
	Diet			3.3
	Exercise			0.6
	Diet and exercise			0.3
Bogardus et al. (172)	VLCD	12 weeks	18	9.9
	VLCD and exercise			11.1
Yamanouchi et al. (173)	Diet	6–8 weeks	24	4.2
	Diet and exercise			7.8
Longer-term studies				
Hartwell et al. (174)	Diabetes education	10 weeks	76	+1.0 (at 6 months)
	Diet			3.5
	Exercise			1.4
	Diet and exercise			0.25
Wing et al. (175)	Diet/placebo exercise	6 months	25	4.0 (at 1 year)
	Diet/intense exercise			7.8
Wing et al. (175)	Diet	1 year	30	3.8
	Diet and exercise			7.9

increase in HDL cholesterol (5.45 mg/dl, or 0.14 mmol/l) and decrease in LDL cholesterol (−14 mg/dl, or 0.36 mmol/l) in comparison with the other three groups. The poor effects observed in the exercise-alone and combination groups may be related to the modest exercise protocol used. In addition, the combination diet and exercise intervention was implemented through successive condensed versions of the individual diet and exercise protocols rather than as a concurrent intervention.

Bogardus et al. (172) compared the effects of 12 weeks of physical training and a 600 kcal/day diet to those of the diet alone in 18 overweight volunteers with IGT or type 2 diabetes. The training program consisted of stretching, light weight lifting, and aerobic exercise. Physical training plus diet and diet alone induced similar losses of body weight (−11.1 and −9.9 kg, respectively). Improvements in body composition, fasting levels of plasma glucose, serum C-peptide, and insulin, as well as in the glycemic response to a mixed meal, were also similar. In this study, the caloric restriction imposed may have been too great to allow the expression of potential additional effects of exercise.

A 6- to 8-week inpatient study performed by Yamanouchi et al. (173) compared daily walking (at least 10,000 steps/day on a flat surface) plus a 1,000–1,600 kcal/day diet to the diet alone in 24 obese patients with type 2 diabetes. In this case, exercise plus diet resulted in superior weight loss compared to diet alone (−7.8 vs. −4.2 kg, respectively). The combination of exercise plus diet also resulted in improved insulin sensitivity, as shown by increased rates of glucose infusion and metabolic clearance during a euglycemic insulin clamp. In contrast to the two studies reviewed above, the success of this diet-plus-exercise intervention may be related both to the intensity of exercise imposed (subjects walked ~8.4 miles/day) and to the use of more moderate caloric restriction.

The comparative effects of exercise interventions on the long-term maintenance of weight loss and metabolic improvements have also been conflicting. Three longer-term studies will be evaluated. One of these (174) showed that diet alone was superior to both exercise alone and the combination of diet and exercise. In contrast, the second two studies (175), which used more frequent and/or longer interventions and more intense exercise, showed that exercise may have a significant long-term impact on weight loss and glycemic control.

A study in 76 patients with type 2 diabetes (174) compared the effects of the behavioral programs used by Kaplan et al. (171; see above) 3 months after termination of treatment and again found superior improvements with diet alone. The diet-alone group maintained a weight loss of 3.5 kg, compared with a weight loss of only 1.4 kg in the exercise-alone group. The group treated with diet plus exercise had a weight loss of only 0.25 kg, while the education-control group gained 1.0 kg. The diet-alone group also showed a statistically superior reduction of fasting blood glucose, which amounted to 44.6 mg/dl (2.5 mmol/l). The education-control and diet-plus-exercise groups decreased their fasting glucose levels by 16.0 (0.9 mmol/l) and 5.4 mg/dl (0.3 mmol/l), respectively. The exercise group showed a 15.7 mg/dl (0.9 mmol/l) increase in fasting glucose. Potential inadequacies of the exercise and combination protocols used were already cited above in the analysis of the short-term results of this study published by Kaplan et al. (171). The possibility that these protocols may not have been of sufficient intensity to provoke an effect of exercise is supported by the finding that 3 months after the completion of treatment, increased physical conditioning as measured by an increase of oxygen consumption was shown only by male subjects in the exercise group (171).

In contrast, studies conducted by Wing et al. (175) found a strong correlation between exercise and the long-term maintenance of weight loss and glycemic control. At 1 year after pretreatment, patients who reported the highest exercise levels lost the most weight and had the greatest decreases of HbA_1 independent of weight loss.

In the first study by Wing et al. (175), 25 patients were randomly assigned to one of two behavioral treatment programs that varied in the intensity of prescribed exercise. The programs, which included a low-calorie diet, met twice weekly for 10 weeks and

then monthly for 6 months. In the intense-exercise condition, patients walked up to 3 miles per session. In the placebo-exercise condition, patients performed light calisthenics and flexibility exercises. One year from study entry, weight losses were 7.8 kg in the intense-exercise group vs. 4.0 kg in the placebo-exercise group. In the second study by Wing et al. (175), 30 patients were randomized to behavioral weight-control programs based on the more extreme conditions of diet alone versus diet plus exercise. These programs met three times a week for 10 weeks, weekly for an additional 10 weeks, and then monthly for a year. The diet-alone group was instructed not to change their activity level, while the diet-plus-exercise group walked 3 miles at each session. The diet-plus-exercise group showed significantly better weight loss than the diet-alone group at both 10 weeks (−9.3 vs. −5.6 kg, respectively) and 1 year (−7.9 vs. −3.8 kg). Although the groups showed similar improvements in fasting glucose and glycosylated hemoglobin, reductions in diabetes medication were more frequent and greater in magnitude in the diet-plus-exercise group.

In obese patients with type 2 diabetes, studies evaluating exercise alone or in combination with diet have differed greatly in methodology and have thus shown inconsistent effects on weight loss and its maintenance. In studies using moderate diet interventions and more intense exercise, superior effects of the combination of diet and exercise versus diet alone have been observed. Further studies in individuals with type 2 diabetes evaluating the combination of moderate diet restriction and more moderate exercise are clearly warranted.

In summary, in people with type 2 diabetes, regular exercise may have therapeutic effects on glycemic control, cardiovascular health, and psychological well-being (125,132,163). For individuals treated with oral antidiabetic agents or insulin, participation in exercise may require an adjustment of food intake or medication dosage (125). In some patients with type 2 diabetes, exercise may increase the risk of cardiac events, lower-extremity soft-tissue and bone injury, and exacerbation of preexisting proliferative retinopathy (125,132). The available data suggest that obese patients with type 2 diabetes should be encouraged to engage in regular exercise; however, in such patients, an exercise program should not be initiated without proper medical supervision.

Pharmacological therapy

According to a 1995 position paper by the North American Association for the Study of Obesity (NAASO), pharmacological weight-loss therapy may be considered as an adjunct to treatment with diet and exercise in individuals with a BMI of 27 or above who have been unable to lose weight and sustain weight loss and who have a comorbid condition such as type 2 diabetes (176). Most recently, a review by the National Task Force on the Prevention and Treatment of Obesity re-emphasized that pharmacological weight-loss therapy should only be administered within a comprehensive treatment program that includes diet and exercise to selected individuals for whom such therapy could improve health and reduce disease risk (177). The National Obesity Task Force has advised that pharmacological weight-loss therapy should be used with caution or not at all in patients with the following conditions: cardiac arrhythmias, symptomatic cardiovascular disease, severe systemic disease (for example, hepatic or renal failure), monoamine oxidase inhibitor use, glaucoma, depression, or major psychiatric disorders.

The weight-loss effects of drugs currently approved for the treatment of obesity generally amount to 2–10 kg beyond the effect of conventional weight-loss therapy alone (177). Response to weight-loss drugs is variable, with some individuals showing little or no response and others showing greater than average response. Weight regain is commonly seen when drug therapy is discontinued (177).

Most drugs currently approved for the treatment of obesity are either catecholaminergic or serotoninergic agents. The weight-reducing effects of both classes of compounds derive mainly from a reduction of caloric intake due to appetite suppression (178). These drugs are therefore considered anorexic or appetite-suppressant agents. Catecholaminergic drugs include mazindol, phentermine, phendimetrazine, diethylpropion, and phenylpropanolamine (177). Amphetamines, which are included within this first category, are generally not recommended for use in obesity treatment because of their high abuse potential (177). Serotoninergic drugs include *dl*-fenfluramine and its *d*-isomer, dexfenfluramine. The antidepressants fluoxetine and sertraline are serotonin-reuptake inhibitors that are not currently approved for use in obesity treatment alone (177), because these agents have shown no evidence of a sustained effect on weight loss.

Combination drug therapy has also been evaluated in the treatment of obesity. The rationale for this approach has been that combining drugs with different mechanisms of action might allow these drugs to be used in smaller doses to achieve equal or greater efficacy and induce fewer side effects than seen with each individual drug alone (177,179). To date, however, no long-term comparisons of combination versus single-drug therapy have been performed (177). The most common combination therapy has been fenfluramine-phentermine (180). Other combinations that have been used include ephedrine-methylxanthines-aspirin and phenylpropanolamine-benzocaine.

Only one drug is presently approved for long-term use in the treatment of obesity. This is the serotoninergic drug dexfenfluramine, which has been approved for use by the Food and Drug Administration (FDA) for up to 1 year. Most studies of weight-loss drugs have been short-term and have generally lasted no more than 3 months (176). In the recent review by the National Obesity Task Force (177), 20 well-controlled published studies that lasted a minimum of 24 weeks were identified. The largest of these was the year-long International Dexfenfluramine Study (181), in which 822 obese patients (from 120 to 360% of ideal body weight) were randomized to treatment with dexfenfluramine (15 mg b.i.d.) or placebo in 24 centers in nine European countries. At the end of 1 year, the 256 drug-treated patients who completed the trial showed significantly greater weight loss than the 227 placebo-treated patients, although this difference was very modest (−9.8 vs. −7.2 kg, respectively). Moreover, more than twice as many drug-treated compared with placebo-treated patients lost >10% of initial body weight (34.9 vs. 17.0%) or >10 kg (32.4 vs. 15.0%).

In 1990, a review concluded that few drugs for the treatment of obesity have been properly assessed in patients with type 2 diabetes (182). The most recent technical review on the nutritional management of patients with diabetes likewise concluded that more studies are needed on the short- and long-term efficacy and safety of weight-loss drugs in patients with type 2 diabetes (125). In type 2 diabetes, there is a need not only to demonstrate that such drugs are efficacious for weight loss but also to demonstrate that such drugs exert no

Table 6—*Placebo-controlled trials of currently approved appetite suppressants in type 2 diabetes*

Reference	Drug/dosage	Treatment period	Number of patients	Net weight loss (kg)*
Crommelin (183)	Mazindol, 1 mg t.i.d.	3 months	40	2.0
Bandisode et al. (184)	Mazindol, 2 mg q.d.	3 months	64	1.4
Gershberg et al. (185)	Phentermine, 30 mg q.d.	4 months	22	3.6
Campbell et al. (186)	Phentermine, 30 mg q.d	6 months	71	3.8
Wales (191)	Fenfluramine, 60 mg q.d.	3 months, 2 months	26 (oral agents) 12 (diet alone)	2.0 0.5
Salmela et al. (192)	Fenfluramine, up to 120 mg q.d.	7 weeks	13	1.3
Stewart et al. (195)	Dexfenfluramine, 15 mg b.i.d.	3 months	38	4.1
Willey et al. (196)	Dexfenfluramine, 15 mg b.i.d.	3 months	34	3.2
Willey et al. (197)	Dexfenfluramine, 15 mg b.i.d.	3 months	20	+0.9
Tauber-Lassen et al. (198)	Dexfenfluramine, 15 mg b.i.d.	1 year	40	3.4

*Weight loss with drug minus weight loss with placebo.

adverse effects on glycemic control and can be administered safely in combination with insulin or oral antidiabetic medications (183). The following section will focus on placebo-controlled trials of currently approved weight-loss drugs that have been performed in patients with type 2 diabetes (Table 6).

Mazindol is an imidazo-isoindole with moderate stimulant properties (182). Its side effects can include nervousness, irritability, and insomnia (178). Mazindol was evaluated in obese type 2 diabetes patients in two 3-month, double-blind trials. In the first trial (183), which was conducted in a total of 40 patients, treatment with 1 mg mazindol t.i.d. resulted in a weight loss of 4.5 kg compared with 2.5 kg with placebo. In the second trial (184), which was conducted in 64 patients, treatment with 2 mg mazindol per day resulted in a weight loss of 5 kg compared with 3.6 kg with placebo.

Phentermine is an amphetamine derivative with less pronounced stimulant properties at anorectic doses than amphetamine itself (182). Its side effects include minor insomnia, nervousness, irritability, and headache (178). One double-blind trial with phentermine lasted 4 months but involved a total of only 22 patients (185). Treatment with 30 mg phentermine daily was associated with an average weight loss of 6.5 kg vs. only 2.9 kg with placebo. Glucose tolerance did not change in the phentermine group but deteriorated in the placebo group. A second double-blind trial of 30 mg phentermine lasted 6 months and involved a total of 71 patients (186). Average weight losses were 5.3 kg in the phentermine group versus only 1.5 kg in the placebo group. No changes in diabetes control were reported.

Unlike catecholaminergic agents, serotoninergic agents are virtually free of stimulant activity (178). Double-blind studies in patients with type 2 diabetes have shown that these agents improve glycemic control, independent of effects on food intake and body weight (187–189). There is some evidence that this improvement in glycemic control involves a direct effect of the drugs on increasing insulin sensitivity even before weight loss occurs (187,188).

Fenfluramine both releases serotonin and prevents its reuptake at the synaptic cleft (190). Its most common side effects include gastrointestinal disturbances such as nausea and diarrhea, drowsiness, and lethargy (178). Depression may occur with abrupt withdrawal. In a double-blind crossover study (191), 38 obese patients with type 2 diabetes were placed on a 1,000 kcal/day diet and received 60 mg fenfluramine per day or placebo for 2–3 months each. In the 26 patients using oral antidiabetic agents, fenfluramine treatment was associated with an additional 2.0-kg loss of body weight and an 18.3% reduction in the area under the glucose tolerance test curve beyond that observed during placebo treatment. The 12 patients whose diabetes was treated with diet alone received fenfluramine for only 2 months and failed to show significant changes in body weight or glucose tolerance.

In a second double-blind crossover study of fenfluramine (192), 13 patients were treated for 7-week periods with increasing doses of up to 120 mg/day or with placebo. During fenfluramine treatment, mean weight loss was 3.1 kg, while during placebo treatment, mean weight loss was 1.8 kg. There was no rebound weight gain after fenfluramine treatment was withdrawn. Blood glucose levels throughout the day were significantly lower during fenfluramine treatment than during placebo. This glucose-lowering effect was dose-related and was most apparent in the postabsorptive state.

Dexfenfluramine (*d*-fenfluramine) possesses twice the anorectic potency of the racemic mixture *dl*-fenfluramine (178). Its side effects, which have generally been minor and transient, include headache, drowsiness, asthenia, gastrointestinal disturbance, and dry mouth (193).

Four placebo-controlled trials of dexfenfluramine in obese patients with type 2 diabetes will be reviewed. One 3-month double-blind parallel trial compared treatment with 15 mg dexfenfluramine b.i.d. to placebo in 38 obese patients whose diabetes was treated with diet alone or a sulfonylurea (195). The dexfenfluramine-treated group showed an average weight loss of 3.7 kg, while the placebo group showed a weight gain of 0.4 kg. Improved glycemic control in the dexfenfluramine group was evidenced by reductions in glycosylated hemoglobin (−1.7%) and fasting glucose (−0.6 mmol/l). In contrast, the placebo group showed no change of glycosylated hemoglobin and an increase (0.6 mmol/l) in fasting glucose.

An additional 3-month trial of 15 mg dexfenfluramine b.i.d. was completed in 34 obese patients whose diabetes was inadequately controlled by maximum doses of metformin, with or without a sulfonylurea (196). Body weight in the dexfenfluramine group was significantly reduced by 3.8 kg; body weight in the placebo group was reduced by only 0.6 kg. The dexfenfluramine group also showed significantly superior improvements, compared with

placebo, in HbA_{1c} (−1.2 vs. −0.4%) and fructosamine (−39.6 vs. −9.2 μmol/l).

Another 3-month trial of 15 mg dexfenfluramine b.i.d. was performed in 20 obese patients under poor glycemic control despite treatment with insulin and a maximum-tolerated dose of metformin (197). In this study, significant changes in body weight were not observed. Median weight was reduced by 1.1 kg in the dexfenfluramine group and by 2.0 kg in the placebo group. Nevertheless, the dexfenfluramine group showed a significant reduction of HbA_{1c} (−1.4 vs. −0.8% for placebo).

The year-long International Dexfenfluramine Study (181) included a subgroup of 40 obese patients with type 2 diabetes (198). At 1 year, patients treated with 15 mg dexfenfluramine b.i.d. maintained significantly better weight loss (−6.3 kg) than did patients treated with placebo (−2.9 kg). The dexfenfluramine-treated group showed significant reductions in fasting blood glucose (−2.2 mmol/l) and HbA_{1c} (−0.9%). In the placebo-treated group, both of these measures of glycemic control remained unchanged.

In a non–placebo-controlled study, the effect of 3 months of treatment with 15 mg dexfenfluramine b.i.d. on body fat distribution was investigated in 10 male type 2 diabetes patients with an abdominal distribution of body fat (defined as a waist-to-hip ratio >0.9) (83). Abdominal adipose tissue area, as measured by magnetic resonance imaging, was significantly reduced from an initial level of 854 to 666 cm^2. This was mainly the result of a selective 32% decrease in visceral fat area. This reduction of visceral fat in abdominally obese men with type 2 diabetes was accompanied by a significant improvement in insulin sensitivity, measured during a euglycemic glucose clamp, as well as a significant reduction in C-peptide levels. Fasting cholesterol and triglyceride levels were also significantly reduced.

As mentioned earlier, combination drug therapy has also been evaluated in the treatment of obesity. The major double-blind placebo-controlled trial of combination therapy to date was conducted by Weintraub et al. (179) with fenfluramine-phentermine. After 6 weeks of treatment with diet, exercise, and behavior therapy without drugs, 121 obese subjects were randomized to receive the combination of 60 mg fenfluramine plus 15 mg phentermine once per day or placebo for 28 weeks. Weight loss at the 34th week of the study was 14.2 kg in subjects who received combination therapy versus only 4.6 kg in those who received placebo. In a subsample who underwent open-label combination therapy, weight loss was maintained for 3 years. Although this latter part of the trial was not placebo-controlled, this finding suggests a sustained effect of combination therapy. The side effects reported with the doses tested were mild (mainly dry mouth). Whether administration of higher doses over time would cause greater distress is not known. However, the Mayo Clinic recently reported the occurrence of unusual valvular heart disease in 24 women who had been taking fenfluramine and phentermine for an average duration of more than a year (199). Eight of the women also had newly diagnosed pulmonary hypertension, and five required surgery to repair or replace damaged heart valves (see NOTE ADDED IN PROOF). In response to a Public Health Advisory issued by the FDA, 28 additional cases of valvular heart disease have been reported (200).

Sibutramine is a novel appetite suppressant that is being considered for approval for weight loss by the FDA. It is currently being evaluated in obese patients with type 2 diabetes. Sibutramine inhibits both norepinephrine and serotonin reuptake (201). In clinical trials, the most common side effects associated with sibutramine use have been constipation, dry mouth, and insomnia (201). Modest increases in blood pressure and heart rate have also been reported. A 3-month trial compared treatment with 15 mg sibutramine once daily versus placebo in 91 patients with type 2 diabetes whose BMIs ranged from 26 to 35. (202). The sibutramine group showed significantly better weight loss (−2.4 kg) than the placebo group (−0.1 kg). The average reduction of glycosylated hemoglobin was 0.4% in the sibutramine group compared with no change in the placebo group. However, a 1.0% or greater reduction in glycosylated hemoglobin was shown by 35% of the sibutramine group versus only 5% of the placebo group.

Recently, an epidemiological study conducted in five European countries observed an association between the use of appetite-suppressant drugs and the development of primary pulmonary hypertension, a rare but often fatal cardiopulmonary disease (194). The annual incidence of primary pulmonary hypertension is 1–2 cases per 1,000,000. Use of an appetite-suppressant drug for more than 3 months increased the odds ratio for primary pulmonary hypertension to 23.1. The National Obesity Task Force (177) has recommended that patients be closely monitored for symptoms that may indicate the development of primary pulmonary hypertension, which include the onset of dyspnea, changes in exercise tolerance, angina, syncope, and lower-extremity edema. In the event of such symptoms, medication should be discontinued and the patient should be further evaluated.

Orlistat is a potent and selective inhibitor of gastric and pancreatic lipase (203) that may be approved by the FDA for use in the treatment of obesity. When administered with a fat-containing meal, Orlistat inhibits the digestion of triglycerides and thus reduces their subsequent absorption (203). A caloric deficit ensues with the increased excretion of fat in the feces. Consistent with this mechanism of action, the major side effects of Orlistat are gastrointestinal symptoms such as abdominal pain, fecal incontinence, nausea, vomiting, and flatulence (203). In a dose-ranging placebo-controlled trial performed in 237 moderately obese individuals, 12 weeks of treatment with the highest dose of Orlistat (120 mg t.i.d.) resulted in 1.75 kg greater weight loss than treatment with placebo (204).

The weight-loss effects of a new fast-release formulation of bromocriptine mesylate are also currently being evaluated in obese patients with type 2 diabetes. Bromocriptine, a dopamine agonist with serotonin antagonist properties, may reduce body weight by inhibiting lipogenesis and reducing hyperinsulinemia (205).

Data obtained in placebo-controlled trials indicate that the weight-loss effects of currently approved appetite-suppressant drugs in patients with type 2 diabetes have been rather modest. Moreover, there currently are few data available on the long-term efficacy or safety of such drugs. Pharmacological weight-loss therapy can also be costly. At a weight-loss center in New York City, the cost of treatment with 15 mg dexfenfluramine b.i.d. amounts to $75 per month, which is not reimbursed by most medical insurance policies (F.X.P.-S., personal communication). Further research is needed on the long-term use of weight-loss agents in patients with type 2 diabetes. This research should address whether such drugs remain effective in terms of weight loss, whether they remain safe, and whether

the observed improvements in glycemic control (195) as well as in comorbid conditions such as hypertension and dyslipidemia are sufficient to justify their cost.

Bariatric surgery

Bariatric surgery is the most radical and costly form of treatment for obesity. This treatment modality is generally recommended only for severely obese individuals (BMI >40) who are well informed and present with acceptable operative risks (206). Bariatric surgery may also be considered in less severely obese individuals (BMI of 35–40) with high-risk comorbid conditions such as poorly controlled type 2 diabetes or obesity-induced physical problems such as otherwise-untreatable joint disease. Since bariatric surgery involves major operative procedures that impart short- and long-term risks and require long-term follow-up, a National Institutes of Health Consensus Development Conference (206) has advised that patient selection should be based on thorough medical, surgical, psychiatric, and nutritional evaluations.

The bariatric operations most commonly in use are the gastric restriction procedures of vertical-banded gastroplasty and gastric bypass (206). These procedures physically limit food intake by restricting gastric capacity (207). Gastric bypass operations also involve bypassing the duodenum and the first portion of the jejunum and induce some degree of malabsorption. With both procedures, weight loss is rapid and maximum weight loss is usually attained 18–24 months after surgery (208). At 2 years, the mean percentage of excess weight lost is 60–70% for gastric bypass compared with 40–60% for gastroplasty (208). Despite slightly better weight loss, gastric bypass is, as described below, associated with greater risk due to malabsorption and the dumping syndrome. The failure rate for current gastric restriction procedures is 5–10% (208).

According to statistics compiled by the National Bariatric Surgery Registry (209), current obesity surgery has a low perioperative risk. In 5,178 patients studied, five deaths occurred within 40 days of surgery. The vast majority (89.7%) of the 3,174 patients on whom complete information was available had no perioperative complications. The most frequent perioperative complications observed were respiratory problems (4.5%) and wound infections (1.6%); the most serious of these were gastrointestinal leakage (0.6%) and deep vein thrombosis (0.3%). In the longer term, gastric restriction procedures impose a risk for malnutrition due to reduced food intake or vomiting (210). Persistent vomiting has been observed in as many as one-third of patients and may arise from abnormal eating behaviors such as gorging or obstruction of the gastric outlet. With gastric bypass, malabsorption may promote deficiencies of vitamin B-12, folate, and iron. Between 12 and 13% of gastric bypass patients suffer from anemia. Because nutrient deficiencies have been linked to increased risk to the developing fetus, use of medically approved birth control during periods of weight loss is advised in women of child-bearing potential, who constitute up to 80% of patients having bariatric surgery (206). Gastric bypass has, in addition, been associated with the dumping syndrome, which may result in symptoms of gastrointestinal distress and hypoglycemia (210). Because of the potential long-term sequelae of gastric restriction surgery, it has been advised that patients who undergo such procedures require lifelong medical monitoring (206).

Ethical, methodological, and psychosocial considerations make randomized clinical trials of bariatric surgery difficult to implement (207). Data on bariatric surgery are thus largely derived from noncontrolled prospective studies. In severely obese patients with type 2 diabetes, such studies have shown that gastric restriction surgery is highly effective in inducing major weight loss and improvements in glycemic control. Such studies have also shown that surgery may prevent the progression to type 2 diabetes in severely obese individuals with IGT. In surgical patients, glycemic control improves before significant weight loss. Thus, glycemic improvement is thought to be mediated largely through the limitation of caloric intake imposed by these operations (211).

One early study evaluated the outcome of gastric surgeries (bypass, gastroplasty, or gastrostomy) in 23 insulin-treated patients (212). The average presurgical weight of these patients was 119.5 kg and decreased to 92.6 kg at 20 months after surgery. The presurgical insulin dosage of these patients averaged 74 U/day. By 6 weeks after surgery, 14 patients were able to discontinue insulin and the remaining 7 patients reduced their dosage by 72%. In six patients who participated in an inpatient metabolic assessment, fasting blood glucose was reduced from a preoperative level of 321 mg/dl (17.8 mmol/l) to 116 mg/dl (6.4 mmol/l) at 5–11 months after surgery. In addition, HbA_{1c} decreased from 11.8 to 7.9%.

A more recent report by Pories et al. (211) presents follow-up data for as long as 14 years on 608 patients who underwent gastric bypass. Included in this report are follow-up data on 146 patients with diabetes and 152 patients with IGT. The overall patient cohort had an initial mean body weight of 138.4 kg, which was reduced to 87.4 kg at 1 year. At 5, 10, and 14 years, patients available for follow-up were maintaining body weights of ~93.4 kg. Despite this impressive weight loss, most patients remained 50% above ideal body weight. Nevertheless, 82.9% of the patients with type 2 diabetes were able to maintain normal levels of blood glucose and glycosylated hemoglobin. Patients who did not attain normoglycemia were generally older and had type 2 diabetes of longer duration. Only two patients with IGT progressed to type 2 diabetes; the remainder achieved normoglycemia.

A nonrandomized controlled study by Long et al. (213) compared progression from IGT to type 2 diabetes in 109 individuals who underwent gastric bypass vs. 27 individuals who declined the operation. The baseline clinical characteristics of the groups did not differ; the average baseline BMI was ~49.5. The length of follow-up averaged 5.8 years. Weight loss in the surgery group approximated 50% of excess body weight; the control group did not lose weight. In the control group, six subjects developed type 2 diabetes, which resulted in a rate of conversion from IGT to type 2 diabetes of 4.72 cases per 100 person-years. In the surgery group, only one person developed type 2 diabetes. This yielded a conversion rate of only 0.15 cases per 100 patient-years. In the surgery group, weight loss was thus associated with more than a 30-fold decrease in the risk of developing type 2 diabetes.

The available data, which derive largely from noncontrolled studies, indicate that gastric surgery may result in long-term weight loss and major improvements of glycemic control in severely obese patients with type 2 diabetes. As stated by the National Institutes of Health Consensus Development Conference (206), there is clearly a need in this area for long-term controlled clinical trials that use adequate numbers of patients studied under standard protocols. One such trial is the ongoing Swedish Obese Subjects (SOS) study (214).

This prospective controlled intervention study is designed to compare 10-year mortality and morbidity in 1,000–4,500 obese men (BMI ≥34) and women (BMI ≥38) treated by gastric surgery or conventional treatment. Each surgical patient will be matched on the basis of 18 prognostic variables to a conventionally treated control patient. Preliminary data indicate that surgery results in average weight reductions of 25 to 40 kg (215). Conventional treatment in primary health care centers has resulted, on average, in no weight reduction (range of −50 to +30 kg) over 2, 4, and 6 years. The 2-year incidence of diabetes was 33-fold lower in the surgery group than in the conventional-treatment group. Weight loss in the surgery group was also associated with three- to fivefold reductions in the 2-year incidences of hypertension, hypertriglyceridemia, and low HDL cholesterol.

Bariatric surgery involves major surgical procedures that impose a risk for short- and long-term complications, many of which remain poorly defined (206). Until data from large, long-term, standardized, controlled trials such as the SOS study become available, the benefits and risks of bariatric surgery versus alternative treatments for severe obesity and complications such as type 2 diabetes from less severe obesity remain difficult to evaluate and compare.

CONCLUSIONS — The studies evaluated in this review are generally consistent with the conclusion that in most obese patients with type 2 diabetes, current weight-control interventions (nonpharmacological and pharmacological) will result in some degree of short-term weight loss. However, no currently available intervention—with the possible exception of bariatric surgery, which is reserved for severely obese individuals only—has consistently promoted the long-term maintenance of major weight loss. For example, although most dietary intervention studies have been relatively short-term, long-term maintenance of significant weight loss (−9 kg over 6 years) was achieved in only one (117) of the six studies summarized in Table 2. Use of VLCDs has generally resulted in impressive initial weight loss, but this weight loss is usually not maintained. As illustrated by the three comparative studies summarized in Table 3 (77,147,148), weight maintenance with a VLCD eventually becomes comparable to that attained with a standard low-calorie diet. The degree of weight loss in behavioral treatment programs is generally modest, but as shown in Table 4, the degree increases and its maintenance becomes better as these programs increase in length. The amount of weight loss that can be achieved in behavioral programs may be increased when such programs include additional emphasis on dietary modifications and exercise. Exercise alone or in combination with diet has had variable effects on weight loss, but studies of exercise have varied greatly in methodology. Only one of the three shorter-term studies summarized in Table 5 (173) found significant additional weight loss with the inclusion of exercise (3.6 kg), and two of the three longer-term studies (175) showed better maintenance of weight loss with exercise (3.8 and 4.1 kg). These studies used more frequent and/or longer and more intense exercise interventions imposed with moderate caloric restriction. Studies of pharmacological weight-loss agents have generally involved small numbers of patients and have been of short duration with modest net effects on weight loss. Only one of the 10 studies reviewed in Table 6 lasted for more than 6 months (198), and none lasted more than a year. A total of only 40 patients were evaluated, and the additional weight loss in the drug-treated group beyond that in the placebo-treated group amounted to only 3.4 kg. Major questions remain regarding the efficacy and safety of the long-term use of pharmacological weight-loss agents in obese patients with type 2 diabetes.

Further research is needed to investigate ways to increase the amount of weight loss attainable with current treatment modalities and to facilitate long-term weight loss maintenance. Since the studies reviewed indicate that combination approaches improve treatment outcome, future research should also focus on investigating optimal ways of combining current treatment modalities. The development of new approaches to the treatment of obesity and perhaps its prevention is suggested by several promising new advances resulting from the application of molecular biological techniques to obesity research. These very recent developments in obesity research include the discoveries of the adipose-tissue protein leptin (216) and its receptor (217) and the mutations underlying several forms of genetically transmitted obesity in rodents (216–218). However, the relevance of these new discoveries to the etiology of human obesity has not yet been defined.

Despite these somewhat discouraging results of various treatment modalities, obese individuals with type 2 diabetes should be encouraged to lose weight because even modest weight loss has been associated with metabolic improvement. However, because weight loss is often difficult to achieve and sustain, obese individuals with type 2 diabetes should also be provided with additional strategies to improve metabolic control that may be more easily accomplished. Such strategies could include improving food choices, spacing food intake better throughout the day, restricting calories very moderately (250–500 kcal less than average daily intake), and exercising regularly (107).

Note Added in Proof

On 15 September 1997, Wyeth-Ayerst Laboratories announced a voluntary and immediate withdrawal from the U.S. market of the weight-loss medications fenfluramine hydrochloride (Pondimin) and dexfenfluramine hydrochloride tablets (Redux). The FDA provided the company with new summary information concerning abnormal echocardiogram findings in asymptomatic patients seen in five centers. These patients had been treated with fenfluramine or dexfenfluramine for up to 24 months, most often in combination with phentermine. Abnormal echocardiogram findings were reported in 92 of 291 subjects evaluated, including 80 reports of aortic regurgitation and 23 reports of mitral regurgitation. These observations reflect a preliminary analysis of pooled information rather than results of a formal clinical investigation.

References

1. American Diabetes Association: *Diabetes 1996: Vital Statistics*. Alexandria, VA, American Diabetes Association, 1996
2. Albu J, Pi-Sunyer FX: Obesity and diabetes. In *Handbook of Obesity*. Bray GA, Bouchard C, James WPT, Eds. New York, Marcel Dekker. In press
3. National Diabetes Data Group: *Diabetes in America*. 2nd ed. Harris MI, Cowie CC, Stern MP, Boyko EJ, Reiber GE, Bennett PH, Eds. Washington, DC, U.S. Govt. Printing Office, 1995 (NIH publ. no. 95-1468)
4. National Institutes of Health Consensus Development Conference Statement: Health implications of obesity. *Ann Intern Med* 103:1073–1077, 1985
5. West KM, Kalbfleish JM: Glucose tolerance, nutrition and diabetes in Uruguay, Venezuela, Malaya and East Pakistan. *Dia-*

betes 15:9–18, 1966
6. West KM, Kalbfleish JM: Influence of nutritional factors on prevalence of diabetes. *Diabetes* 20:99–108, 1971
7. Van Itallie TB: Health implications of overweight and obesity in the United States. *Ann Intern Med* 103:983–988, 1985
8. Westlund K, Nicolaysen R: Ten-year mortality related to serum cholesterol: a follow-up of 3751 men aged 40–49. *Scand J Clin Lab Invest* 30:1–24, 1972
9. Lew EA, Garfinkel L: Variations in mortality by weight among 750,000 men and women. *J Chronic Dis* 32:563–576, 1979
10. Larsson B, Bjorntorp P, Tibblin G: The health consequences of moderate obesity. *Int J Obesity* 5:97–116, 1981
11. Medalie JH, Papier CM, Herman JB, Goldbourt V, Tamir S, Neufeld HN, Riss E: Diabetes mellitus among 10,000 adult men. I. Five-year incidence and associated variables. *Isr J Med Sci* 10:681–697, 1974
12. Colditz GA, Willet WC, Stampfer MJ, Manson JE, Hennkens CH, Arky RA, Speizer FE: Weight as a risk factor for clinical diabetes in women. *Am J Epidemiol* 132:501–513, 1990
13. Knowler WC, Pettit PJ, Savage PJ, Bennett PH: Diabetes incidence in Pima Indians: contributions of obesity and parental diabetes. *Am J Epidemiol* 113:144–156, 1981
14. Modan M, Karasik A, Halkin H, Fuchs Z, Lusky A, Shitrit A, Modan B: Effect of past and concurrent body mass index on prevalence of glucose intolerance and type 2 (non-insulin-dependent) diabetes and on insulin response: the Israel Study of Glucose Intolerance, Obesity and Hypertension. *Diabetologia* 29:82–89, 1986
15. Everhart JE, Pettitt DJ, Bennett PH, Knowler WC: Duration of obesity increases incidence of NIDDM. *Diabetes* 41:235–240, 1992
16. Holbrook TL, Barrett-Connor E, Wingard DL: The association of lifetime weight and weight control patterns with diabetes among men and women in an adult community. *Int J Obesity* 13:723–729, 1989
17. Sparrow D, Borkan GA, Gerzof SG, Wisniewski C, Silbert CK: Relationship of fat distribution to glucose tolerance: results of computed tomography in male participants of the Normative Aging Study. *Diabetes* 35:411–415, 1986
18. Gray DS, Fujioka K, Colletti PM, Kim H, Devine W, Cuyegkeng T, Pappas T: Magnetic-resonance imaging used for determining fat distribution in obesity and diabetes. *Am J Clin Nutr* 54:623–627, 1991
19. Fujimoto WY, Bergstrom RW, Boyko EJ, Leonetti DL, Newell-Morris LL, Wahl PW: Susceptibility to development of central adiposity among populations. *Obesity Res* 3:179s–186s, 1995
20. Lundgren H, Bengtsson C, Blohme G, Lapidus L, Sjostrom L: Adiposity and adipose tissue distribution in relation to incidence of diabetes in women: results from a prospective population study in Gothenburg, Sweden. *Int J Obesity* 13:413–423, 1989
21. Haffner S, Mitchell B, Hazuda H, Stern M: Greater influence of central distribution of adipose tissue on incidence of non-insulin-dependent diabetes in women than in men. *Am J Clin Nutr* 53:1312–1317, 1991
22. Ohlson LO, Larsson B, Svardsudd K, Welin L, Eriksson H, Wilhelmsen L, Bjorntorp P, Tibblin G: The influence of body fat distribution on the incidence of diabetes mellitus. *Diabetes* 34:1055–1058, 1985
23. Henry RR, Gumbiner B: Benefits and limitations of very-low-calorie diet therapy in obese NIDDM. *Diabetes Care* 14:802–823, 1991
24. Hamilton CC, Geil PB, Anderson JW: Management of obesity in diabetes mellitus. *Diabetes Educ* 18:407–410, 1992
25. Albu J, Konnarides C, Pi-Sunyer FX: Weight control: Metabolic and cardiovascular effects. *Diabetes Rev* 3:335–347, 1995
26. Olefsky JM, Kolterman OG, Scarlett JA: Insulin action and resistance in obesity and noninsulin-dependent type 2 diabetes mellitus. *Am J Physiol* 243:E15–E30, 1982
27. Ward WK, Beard JC, Porte D Jr: Clinical aspects of islet β-cell function in non-insulin-dependent diabetes mellitus. *Diabetes Metab Rev* 2:297–313, 1986
28. Reaven GM: Banting Lecture 1988: Role of insulin resistance in human disease. *Diabetes* 37:1595–1607, 1988
29. Galloway JA: Treatment of NIDDM with insulin agonists or substitutes. *Diabetes Care* 13:1209–1239, 1990
30. Genuth JF: Insulin use in NIDDM. *Diabetes Care* 13:1240–1264, 1990
31. Van Itallie TB: Obesity: adverse effects on health and longevity. *Am J Clin Nutr* 32: 2723–2733, 1979
32. Stamler R, Stamler J, Riedlinger WF, Algera G, Roberts RH: Weight and blood pressure, findings in hypertension screening of 1 million Americans. *JAMA* 240:1607–1610, 1978
33. Hubert HB, Feinleib M, McNamara PM, Castelli WP: Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation* 67:968–977, 1983
34. Blackburn GL, Read JL: Benefits of reducing revisited. *Postgrad Med* 60:13–18, 1984
35. Lapidus L, Bengtsson C, Larsson B, Pennert K, Rybo E, Sjostrom L: Distribution of adipose tissue and risk of cardiovascular disease and death: a 12 year follow up of participants in the population study of women in Gothenburg, Sweden. *Br Med J* 289:1257–1261, 1984
36. Larsson B, Svardsudd K, Welin L, Wilhelmsen L, Bjorntorp P, Tibblin G: Abdominal adipose tissue distribution, obesity, and risk of cardiovascular disease and death: 13 year follow up of participants in the study of men born in 1913. *Br J Med* 288:1401–1404, 1984
37. Donahue RP, Abbott RD, Bloom E, Reed DM, Yano K: Central obesity and coronary heart disease in men. *Lancet* i:821–824, 1987
38. Ducimetiere P, Richard JL: The relationship between subsets of anthropometric upper versus lower body measurements and coronary heart disease risk in middle-aged men: the Paris Prospective Study. I. *Int J Obesity* 13:111–122, 1989
39. Van Gaal L, Rillaerts E, Creten W, De Leeuw I: Relationship of body fat distribution pattern to atherogenic risk factors in NIDDM: Preliminary results. *Diabetes Care* 11:103–106, 1988
40. Kissebah AH, Vydelingum N, Murray R, Evans DJ, Hartz AJ, Kalkoff RF, Adams PW: Relation of body fat distribution to metabolic complications of obesity. *J Clin Endocrinol Metab* 54:254–260, 1982
41. Krotkiewski M, Bjorntorp P, Sjostrom L, Smith U: Impact of obesity on metabolism in men and women: importance of regional adipose tissue distribution. *J Clin Invest* 72:1150–1162, 1983
42. Dowling HJ, Pi-Sunyer FX: Race-dependent health risks of upper body obesity. *Diabetes* 42:537–543, 1993
43. Kissebah AH, Peiris AN: Biology of regional body fat distribution: relationship to non-insulin-dependent diabetes mellitus. *Diabetes Metab Rev* 5:83–91, 1989
44. Bjorntorp P: Regional obesity. In *Obesity*. Bjorntorp P, Brodoff BN, Eds. Philadelphia, Lippincott, 1992, p. 579–586
45. Newburgh LH: Control of hyperglycemia of obese "diabetics" by weight reduction. *Ann Intern Med* 17:935–942, 1942
46. Hughes TA, Gwynne JT, Switzer BR, Herbst C, White G: Effects of caloric restriction and weight loss on glycemic control, insulin release and resistance, atherosclerotic risk in obese patients with type 2 diabetes mellitus. *Am J Med* 77:7–17, 1984
47. DiBiase G, Mattioli PL, Contaldo F, Mancini M: A very-low-calorie formula diet (Cambridge diet) for the treatment of diabetic-obese patients. *Int J Obesity* 5:319–324, 1981
48. Henry RR, Scheaffer L, Olefsky JM: Glycemic effects of intensive caloric restriction and isocaloric refeeding in non-insulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 61:917–925, 1985
49. Henry RR, Wallace P, Olefsky JM: Effects of weight loss on mechanisms of hyper-

glycemia in obese non-insulin-dependent diabetes mellitus. *Diabetes* 35:990-998, 1986
50. Henry RR, Wiest-Kent TA, Scheaffer L, Kolterman OG, Olefsky JM: Metabolic consequences of very-low-calorie diet therapy in obese non-insulin-dependent diabetic and nondiabetic subjects. *Diabetes* 35:155–164, 1986
51. Amatruda JM, Richeson JF, Well SL, Brodows RG, Lockwood DH: The safety and efficacy of a controlled low-energy ('very-low-calorie') diet in the treatment of non-insulin-dependent diabetes and obesity. *Arch Intern Med* 148:873–877, 1988
52. Kelley DE, Wing R, Buonocore C, Sturis J, Polonsky K, Fitzsimmons M: Relative effects of calorie restriction and weight loss in noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 77:1287–1293, 1993
53. Gumbiner B, Wendel JA, McDermott MP: Effects of diet composition and ketosis on glycemia during very-low-energy-diet therapy in obese patients with non-insulin-dependent diabetes mellitus. *Am J Clin Nutr* 63:110–115, 1996
54. UKPDS Group: U.K. Prospective Diabetes Study 7: response of fasting plasma glucose to diet therapy in newly presenting type 2 diabetic patients. *Metabolism* 39:905–912, 1990
55. Liu GC, Coulston AM, Lardinois CK, Hollenbeck CB, Moore JG, Reaven GM: Moderate weight loss and sulfonylurea treatment of non-insulin-dependent diabetes mellitus. *Arch Intern Med* 145:665–669, 1985
56. Wing RR, Koeske R, Epstein LH, Nowalk MP, Gooding W, Becker D: Long-term effects of modest weight loss in type 2 diabetic patients. *Arch Intern Med* 147:1749–1753, 1987
57. Schneider SH, Khachadurian AK, Amorosa LF, Clemow L, Ruderman NB: Ten-year experience with an exercise-based outpatient life-style modification program in the treatment of diabetes mellitus. *Diabetes Care* 15:1800–1810, 1992
58. Goldstein DJ: Beneficial health effects of modest weight loss. *Int J Obesity* 16:397–415, 1992
59. Watts NB, Spanheimer RG, DiGirolamo M, Gebhart SSP, Musey VC, Siddiq K, Phillips LS: Prediction of glucose response to weight loss in patients with non-insulin-dependent diabetes mellitus. *Arch Intern Med* 150:803–806, 1991
60. Savage PJ, Bennion LJ, Flock EV, Nagulesparan M, Mott D, Roth J, Unger RH, Bennett PH: Diet-induced improvement of abnormalities in insulin and glucagon secretion and in insulin receptor binding in diabetes mellitus. *J Clin Endocrinol Metab* 48:999–1007, 1979
61. Lasksko M, Uusitupa M, Takala J, Majander H, Reijonen T, Penttila I: Effects of hypocaloric diet and insulin therapy on metabolic control and mechanisms of hyperglycemia in obese non-insulin-dependent diabetic subjects. *Metabolism* 37:1092–1100, 1988
62. Zawadzki JK, Bogardus C, Foley JE: Insulin action in obese non-insulin-dependent diabetics and in their isolated adipocytes before and after weight loss. *Diabetes* 36:227–236, 1987
63. Friedman JE, Dohm GL, Leggett-Frazier N, Elton CW, Tapscott EB, Poires WJ, Caro JF: Restoration of insulin responsiveness in skeletal muscle of morbidly obese patients after weight loss: effect on muscle glucose transport and glucose transporter GLUT4. *J Clin Invest* 89:701–705, 1992
64. Pi-Sunyer FX: Weight and non-insulin-dependent diabetes mellitus. *Am J Clin Nutr* 63 (Suppl.):426S–429S, 1996
65. Gumbiner R, Polonsky KS, Beltz WF, Griver K, Wallace P, Brechter G, Henry RR: Effects of weight loss and reduced hyperglycemia on the kinetics of insulin secretion in obese non-insulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 70:1594–1603, 1990
66. Henry RR, Brechtel G, Griver K: Secretion and hepatic extraction of insulin after weight loss in obese non-insulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 66:979–986, 1987
67. DeFronzo RA: The triumvirate: β-cell, muscle, liver: a collusion responsible for NIDDM. *Diabetes* 37:667–687, 1988
68. Porte D Jr: β-cells in type 2 diabetes mellitus. *Diabetes* 40:166–180, 1991
69. Stern MP, Patterson JK, Haffner SM, Hazuda HP, Mitchell BD: Lack of awareness and treatment of hyperlipidemia in type 2 diabetes in a community survey. *JAMA* 262:360–364, 1989
70. Fontbonne A, Eschwege E, Cambien F, Richard J-L, Ducimetiere P, Thibult N, Warnet J-M, Claude J-R, Rosselin G-E: Hypertriglyceridemia as a risk factor of coronary heart disease mortality in subjects with impaired glucose tolerance in diabetes: results from the 11-year follow-up of the Paris Prospective Study. *Diabetologia* 32:300–304, 1989
71. Nikkila EA: High-density lipoproteins in diabetes. *Diabetes* 30 (Suppl. 2):82–87, 1981
72. Howard BV, Savage PJ, Nagulesparan M, Bennion LJ, Davis M, Bennett P: Changes in plasma lipoproteins accompanying diet therapy in obese diabetics. *Atherosclerosis* 33:445–456, 1979
73. Bauman WA, Schwartz E, Rose HG, Eisenstein HN, Johnson DW: Early and long-term effects of acute caloric deprivation in obese diabetic patients. *Am J Med* 85:38–46, 1988
74. Hanefeld M, Weck M: Very low calorie diet therapy in obese non-insulin dependent diabetes patients. *Int J Obesity* 13 (Suppl. 2):33–37, 1989
75. Uusitupa MIJ, Laakso M, Sarlund H, Majander H, Takala J, Penttila I: Effects of a very-low-calorie diet on metabolic control and cardiovascular risk factors in the treatment of obese non-insulin-dependent diabetics. *Am J Clin Nutr* 51:768–773, 1990
76. Friedman CI, Falko JM, Patel ST, Kim MH, Newman HAI, Barrows H: Serum lipoprotein response during active and stable weight reduction in reproductive obese females. *J Clin Endocrinol Metab* 55:258–262, 1982
77. Wing RR, Blair E, Marcus M, Epstein LH, Harvey J: Year-long weight loss treatment for obese patients with type 2 diabetes: does including an intermittent very-low-calorie diet improve outcome? *Am J Med* 97:354–362, 1994.
78. Stern MP, Patterson JK, Haffner SM, Hazuda HP, Mitchell BD: Lack of awareness and treatment of hyperlipidemia in type 2 diabetes in a community survey. *JAMA* 262:360–364, 1989
79. Feingold KR, Grunfeld C, Pang M, Doerrler W, Krauss RM: LDL subclass phenotypes and triglyceride metabolism in non-insulin-dependent diabetes. *Arteriosclerosis* 12:1496–1502, 1992
80. Anderson JW, Brinkman-Kaplan V, Hamilton CC, Logan JE, Collins RW, Gustafson NJ: Food-containing hypocaloric diets are as effective as liquid-supplement diets for obese individuals with NIDDM. *Diabetes Care* 17:602–604, 1994
81. American Diabetes Association: Detection and management of lipid disorders in diabetes (Consensus Statement). *Diabetes Care* 19 (Suppl. 1):S96–S102, 1996
82. Pascale RW, Wing RR, Blair EH, Harvey JR, Guare JC: The effect of weight loss on change in waist-to-hip ratio in patients with type 2 diabetes. *Int J Obesity* 16: 59–65, 1991
83. Marks SJ, Moore NR, Clark ML, Strauss BJG, Hockaday TDR: Reduction of visceral adipose tissue and improvement of metabolic indices: effect of dexfenfluramine in NIDDM. *Obesity Res* 4:1–9, 1996
84. Krosnik A: Economic impact of type 2 diabetes mellitus. *Prim Care* 15:423–431, 1988
85. Collins RW, Anderson JW: Medication cost savings associated with weight loss for obese non-insulin-dependent diabetic men and women. *Prevent Med* 24:369–374, 1995
86. Lean MEJ, Powrie JK, Anderson AS, Garthwaite PH: Obesity, weight loss and prognosis in type 2 diabetes. *Diabet Med* 7: 228–233, 1990
87. Chaturvedi N, Fuller JH: Mortality risk by

body weight and weight change in people with NIDDM: the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetes Care* 18:766–774, 1995
88. Eriksson K-F, Lindgarde F: Prevention of type 2 (non-insulin-dependent) diabetes mellitus by diet and physical exercise. *Diabetologia* 34: 891–898, 1991
89. Kuczmarski RJ, Flegal KM, Campbell SM, Johnson CL: Increasing prevalence of overweight among US adults: the National Health and Nutrition Examination Surveys. *JAMA* 272:205–211, 1994
90. Troiano RP, Flegal KM, Kuczmarski RJ, Campbell SM, Johnson CL: Overweight prevalence and trends for children and adolescents: the National Health and Nutrition Examination Surveys, 1963 to 1991. *Arch Pediatr Adolesc Med* 149:1085–1091, 1995
91. Freedman DS, Srinivasan SR, Valdez RA, Williamson DF, Berenson GS: Secular increases in relative weight and adiposity among children over two decades: the Bogalusa Heart Study. *Pediatrics* 99: 420–426, 1997
92. The National Task Force on Prevention and Treatment of Obesity: Towards prevention of obesity: research directions. *Obesity Res* 2:571–584, 1994
93. Jeffery RW: Community programs for obesity prevention: the Minnesota Heart Health Program. *Obesity Res* 3 (Suppl. 2): 283s–288s, 1995
94. Kumanyika S: Diet and chronic disease issues for minority populations. *J Nutr Educ* 22:89–96, 1990
95. Carter JS, Pugh JA, Monterrosa A: Non-insulin-dependent diabetes in minorities in the United States. *Ann Intern Med* 125:221–232, 1996
96. Byers T: The epidemic of obesity in American Indians. *Am J Dis Child* 146:285–286, 1992
97. Knowler WC, Pettitt DJ, Saad MF, Charles MA, Nelson RG, Howard BV, Bogardus C, Bennett PH: Obesity in the Pima Indians: its magnitude and relationship with diabetes. *Am J Clin Nutr* 53:1543S–1551S, 1991
98. Broussard BA, Sugarman JR, Bachman-Carter K, Booth K, Stephenson L, Strauss K, Gohdes D: Towards comprehensive obesity prevention programs in Native American communities. *Obesity Res* 3 (Suppl. 2): 289s–297s, 1995
99. Ravussin E, Valencia ME, Esparza J, Bennett PH, Schulz LO: Effects of a traditional lifestyle on obesity in Pima Indians. *Diabetes Care* 17:1067–1074, 1994
100. Heath GW, Wilson RH, Smith J, Leonard BE: Community-based exercise and weight control: diabetes risk reduction and glycemic control in Zuni Indians. *Am J Clin Nutr* 53:1642S–1646S, 1991
101. Stark O, Atkins E, Wolff OH, Douglas JWB: Longitudinal study of obesity in the National Survey of Health and Development. *Br Med J* 283:13–17, 1981
102. Epstein LH, Valoski A, Wing RR, McCurley J: Ten-year follow-up of behavioral, family-based treatment for obese children. *JAMA* 264:2519–2523, 1990
103. Wing RR: Changing diet and exercise behaviors in individuals at risk for weight gain. *Obesity Res* 3 (Suppl. 2):277s–282s, 1995
104. Jeffery RW: Minnesota studies on community-based approaches to weight loss and control. *Ann Intern Med* 119:719–721, 1993
105. Wilson R, Horton E: Workshop report: prevention and early treatment of NIDDM. *Diabetes Care* 16 (Suppl. 1):376–377, 1993
106. Brown SA, Upchurch S, Anding R, Winter M, Ramirez G: Promoting weight loss in type II diabetes. *Diabetes Care* 19:613–624, 1996
107. American Diabetes Association: Nutrition recommendations and principles for people with diabetes mellitus (Position Statement). *Diabetes Care* 19 (Suppl. 1):S16–S19, 1996
108. West KM: Diet therapy of diabetes: an analysis of failure. *Ann Intern Med* 79:425–434, 1973
109. Close EJ, Wiles PG, Lockton JA, Walmsley D, Oldham J, Wales JK: Diabetic diets and nutritional recommendations: what happens in real life? *Diabet Med* 9:181–188, 1992
110. Milne RM, Mann JI, Chisolm AW, Williams SM: Long-term comparison of three dietary prescriptions in the treatment of NIDDM. *Diabetes Care* 17:74–80, 1994
111. Eckel RH, Yost TJ: Weight reduction increases adipose tissue lipoprotein lipase responsiveness in obese women. *J Clin Invest* 80:992–997, 1987
112. Leibel RL, Rosenbaum M, Hirsch J: Changes in energy expenditure resulting from altered body weight. *JAMA* 332:621–628, 1995
113. Hanefeld M, Fischer S, Schmechel H, Rothe G, Schulze J, Dude H, Schwanebeck U, Julius U: Diabetes Intervention Study: multi-intervention trial in newly diagnosed NIDDM. *Diabetes Care* 14:308–317, 1991
114. Franz MJ, Monk A, Barry B, McClain K, Weaver T, Cooper N, Upham P, Bergenstal R, Mazze RS: Effectiveness of medical nutrition therapy provided by dietitians in the management of non-insulin-dependent diabetes mellitus: a randomized, controlled clinical trial. *J Am Diet Assoc* 95:1009–1017, 1995
115. Laitinen JH, Ahola IE, Sarkkinen ES, Winberg RL, Harmaakorpi-Ivonen PA, Uusitupa MI: Impact of intensified dietary therapy on energy and nutrient intakes and fatty acid composition of serum lipids in patients with recently diagnosed non-insulin-dependent diabetes mellitus. *J Am Diet Assoc* 93:276–283, 1993
116. Heller SR, Clarke P, Daly H, Davis I, McCulloch DK, Allison SP, Tattersall RB: Group education for obese patients with type 2 diabetes: greater success at less cost. *Diabet Med* 5:552–556, 1988
117. Hadden DR, Blair ALT, Wilson EZ, Boyle DM, Atkinson B, Kennedy AL, Buchanan KD, Merrett JD, Montgomery DAD, Weaver JA: Natural history of diabetes presenting age 40–69 years: a prospective study of the influence of intensive dietary therapy. *Quart J Med* 59:579–598, 1986
118. Technology Assessment Conference Panel: Methods for voluntary weight loss and control: Technology Assessment Conference statement. *Ann Intern Med* 119:764–770, 1993
119. Wadden TA: Treatment of obesity by moderate and severe caloric restriction: results of clinical research trials. *Ann Intern Med* 119:688–693, 1993
120. Jeffery RW: Behavioral treatment of obesity. *Ann Behav Med* 9:20–24, 1987
121. Perri MG, Sears SF, Clark JE: Strategies for improving maintenance of weight loss: toward a continuous care model of obesity management. *Diabetes Care* 16:200–209, 1993
122. Perri MG, McAllister DA, Gange JJ, Jordan RC, McAdoo WG, Nezu AM: Effects of four maintenance programs on the long-term management of obesity. *J Consult Clin Psychol* 56:529–534, 1988
123. Coulston AM, Hollenbeck CB, Swislock ALM, Reaven GM: Persistence of hypertriglyceridemic effect of low fat, high carbohydrate diets in NIDDM patients. *Diabetes Care* 12:94–101, 1989
124. Vinik AI, Lauterio TJ, Wing RR: Should the bee suck honey or lard? That is the question. *Diabetes Care* 16:1045–1047, 1993
125. Franz MJ, Horton ES, Bantle JP, Beege CA, Brunzell JD, Coulston AM, Henry RR, Hoogwerf BJ, Stacpoole PW: Nutrition principles for the management of diabetes and related complications (Technical Review). *Diabetes Care* 17:490–518, 1994
126. Garg A: High-monounsaturated fat diet for diabetic patients: is it time to change the current dietary recommendations? *Diabetes Care* 17:242–246, 1994
127. Lissner L, Levitsky DA, Strupp BJ, Kalkwarf HJ, Roe DA: Dietary fat and the regulation of energy intake in human subjects. *Am J Clin Nutr* 46:886–892, 1987
128. Kendall A, Levitsky DA, Strupp BJ, Lissner L: Weight loss on a low-fat diet: consequence of the imprecision of the control of food intake in humans. *Am J Clin Nutr* 53:1124–1129, 1991
129. Prewitt TE, Schmeisser D, Bowen PE, Aye P, Dolecek TA, Langenberg P, Cole T, Brace L: Changes in body weight, body composition, and energy intake in women fed

high- and low-fat diets. *Am J Clin Nutr* 54:304–310, 1991
130. Shah M, Garg A: High-fat and high-carbohydrate diets and energy balance. *Diabetes Care* 19:1142–1152, 1996
131. American Diabetes Association: Nutritional recommendations and principles for individuals with diabetes mellitus: 1986. *Diabetes Care* 10:126–132, 1987
132. National Institutes of Health: Consensus development conference on diet and exercise in non-insulin-dependent diabetes mellitus. *Diabetes Care* 10:639–644, 1987
133. McCarron DA, Oparil S, Chait A, Haynes B, Kris-Etherton P, Stern JS, Resnick LM, Clark S, Morris CD, Hatton DC, Metz JA, McMahon M, Holcomb S, Snyder GW, Pi-Sunyer FX: Nutritional management of cardiovascular risk factors. *Arch Intern Med* 157:169–177, 1997
134. Pascale RW, Wing RR, Butler BA, Mullen M, Bononi P: Effects of a behavioral weight loss program stressing calorie restriction versus calorie plus fat restriction in obese individuals with NIDDM or a family history of diabetes. *Diabetes Care* 18:1241–1248, 1995
135. Peterson CM, Jovanovic-Peterson L: Randomized crossover study of 40% vs. 55% carbohydrate weight loss strategies in women with previous gestational diabetes mellitus and non-diabetic women of 130–200% ideal body weight. *J Am Coll Nutr* 14:369–375, 1995
136. Garg A, Bonanome A, Grundy SM, Zhang Z-J, Unger RH: Comparison of a high-carbohydrate diet with a high-monounsaturated-fat diet in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med* 319:829–834, 1988
137. Garg A, Grundy S, Koffler M: Effect of high carbohydrate intake on hyperglycemia, islet function, and plasma lipoproteins in NIDDM. *Diabetes Care* 15:1572–1580, 1992
138. Rasmussen OW, Thomsen C, Hansen KW, Vesterlund M, Winther E, Hermansen K: Effects on blood pressure, glucose and lipid levels of a high-monounsaturated fat diet compared with a high carbohydrate diet in NIDDM subjects. *Diabetes Care* 16:1565–1571, 1993
139. Low CC, Grossman EB, Gumbiner B: Potentiation of effects of weight loss by monounsaturated fatty acids in obese NIDDM patients. *Diabetes* 45:569–575, 1996
140. The National Task Force on the Prevention and Treatment of Obesity: Very low-calorie diets. *JAMA* 270:967–974, 1993
141. Blackburn GL, Bistrian BR, Flatt JP, Sizer J: Role of a protein sparing modified fast in a comprehensive weight reduction program. In *Recent Advances in Obesity Research: I.* Howard AN, Ed. London, Newman, 1975, p. 279–281
142. Wadden TA: The treatment of obesity: an overview. In *Obesity: Theory and Therapy.* 2nd ed. Stunkard AJ, Wadden TA, Eds. New York, Raven, 1993, p. 197–217
143. Wing RR: Use of very-low-calorie diets in the treatment of obese persons with non-insulin-dependent diabetes mellitus. *J Am Diet Assoc* 95:569–572, 1995
144. Wadden TA, Stunkard AJ: Controlled trial of very low calorie diet, behavior therapy, and their combination in the treatment of obesity. *J Consult Clin Psychol* 54:482–488, 1986
145. Sikand G, Kondo A, Foreyt JP, Jones PH, Gotto AM: Two year follow-up of patients treated with very low calorie dieting and exercise training. *J Am Diet Assoc* 88:487–488, 1988
146. Wadden TA, Sternberg JA, Letizia KA, Stunkard AJ, Foster GD: Treatment of obesity by very low calorie diet, behavior therapy, and their combination: a five-year perspective. *Int J Obesity* 13 (Suppl. 2):39–46, 1989
147. Wing RR, Blair EH, Bononi P, Marcus MD, Watanabe R, Bergman RN: Caloric restriction per se is a significant factor in improvements in glycemic control and insulin sensitivity during weight loss in obese NIDDM patients. *Diabetes Care* 17:30–36, 1994
148. Wing RR, Marcus MD, Salata R, Epstein LH, Miaskiewicz S, Blair EH: Effects of a very-low-calorie diet on long-term glycemic control in obese type 2 diabetic subjects. *Arch Intern Med* 151:1334–1340, 1991
149 Foster GD, Wadden TA, Peterson FJ, Letizia KA, Bartlett SJ, Conill AM: A controlled comparison of three very-low-calorie diets: effects on weight, body composition and symptoms. *Am J Clin Nutr* 55:811–817, 1992
150. Nagulesparan M, Savage PJ, Bennion LJ, Unger RH, Bennett PH: Diminished effect of caloric restriction on control of hyperglycemia with increasing known duration of type 2 diabetes mellitus. *J Clin Endocrinol Metab* 53:560–568, 1981
151. Wing RR: Behavioral treatment of obesity: its application to type 2 diabetes. *Diabetes Care* 16:193–199, 1993
152. Foreyt JP: Evidence for success of behavior modification in weight loss and control. *Ann Intern Med* 119:698–701, 1993
153. Guare JC, Wing RR, Grant A: Comparison of obese NIDDM and nondiabetic women: short- and long-term weight loss. *Obesity Res* 3:329–335, 1995
154. Wing RR, Shoemaker M, Marcus MD, McDermott M, Gooding W: Variables associated with weight loss and improvements in glycemic control in type 2 diabetic patients in behavioral weight control programs. *Int J Obesity* 14:495-503, 1990
155. Kumanyika SK: Obesity in black women. *Epidemiol Rev* 9:31–50, 1987
156. Wing RR, Anglin K: Effectiveness of a behavioral weight control program for blacks and whites with NIDDM. *Diabetes Care* 19:409–413, 1996
157. Darga LL, Holden JH, Olson SM, Lucas CP: Comparison of cardiovascular risk factors in obese blacks and whites. *Obesity Res* 2:239–245, 1994
158. Kahn HS, Williamson DF, Stevens JA: Race and weight change in US women: the roles of socioeconomic and martial status. *Am J Public Health* 81:319–323, 1991
159. Kumanyika SK, Obarzanek E, Stevens VJ, Hebert PR, Whelton PK: Weight-loss experience of black and white participants in NHLBI-sponsored clinical trials. *Am J Clin Nutr* 53:1631S–1638S, 1991
160. McNabb WL, Quinn MT, Rosing L: Weight loss program for inner-city black women with non-insulin-dependent diabetes mellitus: PATHWAYS. *J Am Diet Assoc* 93:75–77, 1993
161. Pronk NP, Wing RR: Physical activity and long-term maintenance of weight loss. *Obesity Res* 2:587–599, 1994
162. Grilo CM, Brownell KD, Stunkard AJ: The metabolic and psychological importance of exercise in weight control. In *Obesity: Theory and Therapy.* 2nd ed. Stunkard AJ, Wadden TA, Eds. New York, Raven, 1993, p. 253–273
163. Horton ES: Role and management of exercise in diabetes mellitus. *Diabetes Care* 11:201–211, 1988
164. King AC, Tribble DL: The role of exercise in weight regulation in nonathletes. *Sports Med* 11:331–349, 1991
165. Blair SN: Evidence for success of exercise in weight loss and control. *Ann Intern Med* 119:702–706, 1993
166. Colvin RH, Olson SB: A descriptive analysis of men and women who have lost significant weight and are highly successful at maintaining the loss. *Addict Behav* 8:287–295, 1983
167. Gormally J, Rardin D, Black S: Correlates of successful response to a behavioral weight control clinic. *J Counseling Psychol* 27:179–191, 1980
168. Kayman S, Bruvold W, Stern JS: Maintenance and relapse after weight loss in women: behavioral aspects. *Am J Clin Nutr* 52:800–807, 1990
169. Klem ML. McGuire MT, Wing RR: The National Weight Control Registry: the diet and exercise behaviors of individuals highly successful at long-term maintenance of weight loss (Abstract). *Obesity Res* 4 (Suppl. 1):7S, 1996
170. Pavlov KN, Krey S, Steffee WP: Exercise as an adjunct to weight loss and maintenance in moderately obese subjects. *Am J Clin Nutr* 49:1115–1123, 1989
171. Kaplan RM, Wilson DK, Hartwell SL, Merino KL, Wallace JP: Prospective evaluation of HDL cholesterol changes after diet and physical conditioning programs for

patients with type 2 diabetes mellitus. *Diabetes Care* 8:343–348, 1985
172. Bogardus C, Ravussin E, Robbins DC, Wolfe RR, Horton ES, Sims EAH: Effects of physical training and diet therapy on carbohydrate metabolism in patients with glucose intolerance and non-insulin-dependent diabetes mellitus. *Diabetes* 33:311–318, 1984
173. Yamanouchi K, Shinozaki T, Chikada K, Nishikawa T, Ito K, Shimizu S, Ozawa N, Suzuki Y, Maeno H, Kata K, Oshida Y, Sata Y: Daily walking combined with diet therapy is a useful means for obese NIDDM patients not only to reduce body weight but also to improve insulin sensitivity. *Diabetes Care* 18:775–777, 1995
174. Hartwell SL, Kaplan RM, Wallace JP: Comparison of behavioral interventions for control of type 2 diabetes mellitus. *Behav Ther* 17:447–461, 1986
175. Wing RR, Epstein LH, Paternostro-Bayles M, Kriska A, Nowalk MP, Gooding W: Exercise in a behavioral weight control programme for obese patients with type 2 (non-insulin-dependent) diabetes. *Diabetologia* 31:902–909, 1988
176. North American Association for the Study of Obesity: Guidelines for the approval and use of drugs to treat obesity: a position paper of the North American Association for the Study of Obesity. *Obesity Res* 3:473–478, 1995
177. The National Task Force on the Prevention and Treatment of Obesity: Long-term pharmacotherapy in the management of obesity. *JAMA* 276:1907–1915, 1996
178. Silverstone T: The place of appetite-suppressant drugs in the treatment of obesity. In *Obesity: Theory and Therapy*. 2nd ed. Stunkard AJ, Wadden TA, Eds. New York, Raven, 1993, p. 275–285
179. Weintraub M: Long-term weight control: the National Heart, Lung and Blood Institute funded multimodal intervention study. *Clin Pharmacol Ther* 51:581–646,1992
180. Atkinson RL, Blank RC, Loper JF, Schumacher D, Lutes RA: Combined drug treatment of obesity. *Obesity Res* (Suppl. 4): 497S–500S, 1995
181. Guy-Grand B, Apfelbaum M, Crepaldi G, Gries A, Lefebvre P, Turner P: International trial of long-term dexfenfluramine in obesity. *Lancet* ii:1142–1145, 1989
182. Carpenter MA, Bodansky HJ: Drug treatment of obesity in type 2 diabetes mellitus. *Diabet Med* 7:99–104, 1990
183. Crommelin RM: Nonamphetamine, anorectic medication for obese diabetic patients: controlled and open investigations of mazindol. *Clin Med* 81: 20–24, 1974
184. Bandisode MS, Boshell BR: Double-blind clinical evaluation of mazindol (42-548) in obese diabetics. *Curr Ther Res* 18:816–824, 1975
185. Gershberg H, Kane R, Hulse M, Pensgen E: Effects of diet and an anorectic drug (phentermine resin) in obese diabetics. *Curr Ther Res* 22:814–820, 1977
186. Campbell CJ, Bhalla IP, Stell JM, Duncan LJP: A controlled trial of phentermine in obese diabetic patients. *The Practitioner* 218:851–855, 1977
187. Pestell RG, Crock PA, Ward GM, Alford FP, Best JD: Fenfluramine increases insulin action in patients with NIDDM. *Diabetes Care* 12:252–258, 1989
188. Scheen AJ, Paolisso G, Salvatore T, Lefebvre PJ: Improvement of insulin-induced glucose disposal in obese patients with NIDDM after 1-wk treatment with *d*-fenfluramine. *Diabetes Care* 14:325–332, 1991
189. Verdy M, Carbonneau L, Verdy I, Belanger R, Bolte E, Chiasson J-L: Fenfluramine in the treatment of non-insulin-dependent diabetics: hypoglycemic versus anorectic effect. *Int J Obesity* 7:289–297, 1983
190. Nathan C: Serotonin agonists. In *Obesity*. Bjorntorp P, Brodoff BN, Eds. Philadelphia, Lippincott, 1992, p. 751–761
191. Wales JK: The effect of fenfluramine on obese, maturity-onset diabetic patients. *Curr Med Res Opin* 6 (Suppl. 1):226–235, 1979
192. Salmela PI, Sotaniemi EA, Viikari J, Solakivi-Jaakkola T, Jarvensivu P: Fenfluramine therapy in non-insulin-dependent diabetic patients: effects on body weight, glucose homeostasis, serum lipoproteins, and antipyrine metabolism. *Diabetes Care* 4:535–540, 1981
193. Turner P: Dexfenfluramine: its place in weight control. *Drugs* 39 (Suppl. 3):53–62, 1990
194. Abenhaim L, Moride Y, Brenot F, Rich S, Benichou J, Kurz X, Higenbottam T, Oakley C, Wouters E, Aubier M, Simonneau G, Begaud B: Appetite-suppressant drugs and the risk of primary pulmonary hypertension. *N Engl J Med* 335:609–616, 1996
195. Stewart GO, Stein GR, Davis TME, Findlater P: Dexfenfluramine in type 2 diabetes: effect on weight and diabetes control. *Med J Aust* 158:167–169, 1993
196. Willey KA, Molyneaux LM, Overland JE, Yue DK: The effects of dexfenfluramine on blood glucose control in patients with type 2 diabetes. *Diabet Med* 9:341–343, 1992
197. Willey KA, Molyneaux LM, Yue DK: Obese patients with type 2 diabetes poorly controlled by insulin and metformin: effects of adjunctive dexfenfluramine therapy on glycaemic control. *Diabet Med* 11:701–704, 1994
198. Tauber-Lassen E, Damsbo P, Henriksen JE, Palmvig B, Beck-Nielsen H: Improvement of glycemic control and weight loss in type 2 (non-insulin-dependent) diabetics after one year of dexfenfluramine treatment (Abstract). *Diabetologia* 33:A124, 1990
199. Connolly HM, Crary JL, McGoon MD, Hensrud DD, Edwards BS, Edwards WD, Schaff HV: Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med* 337:581–588, 1997
200. Graham DJ, Green L: Further cases of valvular heart disease associated with fenfluramine-phentermine (Letter). *N Engl J Med* 337:635, 1997
201. Ryan DH, Kaiser P, Bray GA: Sibutramine: a novel new agent for obesity treatment (Abstract). *Obesity Res* 3 (Suppl. 4):553S–559S, 1995
202. Griffiths J, Brynes AE, Frost G, Bloom SR, Finer N, Jones SP, Romanec FM: Sibutramine in the treatment of overweight non-insulin dependent diabetics. *Int J Obesity* 19 (Suppl. 2):41, 1995
203. Drent ML, van der Veen EA: First clinical studies with Orlistat: a short review. *Obesity Res* 3 (Suppl. 4):623S–625S, 1995
204. Drent ML, Larsson I, William-Olsson T: Orlistat (Ro 18-0647), a lipase inhibitor, in the treatment of human obesity: a multiple dose study. *Int J Obesity* 19:221–226, 1995
205. Cincotta AH, Meier AH: Bromocriptine (Ergoset) reduces body weight and improves glucose tolerance in obese subjects. *Diabetes Care* 19:667–670, 1996
206. Gastrointestinal Surgery for Severe Obesity: NIH Consensus Development Conference Statement 1991 March 25–27. *Am J Clin Nutr* 55:615S–619S, 1992
207. Kral JG: Overview of surgical techniques for treating obesity. *Am J Clin Nutr* 55:552S–555S, 1992
208. Brolin RE: Critical analysis of results: weight loss and quality of data. *Am J Clin Nutr* 55:577S–581S, 1992
209. Mason EE, Renquist RE, Jiang D: Perioperative risks and safety of surgery for severe obesity. *Am J Clin Nutr* 55:573S–581S, 1992
210. Halverson JD: Metabolic risk of obesity surgery and long-term follow-up. *Am J Clin Nutr* 55:602S–605S, 1992
211. Pories WJ, Swanson MS, MacDonald KG, Long SB, Morris PG, Brown BM, Barakat HA, deRamon RA, Israel G, Dolezal JM, Dohm L: Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. *Ann Surg* 222:339–352, 1995
212. Herbst CA, Hughes TA, Gwynne JT, Buckwalter JA: Gastric bariatric operation in insulin-treated adults. *Surgery* 95:209–214, 1984
213. Long SD, O'Brien K, MacDonald KG, Leggett-Frazier N, Swanson MS, Pories WJ, Caro JF: Weight loss in severely obese subjects prevents the progression of impaired glucose tolerance to type 2 diabetes. *Diabetes Care* 17:372–375, 1994
214. Sjostrom L, Larsson B, Backman L, Bengtsson C, Bouchard C, Dahlgren S, Hallgren P, Jonsson E, Karlsson J, Lapidus L, Lindroos A-K, Lindstedt S, Lissner L, Narbro

K, Naslund I, Olbe L, Sullivan M, Sylvan A, Wedel H, Agren G: Swedish Obese Subjects (SOS): recruitment for an intervention study and a selected description of the obese state. *Int J Obesity* 16:465–479, 1992
215. Sjostrom L: Obesity and weight change in relation to disease (Abstract). *Obesity Res* 4 (Suppl. 1):3S, 1996
216. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM: Positional cloning of the mouse *obese* gene and its human homologue. *Nature* 372:425–432, 1994
217. Chua SC, Chung WK, Wu-Peng S, Zhang Y, Liu S-M, Tartaglia L, Leibel RL: Phenotypes of mouse *diabetes* and rat *fatty* due to mutations in the OB (leptin) receptor. *Science* 271:994–996, 1996
218. Fan W, Boston BA, Kesterson RA, Hruby VJ, Cone RD: Role of melanocortinergic neurons in feeding and the *agouti* obesity. *Nature* 385:165–168, 1997