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The management of the obese diabetic patient

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Obesity is a major worldwide epidemic that is associated with a significantly increased risk of type 2 diabetes, cardiovascular disease, and premature death [1] [2]. Obesity is associated with increased mortality, especially when it coexists with diabetes. In a 12-year follow-up study of more than 700,000 patients, a weight of more than 50% above average was associated with a twofold increase in mortality. The presence of diabetes, in addition to obesity, raised mortality by five to eight fold [3]. In the past few decades, the prevalence of obesity in the United States and worldwide has increased dramatically. Approximately 60% of Americans are overweight or obese with a body mass index (BMI) of 25 kg/m² or higher [4].

Overweight and obese individuals are at increased risk for developing type 2 diabetes [5] [6] [7]. In fact, there is an inverse relationship between BMI and the age of diabetes onset in obese adults who are younger than 70 years old [8]. The duration and degree of obesity, central distribution of weight, and recent weight gain are all independent risk factors for type 2 diabetes [3]. Studies have shown that weight loss by caloric restriction and exercise could prevent type 2 diabetes in overweight and obese individuals. The Finnish Diabetes Prevention Study showed that a weight loss of at least 5% of initial body weight reduced the risk of progression to diabetes in high-risk, overweight patients with impaired glucose tolerance [9]. In the United States, the Diabetes Prevention Program Research Group showed that lifestyle changes (caloric restriction and exercise) or treatment with metformin reduced the incidence of diabetes in persons at high risk; the lifestyle intervention was more effective than metformin [10]. These effective interventions are slow to be implemented into the daily life of Americans. Over the next decade this dual epidemic is predicted to grow because the number of people who are afflicted with obesity and diabetes continues to rise at an alarming rate.

Currently, 17 million Americans are estimated to have diabetes mellitus (DM). Type 2 diabetes accounts for most (about 95%) of these patients. Diabetes is the leading cause of renal failure, blindness, and amputations in adults. It is a major risk factor for heart disease, stroke, and birth defects. Diabetes decreases the average life expectancy, independently of the degree of overweight, and costs the nation

\$98 billion annually in health-related expenditures [11]. The United Kingdom Prospective Diabetes Study (UKPDS), the Diabetes Control and Complications Trial (DCCT), and the Japanese Kumamoto study showed that aggressive glycemic control in diabetes slowed the progression of microvascular disease, including retinopathy, nephropathy, and neuropathy [12] [13] [14] [15]. For every 1% decrease in hemoglobinA1c [HgbA1c (glycosylated hemoglobin)], microvascular complications decreased 35%, diabetes-related mortality decreased 25%, and all-cause mortality decreased 7% [13]. A continuous, positive relationship exists between HgbA1c level and the risk of complications. As diabetic control worsens, diabetic complications increase.

In the National Health and Nutrition Examination Survey III (NHANES III), only 50% of diabetics were able to achieve a HgbA1c of 7% or less with available aggressive management [16]. Data from NHANES III showed that less than one third of patients who have diabetes have their HgbA1c measured more than once a year; nearly 20% of patients who are being treated for diabetes have a HgbA1c that is greater than 9.5% [16].

Obesity is present in most patients who have type 2 DM. When present, obesity complicates the management of diabetes, especially the goal of achieving tight glycemic control [17] [18]. First, tight glycemic control should be achieved, but not at the expense of adipose tissue accumulation, especially in the visceral adipose depot. Second, weight control must be achieved without losing sight of the need for tight glycemic control. Moreover, cardiovascular risk factors are likely exacerbated by obesity in type 2 DM. Special attention must be paid to control of cardiovascular risk factors in the obese patient who has type 2 diabetes; treatment and control of obesity by caloric restriction and exercise is likely to result in tighter glycemic control and the reduction of cardiovascular risk factors.

Antidiabetic therapy in obese patients

In the obese diabetic patient, just as is in other diabetic patients, microvascular disease is primarily related to the presence of hyperglycemia [12] [13] [14] [15]. Uncontrolled hyperglycemia is also responsible for an unfavorable lipoprotein pattern, an increase in glycosylation end-products in all tissues, and an increased risk of thrombotic events [19]. Therefore, tight glycemic control is warranted in the obese diabetic patient. Goals for glycemic control as recommended by the American Diabetes Association include: a preprandial glucose of 90 to 130 mg/dL, a bedtime glucose of 110 to 150 mg/dL, and a HgbA1c level of less than 7% [20]. The American College of Endocrinology has proposed stricter guidelines which include: a preprandial glucose of less than or equal to 110 mg/dL, postprandial glucose of less than or equal to 140 mg/dL, and HgbA1c level of less than or equal to 6.5% [21].

Diet and exercise are important in maintaining glycemic control in type 2 diabetics. Physical activity, in particular, improves insulin sensitivity, independent of weight loss, and, thus, plays an important role in the strategy of achieving glycemic control in the obese diabetic patient [22]. Supplementation of diet and exercise with oral pharmacotherapy is often needed to maintain glycemic control. Oral agents have been developed that address the two main defects in type 2 diabetes, insulin resistance and β -cell dysfunction [23]. The different classes of hypoglycemic agents, when used to normalize blood glucose, have variable effects on weight gain, the rates of hypoglycemic events, and the degree of hyperinsulinemia [14] [24]. These factors are important to consider in the management of the obese patient who has type 2 diabetes (Table 1).

Table 1. Oral medications and insulin for the treatment of type 2 diabetes: effects on weight and hypoglycemia

men;
severe
heart
failure;
hepatic
dysfunction

Abbreviations: CHF, congestive heart failure; †, ††, †††, degree of weight change or hypoglycemia; (-), no change in weight or hypoglycemia.

Oral agents for treatment of hyperglycemia

Sulfonylureas (eg, glyburide, glipizide, chlorpropamide, glimepiride) and nonsulfonylurea secretagogues (eg, repaglinide, nateglinide) bind to receptors on the surface of pancreatic β cells and stimulate the release of insulin. Although hyperinsulinemia is believed to be a precursor for cardiovascular disease, the UKPDS showed that sulfonylurea or insulin therapy was not associated with increased cardiovascular mortality [13]. Adverse effects of insulin secretagogues are hypoglycemic episodes and weight gain. Third generation sulfonylurea and nonsulfonylurea secretagogues may be associated with lower rates of hypoglycemia and less weight gain than the older sulfonylurea [27] [53] [54] [55]. The nonsulfonylurea secretagogues, with a rapid onset of action and short duration of action, are designed for mealtime dosing [28] and significantly reduce postprandial and fasting blood glucose and HgbA1c [27] [29]. Increases in fasting insulin levels, mean weight gain, and hypoglycemic events may be similar to those produced by sulfonylurea treatments [27] [28] [29]. In general, the more efficacious the treatment in reducing hyperglycemia, the more often weight gain, hyperinsulinemia, and hypoglycemia are seen [27] [28].

Insulin sensitizers, in contrast with insulin secretagogues, theoretically should decrease insulin levels without increasing weight or producing hypoglycemia, as long as they are not combined with insulin secretagogues. There are two classes of insulin sensitizers: biguanide and thiazolidinediones.

Metformin, a biguanide, works by improving insulin sensitivity and reducing hepatic glucose output [16]. Metformin is particularly beneficial for the obese diabetic patient, because it reduces hyperinsulinemia and promotes weight loss [14]. In the UKPDS, a 10-year randomized, controlled trial, intensive blood glucose control in overweight type 2 diabetics effectively resulted in risk reductions of 32% for any diabetes-related endpoint, 42% for diabetes-related death, and 36% for all-cause mortality [14]. Although all patients who had type 2 diabetes in the UKPDS experienced weight gain over the 10-year period of follow-up, obese patients who were allocated to metformin gained the least amount of weight and had the fewest hypoglycemic attacks, compared with patients who were treated with insulin or sulfonylurea [14]. Patients who were given or metformin or were treated conventionally with diet, gained 1 kg to 2 kg during the study, whereas those who were given sulfonylurea or insulin had a weight gain of 5 kg to 7 kg (Fig. 1 [Not Available]) [14]. There was no significant difference among insulin, sulfonylurea, and metformin in glycemic control and microvascular risk reduction. In another large randomized, controlled study, a mean weight loss of 3.8 kg was observed in obese type 2 diabetic patients who were treated with metformin monotherapy for 29 weeks [25]. The best study that showed metformin, may, in fact, produce weight loss was of the 3234 prediabetic patients of the Diabetes Prevention Program [10]. Over 3 years, the average weight loss was 5.6 kg, 2.1 kg, and 0.1 kg in the patients who were randomized to receive lifestyle changes (caloric restriction and exercise), metformin, or placebo, respectively [10]. Metformin also has beneficial effects on the lipid profile [25]. Thus, metformin is a drug of choice in the treatment of the obese diabetic patient. Side effects of metformin include nausea and diarrhea; however, it is reasonably well tolerated by most patients. Lactic acidosis is a rare, but serious, complication that is more likely to occur in patients who have renal insufficiency, secondary to the accumulation of

metformin. Metformin is contraindicated in patients who have renal insufficiency, congestive heart failure, hepatic disease, and alcohol abuse.

Fig. 1. (Figure not Available) Changes in fasting plasma glucose (FPG), HgbA_{1c}, body weight, and serum insulin levels over 10 years in patients who had type 2 diabetes on various treatment modalities. (From U.K. Prospective Diabetes Study Group. Effect of intensive blood glucose control with melformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;352:854–65; with permission.)

A newer class of antidiabetic agents, the thiazolidinediones (glitazones), bind to nuclear peroxisome-proliferator activated receptor- γ (PPAR- γ) that is found in adipose and muscle cells to increase peripheral uptake of glucose by skeletal muscle cells. This enhances insulin sensitivity and decreases serum insulin levels [41] [42] [56]. The glitazones also reduce lipolysis, and, thus, free fatty acid levels and improve high-density lipoprotein (HDL) and triglyceride levels. Studies in type 2 diabetics showed that the addition of a glitazone to sulfonylurea or insulin monotherapy resulted in better glycemic control, but was associated with hypoglycemia and weight gain [41] [43] [44] [45]. Hypoglycemia is a common adverse effect of glitazone-insulin combination, but it can be avoided with a gradual reduction of the insulin dosage [43] [44]. The significance of weight gain from glitazones is difficult to assess. Despite the weight gain, the glitazones are beneficial because they redistribute fat from visceral to subcutaneous areas [46] [47] [48]. In addition, some of the weight gain is the result of peripheral edema and an increase in extracellular fluid [57]. Therefore, these agents must be used with caution in patients who have congestive heart failure. In addition, liver functions tests must be monitored closely.

α -Glucosidase inhibitors, such as acarbose, work by delaying intestinal carbohydrate absorption and reducing postprandial hyperglycemia. Acarbose, when given alone or in combination with sulfonylurea, metformin, or insulin resulted in improvement of glycemic control [34] [58] [59] and is particularly beneficial for the obese diabetic patient because it reduces hyperinsulinemia and does not produce weight gain [34] [35]. One randomized, placebo-controlled trial showed a small, but statistically significant, weight loss of 0.46 kg in obese type 2 diabetic patients who were treated with acarbose for 12 months [36]. Common side effects include diarrhea, flatulence, and abdominal discomfort; slow titration may lessen these effects.

Because of the progressive nature of β -cell dysfunction in type 2 diabetes, monotherapy with oral agents usually fails over time [13] [26]. In the UKPDS, the patients who were treated with monotherapy achieved an initial improvement in HgbA_{1c}, regardless of the agent used; however, monotherapy failed to maintain HgbA_{1c} at less than 7% over time [60]. Thus, combination therapy often is needed. Combination therapy is generally more effective than monotherapy because it yields additive effects on HgbA_{1c} reduction [23] but it may compound the weight gain and the frequency of hypoglycemic events.

Insulin therapy

Because of the progressive loss of β -cell function, eventually the insulin secretory capacity is insufficient to overcome the insulin resistance; a state of relative insulin deficiency develops in patients who have type 2 diabetes. Thus, when other therapeutic measures fail to normalize blood glucose, the initiation of insulin therapy becomes necessary [61]. Edelman and Henry [62] reviewed the use of insulin for the treatment of type 2 DM. They concluded that obese diabetic patients could and should be evaluated for intensive insulin therapy. The candidates should be motivated, compliant, and able to do home glucose monitoring and insulin administration. The adverse effects and potential risks of intensive insulin treatment included weight gain, which was directly associated with increased hyperinsulinemia [18] [63] [64] [65]. Hyperinsulinemia has been associated with atherosclerotic risk factors, although a cause

and effect relationship has not been proven [66]. In the UKPDS, intensive blood glucose control with either insulin or sulfonylurea therapy significantly decreased the progression of microvascular disease and was not associated with increased cardiovascular mortality. Patients who were allocated to insulin gained more weight and had more hypoglycemic events than patients who were allocated to sulfonylurea [16] [60]. It is not known if the benefit of glucose control that is achieved with intense insulin therapy offsets the effect of hyperinsulinemia on cardiovascular disease. This is currently being investigated.

The first types of insulin that were used in the treatment of diabetes were bovine and porcine insulin compounds that differ from the human insulin by 1 to 3 amino acid residues [67]. In the 1980s, biosynthetic human insulin became widely available [68] and protein engineering allowed the development of insulin analogs (Table 2 [Not Available]). Insulin analogs are molecules that differ from human insulin in amino acid sequence but are capable of binding and activating the human insulin receptor. These include two rapid acting insulins, lispro and aspart, and the long-acting insulin, glargine

Table 2. Characteristics of insulin preparations [Table not Available]

Adapted from Hirsch IB. Pharmacotherapeutics of insulin therapy. Optimizing insulin therapy in patients with diabetes. Lawrenceville (NJ): Clinical Connexion 2002. p. 7–12.

Traditionally, twice daily injections of short-acting (regular) and intermediate acting (NPH) insulin have been used to treat diabetes. This regimen does not accurately reproduce normal physiologic insulin secretion [69]. Subcutaneous injection of regular insulin produces its peak effect in 2 hours and lasts 3 to 6 hours, which may lead to inadequate postprandial glucose control, postprandial hyperinsulinemia, and, possibly, late hypoglycemia [69] [70]. Intermediate-acting NPH insulin reaches its peak effect at 6 to 10 hours, lasts 10 to 18 hours with considerable inter- and intrasubject variations in bioavailability, and, when given at dinnertime, may cause nocturnal hypoglycemia [70] [71]. For obese patients who have type 2 diabetes and require insulin, physiologic regimens, such as basal and bolus therapy with long-acting (glargine) insulin and rapid-acting (lispro or aspart) insulin, may be more beneficial. Unlike regular insulin, lispro and aspart are absorbed more quickly and have a rapid onset of action [69] [71] [72]; they are ideal for improving postprandial glucose control [73]. Perhaps the greatest advantage of lispro or aspart is that it can be injected at meal time; however, to avoid early postprandial hypoglycemia, patients must be taught to check their glucose levels before meals and to adjust the insulin dose according to their current glucose level and the carbohydrate content of their meal [68].

Insulin glargine is a novel recombinant human insulin analog with low aqueous solubility at neutral pH [74]. Glargine is produced as an injection solution with a pH of 4. When the solution is injected into the subcutaneous tissue, it immediately neutralizes which results in microprecipitates of insulin. The slow release of small amounts of insulin into the bloodstream results in a relatively constant serum level over 24 hours. The advantage of insulin glargine is that it produces less nocturnal hypoglycemia, and, in some studies, less weight gain [75]. The lesser weight gain that was seen with insulin glargine is attributed to the less frequent hypoglycemia, and, thus, the decreased need to increase caloric supplementation [76]. The use of insulin glargine, compared with NPH, is also associated with lower postdinner glucose levels [76].

The major limitation of insulin is that the standard route of administration is subcutaneous injection. Preliminary studies on inhaled insulin therapy are so far promising. If successful, these agents may revolutionize the treatment of diabetes [77] [78].

Combination insulin and oral therapy

Hypoglycemic agents that are not likely to produce weight gain should be used in the obese diabetic patient whenever possible (ie, when endogenous insulin secretion is adequate). If insulin secretagogues or exogenous insulin need to be used, it is beneficial to combine them with either insulin sensitizing agents, carbohydrate blockers, or weight loss-producing agents (eg, sibutramine or orlistat) to minimize weight gain and the amount of insulin that is needed to achieve glycemic control. Metformin, in particular, but also sulfonylureas and acarbose, when combined with insulin, minimize weight gain in type 2 diabetics [57]. The combination of insulin and metformin is used widely and is a successful strategy. Several randomized clinical trials showed that the combination of exogenous insulin with metformin in the treatment of hyperglycemia in the type 2 diabetic patient led to a reduction in the total daily dosage of insulin that was required, improved HgbA1c, and minimized weight gain [79] [80] [81] [82]. The insulin-sulfonylurea combination reduced the total daily dosage of required insulin to achieve a given level of glycemic control and modestly improved glycemic control. The Veterans Affairs Cooperative Study in Type II Diabetes showed that some patients were able to achieve near-normal glycemic control with Bedtime Insulin and Daytime Sulfonylurea (BIDS therapy) [83]. In a meta-analysis of more than 40 randomized, controlled trials in type 2 diabetics, combination insulin-sulfonylurea therapy was not associated with weight gain [84]. Sulfonylurea may induce a more physiologic release of insulin during the day in response to increased glucose levels with meals. In addition, combining sulfonylurea and insulin resulted in a 30% reduction in the total amount of insulin that was required daily to maintain a certain level of glycemic control [85] [86]. Similarly, the addition of repaglinide in patients who had type 2 diabetes that was suboptimally controlled on insulin monotherapy resulted in significant reductions in HgbA1c, postprandial glucose levels, and required insulin dosage, with no change in the hypoglycemic risk [30]. The repaglinide-insulin combination therapy, however, was not as effective in reducing HgbA1c and was associated with more weight gain, compared with metformin-insulin therapy (2.7 kg vs. 0.9 kg, respectively) [31]. Adding acarbose to insulin treatment was beneficial in reducing postprandial hyperglycemia, especially in patients who consumed a high carbohydrate diet [87]. Studies showed that this combination moderately reduced the HgbA1c by 0.4% to 0.7% and variably reduced weight, triglyceride levels, and insulin dosage [34] [36] [59].

Antiobesity therapy in patients who have type 2 diabetes mellitus

Weight control is an important part of diabetes management. Diet and exercise improve glycemic control and weight control. These interventions should be initiated early in the management of diabetes and should continue throughout the duration of the treatment in the obese diabetic patient [88]. The guidelines for the treatment of obesity as published under the sponsorship of National Heart, Lung, and Blood Institute (NHLBI) should be followed for the obese patient who has type 2 diabetes as for other obese patients [89]. Whether some of these guidelines need to be modified specifically for the obese patient with type 2 DM needs to be determined.

Weight loss by caloric restriction

Caloric restriction and consequent weight loss in obese diabetic patients greatly improves their metabolic control because it results in improved insulin action in liver and muscle, and, frequently results in improved β -cell response to insulin secretory stimuli [88]. In addition, weight control improves cardiovascular disease risk factors, such as hypertension and dyslipidemia [88]. Weight control can and must be achieved through a medically supervised, moderately restricted-calorie diet and an exercise program with long-term maintenance goals [90]. Recently studies showed that even moderate weight loss, when sustained, significantly improves the patient's metabolic profile and prolongs their life

expectancy [91] [92] [93] [94]. Patients who had type 2 DM who underwent a 16-week lifestyle modification program and lost at least 5% of their initial body weight, had a significant improvement in HgbA1c that was sustained at a 1-year follow-up. These patients also had significant reductions in their need for diabetic medications [95]. The effect of weight loss, through a program of diet and exercise, on macrovascular complications in patients who have type 2 DM is the subject of a large, multicenter national study (Look AHEAD study).

Effectiveness of weight-reducing programs for obese patients who have type 2 diabetes may be decreased by treatment with large dosages of insulin. In such instances, the danger of hypoglycemia must be recognized and the blood glucose must be monitored closely with frequent decreases in insulin, as necessary. Some of the postulated reasons for weight gain with insulin therapy are decreased thermogenesis [96] [97] and increased appetite [98]. Thus, it may be impossible to achieve weight loss with caloric restriction unless insulin (or oral agents which increase insulin levels) is being adequately adjusted to the lower calorie diet that is prescribed.

Despite good success in the short term, most obese patients are unable to maintain a modest long-term reduction in their weight [96]. Obese patients who have type 2 diabetes may be more resistant to weight loss and its maintenance because antidiabetic drugs, such as insulin and sulfonylurea, often promote weight gain [13] [63]. These patients would likely benefit from the addition of weight management drugs, such as sibutramine and orlistat (Table 3), as adjunctive therapy to the traditional interventions of low calorie diet, physical activity, and behavior management [99].

Medication	Mechanism of action	Adverse effects	Recommended dosage	Contraindications
Sibutramine	Selective serotonin and norepinephrine reuptake inhibitor; enhances satiety and increase energy expenditure	Hypertension, tachycardia, headache, insomnia, dry mouth, constipation	Start with 10 mg daily, increase to 15 mg daily after 4 weeks. A maximum daily dosage of 20 mg has been used in type 2 diabetes.	Coronary artery disease, arrhythmias, congestive heart failure, stroke, poorly-controlled hypertension, severe hepatic dysfunction, or severe renal impairment
Orlistat	Gastrointestinal lipase inhibitor; decreases the absorption of dietary fat by 30%	Fecal incontinence, flatulence, vitamin malabsorption	120 mg, three times a day, with meals	Acute gastrointestinal illnesses

Sibutramine

Sibutramine is a selective serotonin and noradrenaline reuptake inhibitor. Blocking of serotonin reuptake produces satiety enhancing; inhibition of norepinephrine uptake increases thermogenesis by way of β -3 adrenoceptors [100] [101]. Sibutramine is recommended as an adjunct to reduced calorie diet in patients with a BMI of 30 kg/m² or higher, or 27 kg/m² or higher in the presence of other risk factors, such as diabetes, hypertension, or dyslipidemia. The use of sibutramine has resulted in significant weight loss

and the maintenance of this weight loss for up to 2 years.

Sibutramine has been successfully used in obese patients who have type 2 diabetes for the purposes of weight loss, weight loss maintenance, and improvement of glycemic control and cardiovascular risk factors. Sibutramine, 15 mg once daily for 12 weeks, along with a customized reduced calorie diet significantly reduced weight compared with placebo (2.4 kg vs. 0.1 kg, respectively) in obese and overweight patients with type 2 diabetes, who were treated previously with diet alone or stable regimens of insulin or oral agents [100]. This was accompanied by improvements in postprandial glucose, fasting glucose, and glycosylated hemoglobin [100]. Several other studies showed the benefits of combining sibutramine and oral hypoglycemic therapy in patients with type 2 diabetes [101] [102] [103] [104]. In obese patients who had type 2 diabetes that was poorly controlled on diet alone or diet plus either a sulfonylurea or metformin, sibutramine produced significantly greater weight loss compared with placebo (4.3 kg or 4.5% vs. 0.4 kg or 0.5%, respectively). The decreases in HgbA1c and fasting plasma glucose correlated with the amount of weight loss [101]. Improvements were also seen in fasting insulin, triglycerides, HDL cholesterol, and quality of life [101]. In obese patients who had poorly controlled type 2 diabetes (HgbA1c of more than 8%) while on maximum doses of sulfonylurea and metformin, the addition of sibutramine 10 mg, twice a day for 6 months, significantly improved glucose levels, insulin resistance, waist circumference, BMI, HgbA1c, and lipid profile. Fasting and postprandial glucose levels decreased below baseline. The mean decrease in HgbA1c was 2.73% with sibutramine [104]. Patients who took sibutramine lost an average of 9.61 kg, whereas those who took placebo gained 0.91 kg [104]. Thus, sibutramine is an effective adjunct to oral hypoglycemic therapy in the obese diabetic patient. The longest study of sibutramine therapy in diabetic patients (12 months) reported a weight loss of 7.1 kg with sibutramine, compared with a 2.1 kg weight loss with diet alone. Improvements were also seen in lipid levels [102]. Sibutramine helps obese patients lose weight and it may also prevent relapse after successful weight reduction. This, however was studied only in nondiabetics (Sibutramine Trial of Obesity Reduction and Maintenance). In this study, nearly 70% of patients who took sibutramine were able to maintain a 5% weight loss at 2 years, compared with only 44% of patients with diet and exercise alone [105].

In the aforementioned studies, sibutramine was safe and well tolerated. The safety and efficacy of sibutramine therapy beyond 2 years has not been established. Sibutramine is known to increase blood pressure by 2 to 3 mm Hg on average; therefore, blood pressure should be carefully monitored during treatment. In the long term, weight loss from sibutramine results in a net decrease in blood pressure [106]. Other side effects of sibutramine include headache, dry mouth, anorexia, constipation, and insomnia; however, these are mild to moderate and transient. Sibutramine should not be used in patients who have a history of coronary artery disease, arrhythmias, congestive heart failure, stroke, poorly-controlled hypertension, severe hepatic dysfunction, or severe renal impairment. Sibutramine is contraindicated in patients who take monoamine oxidase inhibitors or other centrally-acting appetite suppressants. Coadministration of sibutramine with other serotonergic agents is not advised; if this is clinically indicated, however, it requires close monitoring [106].

Orlistat

Orlistat, a specific inhibitor of gastrointestinal (GI) lipases, decreases the absorption of dietary triglycerides from the gastrointestinal tract in a dosage-dependent manner. At the maximum effective dosage of 120 mg, three times a day, orlistat reduced the absorption of dietary fat by 30% [107]. When given in combination with a mild calorie-restricted diet, orlistat produced more significant and long-lasting weight loss than diet alone [106] [107] [108] [109] [110] [111]. In addition, a recent epidemiologic prediction model suggested that orlistat is a cost-effective treatment for obese patients who have type 2 diabetes [108].

In obese patients who have type 2 diabetes, orlistat therapy for 24 to 52 weeks, decreased weight, HgbA1c, fasting plasma glucose, and low-density lipoprotein (LDL) cholesterol, compared with placebo [109]. Over a 1-year period, orlistat, 120 mg three times a day, given in combination with a low calorie diet [110] to obese patients who had type 2 diabetes that was maintained on oral sulfonylurea, produced a 6.2% decrease in body weight compared with a 4.3% weight loss in the group who took placebo [110]. The improvement in HgbA1c was proportional to the amount of weight lost. Those who lost 5% to 10% of their body weight had a mean decrease in HgbA1c of 0.95%. Those who lost more than 10% of body weight had an average decrease in HgbA1c of 1.53%. In addition, improvements were seen in total cholesterol, LDL, triglycerides, apo-lipoprotein B, the LDL:HDL ratio, and waist circumference. In obese patients who had type 2 diabetes that was poorly controlled by insulin therapy, the addition of orlistat resulted in significant reductions in weight, HgbA1c, fasting blood glucose, and LDL cholesterol [111]. Of particular significance for the obese diabetic patient, orlistat therapy reduced the dosage of insulin that was needed to maintain glycemic control. Thus, in the obese type 2 diabetic patient who requires insulin, orlistat may be used to counteract the weight gain. Possible side effects of orlistat include, the reduction of serum levels of fat-soluble vitamins and beta-carotene. GI side effects are mild to moderate and usually transient.

Overall, as part of an integrated program of diet, exercise, and behavior management, nearly one third of obese patients who had type 2 diabetes achieved a weight loss of up to 10% of initial body weight after 1 year of treatment with either sibutramine or orlistat. The weight loss resulted in decreased HgbA1c, decreased blood pressure, and improved lipid profiles [100] [112] [113]. Furthermore, in a short-term study, orlistat improved glucose tolerance and decreased the risk of progression to type 2 diabetes in patients who had impaired glucose tolerance [114]. A combination of sibutramine and orlistat therapy may be beneficial in severely obese patients who have type 2 diabetes, because each drug works differently to induce weight loss; however, this needs to be evaluated in randomized clinical trials. Studies are also needed to assess the long-term efficacy and safety of sibutramine and orlistat therapy on morbidity and mortality in obese patients who have type 2 diabetes.

Other agents

Glucagon-like peptide (GLP-1), is an insulinotropic gut hormone that is released into the bloodstream after eating; abnormalities in GLP-1 function are believed to contribute to the inappropriate insulin secretion that is seen in type 2 diabetes [115] [116] [117]. In patients who have type 2 diabetes, the administration of exogenous GLP-1 enhanced the glucose responsiveness of pancreatic β cells, which resulted in increased insulin secretion and decreased plasma glucose [115] [118]. In addition, GLP-1 acts on the central nervous system to produce a satiating effect and is believed to improve glycemic control by decreasing the desire for food, delaying gastric emptying, reducing glucagon levels, and enhancing insulin sensitivity [119] [120] [121]. Also, stimulation of GLP-1 receptors in certain areas of the brain elicits strong taste aversions [122]. Therefore, GLP-1 and its analogs are promising agents for weight and glycemic control in the obese patient who has type 2 diabetes.

In patients who have type 2 diabetes, GLP-1 infusion significantly enhanced satiety and fullness, reduced energy intake by 27% [123], and produced significant improvement in glucose levels, compared with placebo [124]. A limitation of GLP-1 is its short half-life, as in vivo, it is rapidly inactivated by the protease dipeptidyl peptidase IV (DPP-IV) [125]. Exendin-4, a more potent and longer-acting analog of GLP-1 that originates in the saliva of *Heloderma suspectum* (Gila monster), was shown to induce satiety and weight loss in rats [126]. Exendin-4 binds and activates the human pancreatic GLP-1 receptor, thus exhibiting the same antidiabetic effects as GLP-1. Unlike GLP-1, exendin-4 is not affected by DPP-IV, and, therefore, remains active in plasma for 6 hours after subcutaneous injection. A synthetic exendin-4, called AC2993, was developed by Amylin Pharmaceuticals (San Diego, CA); this drug is now in phase

III trials.

Other agents that are presently being studied for weight loss may prove to be beneficial in type 2 DM. Selective β -3 adrenoreceptor agonists induced weight loss and produced a weight-independent improvement in insulin resistance and glucose intolerance in animal studies [99]. When these studies were attempted in humans, however, little benefit was seen. This was attributed to the fact that the agents that were used in the earlier studies were not selective for the human β -3 adrenergic receptor. New β -3 agonists are being developed that have a higher selectivity for humans [99].

Leptin is an adipocyte-derived hormone that is released into the blood stream and acts as a satiety signal in the brain. In the first clinical study in humans, subcutaneous administration of a biosynthetic leptin reduced body fat and decreased weight in a dose-dependent manner [99]. Thus, leptin is another potential weight-reducing agent for obese diabetic patients. Further studies on the safety and efficacy of leptin are needed before it can become an acceptable treatment for weight reduction [99].

Bariatric surgery

In the severely obese patient ($\text{BMI} > 40 \text{ kg/m}^2$), diet, behavior modification, and drug therapy are often unsuccessful in the long term. Severely obese patients may lose weight initially on these treatments, but may be unable to maintain the weight lost. The cumulative recidivism rate for diet therapy is close to 100% at 5 years [127] [128]. Moreover, the limited weight reduction with sibutramine and orlistat may not be acceptable in the long-term in severely obese patients who need to lose and maintain larger amounts of weight [129].

The weight loss that is achieved with bariatric surgery in severely obese patients is significantly larger and longer-lasting than the weight loss that is achieved with diet and pharmacotherapy [130] [131] [132] [133] [134]. Within 2 years of gastric bypass, nearly two thirds of excess body weight is lost. Most of this weight loss is maintained for many years after surgery [131] [135]. In nearly 600 patients who underwent gastric bypass, the loss of more than 50% of excess body weight was maintained for up to 14 years [135]. A large percentage of patients who had diabetes or glucose intolerance and underwent gastric bypass, developed marked resolution of their glucose intolerance with improvements in hyperglycemia, hyperinsulinemia, insulin resistance, hypertension, dyslipidemia, and other comorbidities [131] [132] [133] [136] [137] [138]. As a result of their improved metabolic profile, most patients were able to significantly reduce the dosage of their antidiabetic medications, especially insulin and sulfonylurea [138] [139]. Studies that were done in the United States and Sweden showed that patients who had type 2 diabetes who underwent bariatric gastric surgery developed normal glucose tolerance within months after the surgery [91] [140]. Patients who had diabetes were shown to benefit from gastropasty, gastric bypass, and biliopancreatic diversion [135] [138] [141] [142] [143]. Thus, in the severely obese diabetic patient ($\text{BMI} > 30 \text{ kg/m}^2$), bariatric surgery is a successful method of achieving long-term weight loss, glycemic control, and resolution of comorbidities.

The indications for bariatric surgery as defined by the National Institutes of Health (NIH) Consensus Conference in 1991, include BMI of 35 kg/m^2 or higher in patients who have comorbidities, such as diabetes, and BMI of 40 kg/m^2 or higher in patients with or without comorbidities [144]. After bariatric surgery, intensive long-term, postoperative care is needed; therefore, potential candidates should be well informed and motivated to ensure proper long-term follow-up and compliance [3]. Bariatric surgery alone will not guarantee successful long-term weight loss because some patients may slowly regain a tolerance for high-fat foods and carbohydrates [132] [145]. Patients need to comply with a diet and exercise program postoperatively. In addition, patients who are unable to cope with the postoperative lifestyle

changes may develop major depression, despite successful weight loss after surgery [146].

The three main categories of bariatric surgery are purely malabsorptive, purely restrictive, and mixed malabsorptive/restrictive [137] [146] [147]. The purely restrictive Vertical Banded Gastroplasty (VBG) and the combined restrictive/malabsorptive Gastric Bypass (GB) are the two most frequently performed bariatric operations in the United States [3]. Both procedures are considered safe with low reported morbidity and mortality [3] [132] [136].

Of the many variations of gastric bypass, the Roux-en-Y gastric bypass (RYGB) is the most popular [132]. Gastric restriction is achieved by creating a small 5 mL to 15 mL upper gastric pouch with a 1 cm outlet orifice [136]. The pouch empties swallowed food into the small intestine through a Roux limb gastrojejunostomy. The degree of malabsorption depends on the extent of the bypass, which minimally consists of the distal stomach, the duodenum, and the proximal jejunum. Most patients who underwent gastric bypass surgery lost 30 pounds in the first month, 60 pounds in 6 months, and 100 pounds in 1 year [148]. They continued to lose weight for a total of 24 months and were able to maintain a weight that was 20% to 30% above their ideal weight for more than 14 years [148]. In addition, comorbidities, such as diabetes and hypertension, resolved rapidly after surgery [139] [148] [149] [150].

Pories and his associates [135] performed gastric bypass on more than 600 morbidly obese patients, including 146 patients who had type 2 diabetes and 152 patients who had impaired glucose tolerance. In 82.9% of the patients who had type 2 diabetes and 98.7% of the patients who had impaired glucose tolerance, gastric bypass resulted in normalization of glucose, insulin, and HgbA1c levels. These results were maintained during the 14 years of follow-up. In a retrospective study of 232 morbidly obese patients who had type 2 diabetes, 154 patients underwent gastric bypass and the 78 control patients did not have the surgery because of personal preference or lack of insurance coverage. In the group who underwent surgery, the mean glucose level decreased from 187 mg/dL and remained at less than 140 mg/dL for up to 10 years of follow-up ([Figs. 2 [Not Available] and 3 [Not Available]]) [151]. More importantly, the mortality rate was 28% in the control group but only 9% in the group that underwent surgery. For every year of follow-up, medically-treated patients had a significantly higher chance of dying compared with those who had undergone gastric bypass surgery (4.5% vs. 1.0%, $P < 0.0001$) [151]. The improvement in mortality that was seen in the group who underwent surgery was largely the result of a decrease in cardiovascular deaths. The long-term effects of bariatric surgery on the morbidity and mortality of the obese diabetic patient have yet to be elucidated in prospective, controlled trials, such as the ongoing Swedish Obese Study [137] [150].

Fig. 2. (Figure not Available) Percentage of excess body weight lost in surgical patients (n = 154). The mean percentage loss of excess body weight reached a maximum of 62.4% 1 year after gastric bypass and remained at approximately 50% out to 14 years. (From MacDonald KG, Long SD, Swanson MS, et al. The gastric bypass operation reduces the progression and mortality of non-insulin-dependent diabetes mellitus. *J Gastrointest Surg* 1997;2:213–20; with permission.)

Fig. 3. (Figure not Available) The mean fasting blood glucose decreased from 187 mg/dL to a 98.9 mg/dL (combination of random and fasting) at 1 year after gastric bypass surgery and remained less than 140 mg/dL out to 10 years. (From MacDonald KG, Long SD, Swanson MS, et al. The gastric bypass operation reduces the progression and mortality of non-insulin-dependent diabetes mellitus. *J Gastrointest Surg* 1997;2:213–20; with permission.)

In general, gastric bypass is more effective than VBG in producing weight loss [132] [145] [152] [153] [154]. In the obese diabetic patient, weight loss and glycemic control are better achieved with the gastric bypass than with VBG [131] [154]. These results are attributed to the fact that patients with VBG often consume excessive amounts of high-calorie liquids and carbohydrates; patients who undergo GB develop an

aversion to sweets because of the development of the dumping syndrome [155]. In purely restrictive procedures, such as VBG, ingested food is temporarily retained in an upper gastric pouch to induce satiety. Gastric restriction works by inducing nausea and vomiting when excess food is ingested. On average, maximal weight loss is achieved over 6 to 9 months; half of this maximal weight loss is maintained at 10 years after surgery [156].

Gastric banding is another kind of purely restrictive bariatric surgery, but is less invasive. The Swedish Adjustable Gastric Band (Obtech Medical AG, Baar, Switzerland) and the Lap-Band System laparoscopically placed adjustable gastric band (LAGB; Lap-Band Systems; BioEnterics, Carpinteria, CA) are two commonly used, adjustable band prosthetics [157] [158] [159]. Gastric banding, which is popular in Europe, is still in its evolving stages; little is known about its long-term effects. Results of the large, multicenter, United States Lap-Band trial have yet to be published. In the United States, the Lap-Band is approved by the Food and Drug Administration for limited distribution [157]. Several studies, however, showed that laparoscopic adjustable gastric banding could be effective in the management of the obese diabetic patient. In one study, surgical obese patients with a BMI of greater than 35 kg/m² who underwent the Lap-Band, had greater decrease in HgbA_{1c}, as well as loss of visceral adipose tissue, compared with controls who did not undergo surgery [160]. In another study, diabetes resolved completely in 64% of severely obese diabetic patients, 1 year after undergoing the Lap Band procedure with normalization of fasting plasma glucose and insulin, and of HgbA_{1c} [161].

Every bariatric surgery, even the most complicated, can now be performed laparoscopically. Laparoscopic surgery is often preferred because it is less invasive and decreases the length of hospital stay [3] [145] [162].

Summary

The prevalence of obesity and diabetes is increasing in the United States and worldwide. These diseases are predicted to explode to epidemic proportions, unless appropriate counteractive measures are taken. Several large studies (DCCT, UKPDS, Kumamoto) clearly showed that intensive glycemic control in the diabetic patient reduced microvascular complications and improved mortality. Despite this, the NHANES III showed that only 50% of diabetics have been able to achieve a HgbA_{1c} level that is less than 7%; this suggests the need for a re-evaluation of our approach to these patients. The management of the obese diabetic patient involves glycemic control and weight reduction. These goals are particularly difficult to achieve in the obese diabetic patient because progressive β -cell dysfunction and increasing insulin resistance necessitates the administration of increasingly higher dosages of insulin, which, in turn, promotes weight gain. A vicious cycle may ensue. Lifestyle modifications with diet and exercise are an essential part of the management of the obese diabetic patient. These measures alone are often insufficient and concomitant pharmacologic therapy is usually required to achieve glycemic and weight control. Oral agents that improve glycemia, decrease insulin resistance, and limit weight gain are desirable. Because of the progressive nature of diabetes, glycemic control with monotherapy often deteriorates over time, which necessitates the addition of other pharmacologic agents, including insulin. When insulin therapy is required in the treatment of the obese diabetic patient, combinations with oral agents that have been shown to minimize the amount of exogenous insulin that is required, may minimize weight gain. In addition, the obese diabetic patient who is poorly controlled with maximum oral hypoglycemic therapy may benefit from weight-reducing agents, such as sibutramine or orlistat. The introduction of these agents at other points in the management of the obese diabetic patients have been successful. Finally, for the severely obese diabetic patient, bariatric surgery may be the only effective treatment. Gastric bypass has been unequivocally shown to produce significant weight loss and improve glycemic control on a long-term basis in the obese diabetic patient. It is recommended that physicians avail themselves of all of these strategies in the management of the obese patient who has

type 2 diabetes.

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