

Management of diabetes across the course of disease: minimizing obesity-associated complications

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Abstract: Obesity increases the risk for developing type 2 diabetes mellitus (T2DM) and this in turn correlates with an elevated probability of long-term diabetes complications once diabetes is established. Interventions aimed at lowering weight via changes in diet and lifestyle have repeatedly been shown to improve glycemic control in patients with T2DM and even to reverse early disease. Weight gain, a potential side effect of treatment for patients with T2DM, is also an important concern, and it has been noted that weight increases associated with antidiabetes therapy may blunt cardiovascular risk reductions achieved by decreasing blood glucose. Among older agents, metformin and acarbose have the lowest risk for weight gain, while sulfonylureas, meglitinides, and thiazolidinediones are all associated with weight increases. Clinical trial results have also consistently demonstrated that treatment with glucagon-like peptide-1 receptor agonists and amylin lowers weight, and that dipeptidyl peptidase-4 inhibitors are weight neutral in patients with T2DM. Conventional human insulin formulations are known to increase weight in patients with T2DM. However, some insulin analogs, particularly insulin detemir, have lower liability for this adverse event. The use of both pharmacologic and surgical therapies aimed at treating obesity rather than lowering blood glucose have the potential to improve glycemic control and even resolve T2DM in some patients.

Keywords: bariatric, diabetes, incretin, insulin, obesity, oral antidiabetes agents

Introduction

Obesity, along with other factors such as advancing age, family history of diabetes, history of gestational diabetes, impaired glucose metabolism, and physical inactivity, are associated with increased risk for type 2 diabetes (T2DM).¹ It has been noted that the prevalence of diagnosed diabetes among adults 18–79 years of age in the USA increased by 41% from 1997 to 2003, and this increase was greatest among obese individuals (body mass index [BMI] ≥ 30 kg/m²).² It is believed that obesity contributes to the development of T2DM by elevating levels of nonesterified free fatty acids, hormones, adipocytokines, and other substances that increase insulin resistance. Obesity-related elevation in proinflammatory molecules, including tumor necrosis factor- α and interleukin-6, are also believed to contribute to the development of both T2DM and metabolic syndrome.³ The prevalence of overweight and obesity among patients with T2DM are both extremely high. Results from the Study to Help Improve Early Evaluation and Management of Risk Factors Leading to Diabetes, for example, indicated that 28% of individuals surveyed with diabetes were overweight (BMI 25–29.99 kg/m²) and 59% were obese (defined as above) (Figure 1).⁴

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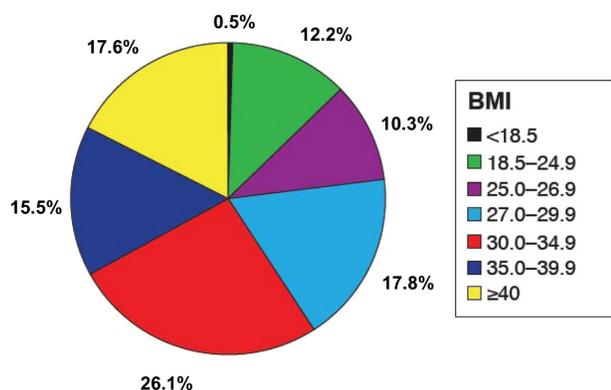


Figure 1 Distribution of body mass index (BMI) values for patients with type 1 or type 2 diabetes mellitus in the Study to Help Improve Early Evaluation and Management of Risk Factors Leading to Diabetes.

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Obesity is not only associated with increased risk for the development of T2DM but also with elevated probability of long-term complications in people with this disease. The risk for these complications is also increased for obese patients in the prediabetic state.^{5,6} Patients with T2DM are at high risk for cardiovascular disease (CVD)-related events,⁷ and overweight/obesity and T2DM are both independent risk factors for the development of CVD.^{7,8} All of these results support the view that overweight/obesity, along with hyperglycemia and other risk factors such as elevated blood pressure and abnormal lipids, act together to determine risk for all-cause and CVD mortality in patients with T2DM.⁹

There are also strong relationships among obesity, diabetes, and cancer risk. For example, meta-analysis of epidemiological data indicated that the relative risk (RR) for postmenopausal breast cancer is ~1.5 for overweight women and >2 for obese women versus women with normal weight.¹⁰ The meta-analysis also found that diabetes is associated with postmenopausal breast cancer, with summary RRs from meta-analyses of 1.15–1.20. The risk for pancreatic cancer is also significantly increased by overweight or obesity or the presence of diabetes.¹¹

Weight gain is also an important concern as a potential side effect of treatment for patients with, or at risk for, T2DM.^{12,13} Control over body weight can significantly decrease the risk for complications in patients with T2DM and should be an important aspect of management for these patients. This review considers the importance of addressing obesity across the course of disease in patients with T2DM to decrease the risk for complications and optimize long-term outcomes. It includes consideration of diet and lifestyle management, effects of

antidiabetes therapy on body weight, and both pharmacologic and surgical interventions aimed at lowering weight.

T2DM and overweight/obesity

Results from numerous large-scale long-term studies have indicated that excess weight is harmful in patients with or without T2DM. Results from the Framingham Study showed that atherosclerotic risk factor clustering is common in both men and women in the general population, worsens with weight gain, and is associated with increased risk of coronary heart disease. This prospective study of 2406 men and 2569 women aged 18–74 years at baseline indicated that a 2.25 kg increase in weight over 16 years was associated with a 20% rise in the summed severity of six CVD risk factors (high-density lipoprotein cholesterol [HDL-C], total cholesterol, BMI, systolic blood pressure, triglycerides, and plasma glucose) in men and a 37% increase in women.¹⁴ The importance of obesity in increasing the risk for diabetes complications was underscored by the Heart Outcomes Prevention Evaluation study. Results from this 4.5-year study of 6620 men and 2182 women (about 32% with diabetes) showed that obesity, in particular, abdominal adiposity, leads to an increased risk for CVD, including myocardial infarction by 23% ($P < 0.01$), congestive heart failure by 38% ($P < 0.03$), and all-cause mortality by 17% ($P < 0.05$).¹⁵

Given the highly negative effects of obesity in patients with or without T2DM, it is not surprising that several studies have demonstrated significant benefits of weight loss for improving glycemic control and reducing risk for diabetes complications and mortality. One-year results of the Look AHEAD (Action for Health in Diabetes) trial showed that clinically significant weight loss in patients with T2DM was associated with improved glycemic control and a more favorable CVD risk profile.¹⁶ This study of 5145 individuals with T2DM showed that intensive lifestyle intervention, which produced a mean 8.6% reduction in body weight, was associated with a significant decrease in mean hemoglobin A1c (HbA_{1c}) from 7.3% to 6.6% (-0.64 ± 0.02 ; $P < 0.001$), significant decreases in systolic (-6.8 ± 0.4 ; $P < 0.001$) and diastolic (-3.0 ± 0.2 ; $P < 0.001$) blood pressure and triglycerides (-30.3 ± 2.0 ; $P < 0.001$), and significant increases in HDL-C ($+3.4 \pm 0.2$; $P < 0.001$).¹⁶ Similarly, a 2-year study of weight reduction achieved via weight-loss diets in moderately obese individuals (14% with T2DM) showed that a low-carbohydrate diet resulted in a 20% decrease in the ratio of total cholesterol to HDL-C and a 4.7 ± 6.5 kg decrease in body weight, and that a Mediterranean diet decreased fasting glucose in patients with T2DM by 32.8 mg/dL (1.82 mmol/L) and body weight by 4.4 ± 6.0 kg.¹⁷ Results obtained after

4 years of the ongoing Look AHEAD trial revealed that, among those with T2DM, intensive lifestyle intervention can provide sustained weight loss along with improvements in fitness, glycemic control, and CVD risk factors.¹⁸

Results from a prospective analysis of data from 4970 overweight individuals with diabetes enrolled in the American Cancer Society's Cancer Prevention Study I with a 12-year mortality follow-up indicated that 34% of the study cohort reported intentional weight loss (based on reply to a questionnaire with the following as choices: "unintentional" loss or gain, "intentional" loss or gain, or "no change"). Intentional weight loss was associated with a 25% reduction in total mortality and a 28% reduction in diabetes- and CVD-related mortality.¹⁹ Data from the weight loss arm of the Trials of Hypertension Prevention showed that even modest weight loss (4.4 kg at 6 months, 2.0 kg at 18 months, and 0.2 kg at 36 months) led to clinically significant long-term risk reductions for hypertension 0.58 (95% confidence interval [CI] 0.36–0.94) at 6 months, 0.78 (95% CI 0.62–1.00) at 18 months, and 0.81 (95% CI 0.70–0.95) at 36 months.²⁰

Effective intervention to decrease obesity can also lower the occurrence of diabetes in at-risk individuals. Results from the Malmo study that included 41 subjects with early T2DM and 181 with impaired glucose tolerance (IGT) indicated that an intervention focused on diet and exercise normalized glucose tolerance in >50% of subjects with IGT and reversed T2DM in >50% of those diagnosed with early disease over 6 years of follow-up.²¹ A second small-scale study randomized (4:1) male health-screening examinees with IGT to standard treatment (n = 356) or an intensive intervention group that included detailed instructions on lifestyle that were repeated every 3–4 months during hospital visits. The cumulative 4-year incidence of diabetes was 9.3% in the control group versus 3.0% in the intervention group ($P < 0.001$).²² The Diabetes Prevention Program included 1079 nondiabetic participants, with IGT and a mean baseline BMI of 33.9 kg/m², who were randomized to intensive lifestyle intervention and followed for 3.2 years. Results from this group of patients showed that each 1 kg of weight loss was associated with a 16% reduction in the risk for development of T2DM.²³ Similarly, findings from a Cochrane meta-analysis of eight controlled trials indicated that interventions aimed at increasing exercise combined with diet modification reduced the risk of T2DM compared with standard recommendations in high-risk groups (people with IGT or metabolic syndrome) (RR 0.63; 95% CI 0.49–0.79). This intervention improved systolic (weighted mean difference –4 mmHg; 95% CI –5 to –2) and diastolic (–2 mmHg; 95% CI –3 to –1) blood pressure levels, respectively.²⁴

All of these results support the American Diabetes Association (ADA), North American Association for the Study of Obesity (now known as The Obesity Society), and American Society for Clinical Nutrition guidelines, which indicate that moderate weight loss (5% of body weight) can decrease insulin resistance, decrease fasting blood glucose, and reduce the need for antidiabetes medications.²⁵ ADA guidelines published in 2011 also recommend such weight loss, and note that 7% reduction along with regular physical activity (150 minutes/week) can reduce the risk for developing diabetes.²⁶

Selection of treatment across the spectrum of disease in T2DM

The two major US treatment algorithms for antidiabetes therapy in patients with T2DM differ substantially. The consensus statement from the ADA/European Association for the Study of Diabetes recommends a stepwise approach to treatment, with initial therapy consisting of diet and lifestyle changes plus metformin and subsequent treatment with sulfonylurea or insulin to achieve HbA_{1c} < 7%.²⁷ In contrast, the American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel recommends more aggressive, individualized combination therapy with a wider range of agents (eg, metformin, thiazolidinediones, incretin-based treatments, insulin) as initial pharmacotherapy for patients with T2DM to achieve HbA_{1c} < 6.5%.²⁸ Both guidelines emphasize the importance of diet and lifestyle modification as an essential part of treatment.^{27,28}

Dietary intervention

The emphasis on diet and lifestyle intervention in newly diagnosed patients with T2DM is supported by results from several clinical trials. Results from the Look AHEAD study showed that 1 year of diet and exercise aimed at weight loss improved glucose disposal rate, fasting plasma glucose, free fatty acids, and adipose tissue distribution in a small cohort of 26 men (mean baseline BMI 32.4 kg/m²) and 32 women (mean baseline BMI 34.8 kg/m²) with T2DM. Results from this study also showed that changes in overall weight (adipose tissue mass) and hepatic fat were the most important determinants of metabolic improvements in these patients.²⁹

A meta-analysis of eleven randomized controlled trials that included 402 patients with T1DM or T2DM indicated that although each of those studies had unique criteria for identifying either low or high glycemic indexes, those considered low significantly decreased HbA_{1c} with a weighted mean difference of –0.5% (95% CI –0.9 to –0.1; $P = 0.02$) versus high-glycemic-index diets. Results from this meta-analysis

also showed that a low-glycemic-index diet significantly decreased episodes of hypoglycemia versus a high-glycemic-index diet in one study (difference of -0.8 episodes per patient per month; $P < 0.01$).³⁰

In considering these results, it is important to note that different types of diets have distinct effects on weight loss in patients with T2DM. Diets that might be considered include low fat, high protein/low carbohydrate (ketogenic and nonketogenic), low glycemic-index, and very low calorie regimens. A clinical comparison of low-fat, restricted-calorie; Mediterranean, restricted-calorie; and low-carbohydrate, nonrestricted-calorie diets indicated that all decreased weight (2.9 kg, 4.4 kg, and 4.7 kg, respectively) in moderately obese patients, (mean baseline BMI 31 kg/m²) but that the low-carbohydrate diet had more favorable effects on lipids and the Mediterranean diet had more favorable effects on glycemic control.¹⁷ Both low-glycemic-index and low-carbohydrate ketogenic diets (<20 g carbohydrate/day) have been shown to lower both HbA_{1c} and body weight in patients with T2DM, but the reductions with the ketogenic diet were significantly greater than those with the low-glycemic-index diet (1.5% versus 0.5%; $P = 0.03$ and 11.1 kg versus 6.9 kg; $P = 0.008$).³¹ A low-carbohydrate nonketogenic diet (30% protein, 50% fat, and 20% carbohydrate) has also been shown to be effective for lowering fasting glucose by 40% and HbA_{1c} by 1.7% versus a standard diet in patients with T2DM.³² A very low calorie diet (450 calories/day) has also been shown to be effective in patients with T2DM. Results from one study of 18 patients who followed this diet for 30 days indicated an 11.7 kg reduction in body weight over this period, and improvements in serum lipids, blood pressure, and glycemia that were sustained over 18 months.³³

Conventional oral antidiabetes therapy

Conventional oral antidiabetes agents include metformin, sulfonylureas, meglitinides, alpha-glucosidase inhibitors, and thiazolidinediones (Table 1).^{27,34} One or more of these agents are generally employed, along with dietary and lifestyle intervention, as initial therapy for patients with T2DM, with varying effects on body weight and, potentially, CVD risk.^{13,27,35}

Metformin

The action of metformin is reduction of hepatic glucose output and reduction of fasting blood glucose levels.²⁷ Treatment with metformin results in HbA_{1c} reductions of 1.0%–2.0%.²⁷ Metformin has a favorable profile with respect to body weight and other CVD risk factors. It does not cause weight gain and it improves both the blood lipid profile and fibrinolytic activity.¹³

Table 1 Oral antihyperglycemic medications available in the USA

Class	Medication
Biguanides	• Liquid metformin ^a (Riomet [®])
	• Metformin ^b (Glucophage [®])
	• Metformin extended-release ^b (Glucophage XR [®] , Fortamet [®] , Glumetza [®])
Thiazolidinediones	• Pioglitazone (Actos [®])
	• Rosiglitazone (Avandia [®]) ^c
Alpha-glucosidase inhibitors	• Acarbose (Precose [®])
Insulin secretagogues	• Miglitol (Glyset [®])
	• Sulfonylureas
	– Glimepiride ^b (Amaryl [®])
	– Glipizide ^b (Glucotrol [®])
	– Glipizide extended-release (Glucotrol XL [®])
	– Glyburide ^b (Micronase [®] , Diabeta [®])
	– Micronized glyburide (Glynase [®])
	• Nonsulfonylurea meglitinides
	– Repaglinide (Prandin [®])
	• D-phenylalanine derivatives
– Nateglinide (Starlix [®])	
DPP-4 inhibitors	• Sitagliptin (Januvia [®])
	• Saxagliptin (Onglyza [™])
Bile acid sequestrant	• Colesevelam (Welchol [®])
Fixed combinations	• Metformin and glipizide (Metaglip [®])
	• Metformin and glyburide (Glucoavance [®])
	• Metformin and pioglitazone (ACTOplus met [®])
	• Pioglitazone and glimepiride (Duetact [®])
	• Rosiglitazone and glimepiride (Avandaryl [®]) ^c
	• Rosiglitazone and metformin (Avandamet [®]) ^c
	• Sitagliptin and metformin (Janumet [®])
	• Repaglinide and metformin (PrandiMet [®])

Notes: ^aLiquid formulation for patients unable to swallow pills; ^bAvailable as a generic medication; ^cOn September 23, 2010, the Food and Drug Administration (FDA) announced regulatory actions with respect to products containing rosiglitazone. The FDA is requiring GlaxoSmithKline (GSK) to implement restrictions on the use of these products through a program to assure their safe use and additional safety labeling changes in response to the agency's review of data that suggest an elevated risk of cardiovascular events. Adapted with permission from *Joslin Clinical Guideline for Pharmacological Management of Type 2 Diabetes*, copyright © 2009 (updated 11/2010) by Joslin Diabetes Center (www.joslin.org). All rights reserved.³⁴

Abbreviation: DPP-4, dipeptidyl peptidase-IV.

Results from one study indicated that 1 year of treatment with metformin decreased triglycerides from baseline by 26.6 mg/dL (0.3 mmol/L) and low-density lipoprotein cholesterol [LDL-C] by 4.6 mg/dL (0.12 mmol/L), and increased HDL-C by 3.1 mg/dL (0.08 mmol/L).³⁶ Weight loss in patients with T2DM taking metformin is associated with reductions in both total body fat and visceral fat in those with abdominal or visceral obesity.³⁷ Results from one study in which patients were treated with metformin (1000 mg/day) for 26 weeks indicated that mean body weight decreased by 2.0 kg ($P < 0.05$ versus placebo), abdominal subcutaneous fat decreased by 0.4 kg, and intraabdominal fat decreased by 0.3 kg (both $P < 0.05$ versus baseline).³⁸ Metformin is associated with gastrointestinal side effects and is contraindicated in patients with renal insufficiency.²⁷

Sulfonylureas

Sulfonylureas lower glycemia by enhancing insulin secretion and their use can lower HbA_{1c} by 1.0%–2.0%.²⁷ Despite the fact that sulfonylureas are still recommended for the treatment of T2DM, the use of these agents is being called into question. Results from a study of 9876 patients with T2DM who were treated with oral glucose-lowering drugs after a myocardial infarction indicated that the risk for cardiovascular mortality was significantly increased (hazard ratio [HR] 1.28; 95% CI 1.14–1.44) versus those who received metformin.³⁹ Results from a second retrospective cohort that included 34,253 patients treated with a sulfonylurea, metformin, rosiglitazone, or pioglitazone in a single academic health care network indicated that the RR for myocardial infarction for those receiving a sulfonylurea was 2.2 (95% CI 1.6–3.1) compared with metformin.⁴⁰ Results from a cohort of 205 adult men with T2DM who were followed for a mean of 9.4 years indicated that those treated with a sulfonylureas alone experienced a mean weight gain of 0.42 kg/year,⁴¹ and it is reasonable to suggest that increased cardiovascular risk with sulfonylureas may be related to the weight gain in patients treated with these drugs. Sulfonylureas are also associated with potentially severe hypoglycemic events.²⁷

Meglitinides

Like sulfonylureas, meglitinides bind to sulfonylurea receptors on pancreatic β -cells (although at a different receptor site) to stimulate insulin secretion. These drugs have shorter half-lives than sulfonylureas and must be administered more often, but they do result in HbA_{1c} reductions of 0.5%–1.5%.²⁷ Meglitinides are also associated with significant weight gain (2.4 kg over 3 months; $P < 0.05$) versus metformin when used for the treatment of patients with T2DM;⁴² results from a meta-analysis of 15 clinical trial results for this class indicated that weight gains as high as 3 kg may occur over 3 months.⁴³ Meglitinides have also been associated with hypoglycemia, but with a frequency lower than that for sulfonylureas.²⁷

Alpha-glucosidase inhibitors

Alpha-glucosidase inhibitors slow digestion of polysaccharides in the proximal small intestine. This results in lowering of HbA_{1c} by 0.5%–0.8% and decreased postprandial glucose levels with low risk for hypoglycemia.²⁷ The alpha-glucosidase inhibitor acarbose decreased HbA_{1c} by 0.8% (95% CI –0.9 to –0.7), according to a meta-analysis of 30 acarbose trials, and was not associated with weight gain in patients with T2DM.⁴⁴ It has been shown to decrease the risks for progression to diabetes and CVD events in patients

with IGT who were treated for a mean of 3.3 years in the Study to Prevent Non-Insulin Dependent DM trial. Results from this study indicated that acarbose treatment resulted in a 25% RR reduction in the development of T2DM (95% CI 0.63–0.90; $P = 0.0015$), and a 49% decrease in risk for CVD events (95% CI 0.28–0.95; $P = 0.03$).⁴⁵ Miglitol, which is the other alpha-glucosidase inhibitor, has been shown to provide similar reductions in HbA_{1c} but is associated with abdominal discomfort.^{46,47} The hypoglycemic potency of alpha-glucosidase inhibitors is less than that of either biguanides or sulfonylureas.¹³ Unfortunately, those treatments are associated with gastrointestinal side effects that have resulted in limited use within the US.

Thiazolidinediones

Thiazolidinediones are modulators of peroxisome proliferator-activated receptor γ modulators that increase the insulin sensitivity of muscle, fat, and liver.²⁷ These drugs lower plasma glucose by enhancing its uptake into tissues and decrease HbA_{1c} by 0.5%–1.4%.²⁷ In adipose tissue, thiazolidinediones act as insulin sensitizers and are potent inhibitors of lipolysis, and they enable mobilization of fat from muscle and liver tissues as well as β -cells. These actions result in amelioration of lipotoxicity and improve insulin sensitivity by reducing insulin secretion, which helps to preserve β -cell function and therefore maintain glycemic control over time.⁴⁸ Thiazolidinediones are associated with weight gain and edema as well as increased risk for congestive heart failure.²⁷ Results from a meta-analysis of four randomized trials that included 14,291 patients (6421 receiving rosiglitazone, 7870 receiving control therapy) with follow-up of 1–4 years indicated that rosiglitazone significantly increased the risk of myocardial infarction (RR 1.42; $P = 0.02$) and heart failure (RR 2.09; $P < 0.001$), but not CVD mortality (RR 0.90; $P = 0.53$).⁴⁹ A recent study that directly compared risks for acute myocardial infarction, acute heart failure, or all-cause mortality among patients ≥ 18 years of age who started treatment with rosiglitazone ($n = 6421$) or pioglitazone ($n = 7870$) between January 1, 2001, and December 12, 2005 indicated that 4.16% of the patients treated with rosiglitazone experienced acute myocardial infarction, acute heart failure, or death versus 4.14% of those treated with pioglitazone (HR 1.03; 95% CI 0.91–1.15; $P = 0.666$) over a median follow-up period of 34 months.⁵⁰ In considering these results, it is worth noting that the 10-year risk for coronary heart disease in patients with T2DM is about 13%.⁵¹ It has also been shown that thiazolidinediones cause bone loss and increase fracture risk in patients with T2DM.⁵² Recent results

have also indicated that long-term treatment with pioglitazone may be associated with increased risk for bladder cancer. A study that included 193,099 patients in the Kaiser Permanente Northern California diabetes registry indicated that any use of pioglitazone was not associated with elevated risk of bladder cancer ($P = 0.8$). However, there was an increased risk (HR 1.4; 95% CI 1.03–2.0) in patients who used pioglitazone for >24 months.⁵³

Incretin-based treatments

Incretins – glucagon-like peptide (GLP)-1 receptor agonists and dipeptidyl peptidase (DPP)-4 inhibitors (Tables 1 and 2)^{27,34,54} – have become increasingly accepted as treatments for patients with T2DM, and their effects on body weight differ from those of conventional oral therapies.⁵⁵ Several mechanisms contribute to the glucose-lowering effects of GLP-1 receptor agonists. These include glucose-dependent stimulation of insulin secretion, reduction of plasma glucagon concentrations, and delay of gastric emptying. These agents lower HbA_{1c} by 0.5%–1.0%.²⁷ The weight loss associated with these agents is believed to result from delayed gastric emptying which maintains a feeling of fullness, thus reducing appetite and food intake as well as the signaling of satiety via direct stimulation of parts of the brain involved in regulation of appetite.⁵⁶ Meta-analyses of results from 21 randomized controlled trials revealed that patients who received GLP-1 receptor agonists ($n = 5429$) had significant reductions in BMI compared to those treated with placebo (difference -0.44 kg/m²; $P = 0.012$) and those who received insulin (difference -1.57 kg/m²; $P < 0.001$).⁵⁷ Meta-analyses of results from eight trials in which GLP-1 receptor agonists were compared with oral antidiabetes agents indicated significantly greater weight loss with the incretin mimetics versus comparators (weighted mean difference -2.37 kg; 95% CI -3.95 to -0.78).⁵⁸ Direct comparison of the two currently approved GLP-1 receptor agonists indicated that liraglutide and exenatide were associated with similar weight reductions (3.24 kg versus 2.87 kg, respectively; $P = 0.2235$). However, liraglutide decreased mean HbA_{1c} to a greater extent than exenatide (1.12% versus 0.79%; $P < 0.0001$).⁵⁹ Analysis of results from studies of liraglutide have shown that the reduction in body weight in patients treated with this agent results primarily from decreases in both subcutaneous and visceral adipose tissue.⁶⁰ The most common adverse events associated with GLP-1 receptor agonists are gastrointestinal events. Long-term treatment of rodents with liraglutide was found to cause thyroid C-cell hyperplasia,⁶¹ but clinical results have not indicated any increased risk for medullary thyroid

cancer.⁵⁴ It has been reported that eight cases of acute pancreatitis occurred during clinical development of exenatide and there were 36 postmarketing reports of acute pancreatitis in exenatide-treated patients. Four patients developed acute or chronic pancreatitis during liraglutide clinical trials.⁶²

Systematic reviews of clinical results for DPP-4 inhibitors indicated that these agents lower HbA_{1c} by 0.5%–0.8% and are generally weight-neutral.^{27,63,64} Since these drugs act via increasing the duration of action of GLP-1, they have low risk for hypoglycemia. DPP-4 inhibitors are available as fixed-dose combinations with metformin. It has been suggested that DPP-4 inhibitors have the potential to interfere with immune function and have been associated with increased risk for upper respiratory infections.²⁷ Evaluation of clinical trial results for sitagliptin has also shown that it is not associated with an increase in risk for cardiovascular events.⁶⁵ A trial designed to compare the efficacy of liraglutide and sitagliptin published in 2010 reported more substantial reductions in HbA_{1c} among patients who received 1.8 mg liraglutide (-1.50% ; 95% CI -1.63 to -1.37) and 1.2 mg liraglutide (-1.24% ; 95% CI -1.37 to -1.11 ; $n = 221$) than those treated with sitagliptin (-0.90% ; 95% CI -1.03 to -0.77 ; $n = 219$).⁶⁶

Pramlintide

Pramlintide, an amylinomimetic, is approved for treatment of elevated postprandial glucose levels in T1DM and T2DM.⁶⁷ Combined analysis of four studies of pramlintide in patients with T2DM indicated that it significantly reduced HbA_{1c} by 0.33% (95% CI 0.14–0.51; $P = 0.004$) and weight by 2.57 kg (95% CI 1.70–3.44; $P < 0.00001$) versus controls.⁶⁸ The adverse events observed most often with pramlintide are nausea and hypoglycemia.⁶⁹

Novel therapy

A new class of glucose-lowering agents that are of particular interest because of their favorable effects on body weight are sodium-glucose co-transporter 2 inhibitors. These agents decrease the reabsorption of glucose and thus increase renal glucose excretion.⁷⁰ Results from a clinical study of dapagliflozin 2.5 mg, 5 mg, or 10 mg versus placebo indicated HbA_{1c} reductions of 0.58%, 0.63%, and 0.82% versus 0.13%, respectively. Reductions in body weight were 1.18 kg, 1.56 kg, and 2.26 kg versus 0.72 kg, respectively.⁷¹ Treatment with sodium-glucose co-transporter 2 inhibitors has been shown to be associated with increased risk for urinary tract and genital infections.⁷¹ Concern about the safety of dapagliflozin has been raised by results indicating that nine of 5478

patients taking dapagliflozin in clinical trials had bladder cancer, compared with one of 3156 patients in the placebo group. In addition, nine of 2223 women taking dapagliflozin had breast cancer, compared with one of 1053 women in the placebo group.^{72,73}

Insulin treatment

A very large percentage of patients with T2DM ultimately require insulin therapy (see Table 2 for examples)³⁴ to maintain control over blood glucose.^{48,74} Insulin remains the most potent medication currently available to achieve tight control over plasma glucose and avoid or delay long-term disease complications among nonhospitalized patients. However, insulin treatment is commonly associated with weight gain,⁷⁵ which varies substantially with the type of insulin employed for treatment (see below). This may be due in part to improved glycemic control resulting in decreased glycosuria, resulting in more glucose absorption and therefore more calories retained. Defensive snacking behaviors, driven by fears of hypoglycemia, can also contribute to weight gain in patients using insulin.⁷⁴ Insulin also has anabolic effects, and this is reflected by the fact that patients with diabetes gain lean as well as fat mass. Results from two studies indicated that 30%–37% of the weight gain associated with insulin treatment was lean mass.^{76,77}

Treatment with an older and commonly used insulin preparation, neutral protamine Hagedorn (NPH) insulin, has been consistently associated with weight gain. Results from one study of insulin therapy in patients with T2DM indicated that patients gained 3.8 kg over 6 months of treatment and most of this gain was fat mass.⁷⁸ This complication of treatment with NPH is significantly decreased with insulin analogs. Meta-analysis of clinical trial results (Figure 2)⁷⁹ indicated that the long-acting insulin analog detemir was associated with less weight gain than NPH insulin in patients with diabetes, although the insulin analog glargine was not (standardized mean difference detemir versus glargine -0.37 kg; $P = 0.048$).⁷⁹ Another meta-analysis of trials found more weight gain with glargine than NPH (pooled mean change -0.33 kg; 95% CI -0.61 to -0.06).⁸⁰

Results from several large-scale clinical trials demonstrated the significantly superior effects of insulin detemir on weight gain versus NPH insulin and insulin glargine. Results from a 24-week study in which either insulin detemir or NPH insulin was added to oral antidiabetes therapy in 476 patients with T2DM indicated a 1.2 kg weight gain with insulin detemir versus 2.8 kg with NPH insulin ($P < 0.001$).⁸¹ Results from a 26-week, randomized, controlled trial that included

271 patients with T2DM who received either insulin detemir or NPH insulin once daily in the evening along with mealtime insulin aspart substituted for two daily doses of insulin (at least one had to be a premix) indicated that weight had increased significantly less with detemir (0.4 kg) than with NPH (1.9 kg) ($P < 0.0001$) at the end of the study.⁸² Another 26-week trial compared insulin detemir and NPH insulin in 505 patients with T2DM who also received insulin aspart at mealtimes. After 26 weeks of treatment, patients receiving insulin detemir gained significantly less weight (1.0 kg) than those who were administered NPH insulin (1.8 kg) ($P = 0.017$).⁸³ A 26-week comparison of insulins detemir and glargine in 385 patients with T2DM who also received mealtime insulin aspart in a basal-bolus regimen showed that there was further significantly less weight gain with insulin detemir (1.2 kg) versus insulin glargine (2.7 kg) ($P = 0.001$).⁸⁴ The reason for decreased weight gain in patients treated with long-acting insulin detemir has not been elucidated, but results from several studies have suggested possible explanations. It may be that acylation and albumin binding used to extend the duration of action for insulin detemir results in a greater influence on hepatocytes than peripheral tissues. This might reduce glucose output from the liver without promoting peripheral lipogenesis.⁸⁵ An effect of insulin detemir in the central nervous system may also contribute to its decreased risk for weight gain versus NPH insulin and insulin glargine. A study in 15 healthy volunteers showed that a bolus injection of insulin detemir during hyperinsulinemic-euglycemic clamp produced a change in the electroencephalogram not observed after injection of regular human insulin. Results from this study also showed that insulin detemir significantly decreased subsequent food intake by 303 kcal versus regular human insulin ($P < 0.04$).⁸⁶

The pharmacokinetic/pharmacodynamic profile for insulin detemir may also contribute to the favorable effects of this agent on body weight. Insulin detemir has a flatter time-action profile versus NPH insulin, providing more consistent plasma levels.⁸⁷ The pharmacokinetic and pharmacodynamic within-subject variation is lower for insulin detemir versus glargine,⁸⁸ and this may also contribute to lower weight gain during treatment.

Adjunctive therapies for management of body weight in patients with T2DM

Pharmacotherapy

The close association between obesity and T2DM suggests that a more proactive approach to weight management in

Table 2 Injectable diabetes medications available in the USA: (A) insulins and (B) incretin mimetics and noninsulin synthetic analogs

A) Insulin type	Product	Onset ^a	Peak ^a	Duration ^a
Rapid acting				
Insulin aspart analog	NovoLog [®]	10–30 min	30 min–3 h	3–5 h
Insulin glulisine analog	Apidra [®]	10–30 min	30 min–3 h	3–5 h
Insulin lispro analog	Humalog [®]	10–30 min	30 min–3 h	3–5 h
Short acting				
Human regular insulin	• Humulin R [®] • Novolin R [®]	30–60 min	2–5 h	Up to 12 h ^b
Intermediate acting				
Human NPH insulin	• Humulin N [®] • Novolin N [®]	90 min–4 h	4–12 h	Up to 24 h ^c
Long acting				
Insulin detemir	Levemir [®]	45 min–4 h	Minimal peak	Up to 24 h ^d
Insulin glargine	Lantus [®]	45 min–4 h	Minimal peak	Up to 24 h ^d
Premixed insulin combinations				
50% NPH; 50% regular	Humulin 50/50 [®]			
70% NPH; 30% regular	Humulin 70/30 [®]			
70% NPH; 30% regular	Novolin 70/30 [®]			
50% lispro protamine suspension, 50% lispro	Humalog Mix 50/50 [®]			
50% aspart protamine suspension, 50% aspart	Novolog Mix 50/50 [®]			
75% lispro protamine suspension, 25% lispro	Humalog Mix 75/25 [®]			
70% aspart protamine suspension, 30% aspart	NovoLog Mix 70/30 [®]			
B) Incretin mimetics and noninsulin synthetic analogs	Mechanism of action	Type of diabetes	# of injections/day	
Exenatide (Byetta [®])	Incretin mimetic that enhances glucose-dependent insulin secretion and several other antihyperglycemic actions of incretins.	2	2	
Liraglutide (Victoza [®])	A GLP-1 receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control.	2	1 (independent of meals)	
Pramlintide (Symlin [®])	Synthetic analog of human amylin, a naturally occurring hormone made in the β -cells, which slows gastric emptying, suppresses glucagon secretion, and regulates food intake. A significant reduction in insulin dose may be required when insulin is used in conjunction with pramlintide.	1 and 2	1–4 (with meals)	

Notes: ^aThe onset, peak, and duration of any insulin type depends on many factors. Patients may experience variations in timing and/or intensity of insulin activity due to dose, site of injection, temperature of the insulin, level of physical activity, in addition to other factors; ^bUsual clinical relevance can be less than 12 hours; ^cUsual clinical relevance can be less than 24 hours. Often requires twice-daily dosing. ^dIndividual response may require twice-daily dosing. Adapted with permission from *Joslin Clinical Guideline for Pharmacological Management of Type 2 Diabetes*, copyright © 2009 (updated 11/2010) by Joslin Diabetes Center (www.joslin.org). All rights reserved.³⁴

Abbreviations: GLP-1, glucagon-like peptide-1; h, hours; min, minutes; NPH, neutral protamine Hagedorn; #, number.

obese individuals without diabetes may have the potential to delay or possibly prevent the onset of T2DM. In patients who already have diabetes, better control of weight has the potential to decrease glucose levels. However, development of pharmacologic agents to manage obesity has been difficult, with many being denied approval and only a few currently in the pipeline (Table 3).⁸⁹

Orlistat blocks absorption of ingested fat by inhibiting pancreatic lipase and it is approved for use in adults and

children ≥ 12 years of age for up to 1 year.⁹⁰ Meta-analysis of results from 29 controlled clinical trials of orlistat has indicated that it produces a mean 2.75 kg weight loss over 52 weeks of treatment.⁹¹ Systematic review of 28 clinical trials for orlistat has also shown that it has significant benefit in improving the lipid profile in patients with diabetes, with significant ($P < 0.05$) reductions versus placebo in total cholesterol (weighted mean difference -0.37 mmol/L) and LDL-C (-0.27 mmol/L).⁹² Results from a 4-year prospective study that

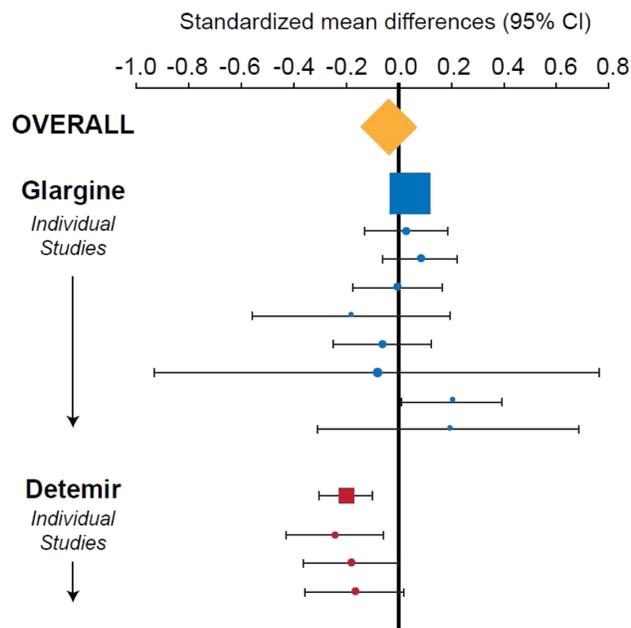


Figure 2 Differences (with 95% confidence intervals [CI]) between long-acting analogs and neutral protamine Hagedorn insulin in the effects on body mass index at endpoint in clinical trials of patients with type 1 or type 2 diabetes mellitus.

Notes: Used with permission from *Diabetes Research and Clinical Practice*, Vol 81, Pages 184–189, M Monami, N Marchionni, E Mannucci. Long-acting insulin analogues versus NPH human insulin in type 2 diabetes: a meta-analysis. © Copyright Elsevier 2008.⁷⁹

included 3305 patients (BMI ≥ 30 kg/m² and normal [79%] or IGT [21%]) indicated that the cumulative incidence of diabetes was 6.2% for orlistat and 9.0% with placebo (37.3% risk reduction; $P = 0.0032$).⁹³ Cetilistat is a novel inhibitor of gastrointestinal and pancreatic lipases that has proceeded to Phase III development. A 14-week (12 weeks of active treatment) study included 612 overweight or obese patients (mean baseline BMI 34.3 kg/m²) with T2DM who were randomized to cetilistat (40 mg, 80 mg, or 120 mg three times daily), or orlistat (120 mg three times daily). Study results indicated similar reductions in body weight of 3.78–4.32 kg for patients treated with 80 mg or 120 mg cetilistat or 120 mg orlistat (all $P \leq 0.01$ versus baseline).⁹⁴

Other agents currently approved for treatment of obesity (each for up to 12 weeks in adults) include phentermine, diethylpropion, and phendimetrazine.⁹⁰ Meta-analysis of results from nine clinical trials with phentermine indicated that it decreased mean body weight by 3.6 kg over 2–24 weeks of treatment,⁹¹ but it has not been specifically evaluated in patients with T2DM in a large-scale controlled clinical trial. Meta-analysis of results from 13 clinical trials of diethylpropion indicate a mean weight reduction of 3.0 kg among obese individuals in studies of 6–52 weeks duration.⁹¹ Phendimetrazine has been shown to result in weight loss of 2.5–5.5 kg over an unspecified period in overweight patients.⁹⁵

While other agents or combinations have been developed for the treatment of obesity, none are currently approved by the Food and Drug Administration (FDA). Sibutramine acts principally by blocking synaptic reuptake of serotonin and noradrenaline;⁹⁶ meta-analysis of results from eight controlled clinical trials of sibutramine in patients with T2DM indicated that decreases in body weight and waist circumference were significantly greater with this agent versus placebo, but sibutramine had minimal effects on glycemic control or lipids. This agent was recently withdrawn from the market in the US due to increased risk for myocardial infarction and stroke,⁹⁷ as reported in the Sibutramine Cardiovascular Outcome Trial.^{98,99} Abbott Laboratories (Abbott Park, IL), the manufacturer of sibutramine, also withdrew sibutramine from other countries and has suspended all activities related to it.¹⁰⁰

Lorcaserin is a selective serotonin receptor agonist that was also developed for the treatment of obesity.¹⁰⁰ The efficacy of lorcaserin was evaluated in a double-blind study in which 3182 obese or overweight adults (mean baseline BMI 36.2 kg/m²) received 10 mg lorcaserin twice daily or placebo for 52 weeks. At week 52, patients in the placebo group continued on this treatment, but patients in the lorcaserin group were randomly reassigned to receive either placebo or lorcaserin. At the end of the first 52 weeks, 47.5% of patients in the lorcaserin group and 20.3% in the placebo group had lost $\geq 5\%$ of their body weight ($P < 0.001$). Among patients who received lorcaserin during year 1 and lost $\geq 5\%$ of their baseline weight, the loss was maintained by 67.9% of those who continued on lorcaserin during year 2 versus 50.3% of those rerandomized to placebo.¹⁰¹ However, administration of lorcaserin was associated with the development of neoplasms in rats and an FDA advisory panel recommended against its approval. The FDA accepted this recommendation and requested more information addressing this issue.¹⁰⁰

Tesofensine is a noradrenaline, dopamine, and serotonin reuptake inhibitor and it has been evaluated for treatment of obesity in a Phase II, randomized, double-blind, placebo-controlled trial that included 203 obese patients with mean baseline BMI of 30 to ≤ 40 kg/m² who were prescribed tesofensine 0.25 mg, 0.5 mg, or 1.0 mg/day or placebo plus an energy-restricted diet for 24 weeks. After 24 weeks, diet and placebo resulted in a 2.0% weight loss versus 4.5%, 9.2%, and 10.6%, respectively for 0.25 mg, 0.5 mg, and 1.0 mg/day tesofensine ($P < 0.0001$).¹⁰² Further development of this agent has been halted while the manufacturer, NeuroSearch (Ballerup, Denmark), seeks a partner to continue commercialization.¹⁰³ Development of another agent that demonstrated efficacy in Phase II trials, velneperit (S-2367), a selective

Table 3 Pharmacotherapy for obesity in the USA

Drug	Mechanism of action	Cardiovascular effects	Weight loss*	Status
Fenfluramine/phentermine resin	5HT-releasing agent and reuptake inhibitor/norepinephrine-releasing agent	Cardiac valvulopathy and pulmonary hypertension	11.0% (34 weeks)	Fenfluramine withdrawn in 1997; phentermine still available
Fenfluramine, dexfenfluramine	5HT-releasing agent and reuptake inhibitors	Cardiac valvulopathy and pulmonary hypertension	3.0%	Both withdrawn in 1997
Sibutramine	Norepinephrine/serotonin reuptake inhibitor; induces satiety/increases energy expenditure	BP and pulse elevations, MI, and stroke risk	3.7%–5.0%	Withdrawn in 2010
Phentermine resin, diethylpropion	Norepinephrine releasing agents	BP and pulse elevations	8.1% (36 weeks)	Approved in 1960s for short-term use
Mazindol	Norepinephrine reuptake inhibitor	BP and pulse elevations	2%–10% (12 weeks)	Discontinued in 1999
Phenylpropanolamine	A ₁ adrenergic agonist	Increased risk of hemorrhagic stroke	0%–2.0% (12 weeks)	Withdrawn from OTC market in 2000
Orlistat	Pancreatic and gastric lipase inhibitor	None known	2.9%–3.4%	FDA approved in 1999 for long-term use
Rimonabant	Endocannabinoid receptor type I blocker	NA	5.0%	Not approved 2007, psychiatric side effects cited
Topiramate/phentermine	GABA receptor modulation	BP and pulse elevations	8.6%	Not approved in 2010, cardiovascular effects and teratogenicity cited
Bupropion/naltrexone	Dopamine, norepinephrine reuptake inhibitor/opioid antagonists	BP elevation	4.8%	Not approved in 2010, FDA requesting preapproval long-term cardiovascular study
Lorcaserin	5HT _{2c} receptor agonist	Possible valvulopathy	3.6%	Not approved in 2010, breast tumors in animals cited
Bupropion/zonisamide	Dopamine norepinephrine reuptake inhibitor/sodium channel modulator	BP elevation	6.1%	Phase IIB/III
Pramlintide/metreleptin	Incretin and adipose tissue hormone with satiety signal in hypothalamus	NA	9.2% (28 weeks)	Phase IIB
Liraglutide	GLP-I agonist	NA	4.5% (20 weeks)	Phase IIB/III

Notes: *Mean weight loss in excess of placebo as percentage initial body weight across 1 year, unless otherwise specified. Used with permission from Apovian and Gokce.⁸⁹
Abbreviations: BP, blood pressure; MI, myocardial infarction; OTC, over the counter; GLP-I, glucagon-like peptide-I; FDA, Food and Drug Administration; NA, not available; GABA, gamma-aminobutyric acid; 5HT, 5-hydroxytryptamine.

neuropeptide YY5-receptor antagonist, has been discontinued due to anticipated difficulties in gaining approval in the US and European Union.^{104,105}

The combinations of bupropion plus naltrexone, bupropion plus zonisamide, and topiramate plus phentermine have all been assessed for treatment of obesity, but none have been approved by the FDA. The combination of bupropion, which is approved for depression and smoking cessation, and naltrexone, an opioid receptor antagonist approved for opioid and alcohol addiction, was assessed for the treatment of obesity.¹⁰⁶ When added to diet and exercise this combination has been shown to result in a loss of 9.3% of body weight (versus 5.1% among patients who received placebo, diet, and exercise; $P < 0.001$) over 56 weeks among obese patients.¹⁰⁷

In February 2011, however, the FDA issued a letter noting concern about the cardiovascular safety profile of naltrexone/bupropion when used long-term in a population of overweight and obese subjects, and requested a preapproval safety study.¹⁰⁸ The combination of bupropion with the antiepileptic drug zonisamide has demonstrated efficacy for decreasing body weight in Phase II trials, but it has not yet progressed to Phase III studies.¹⁰⁹ Phentermine has been studied in combination with low-dose topiramate, an antiepileptic agent that is also used as a preventive treatment for migraines. Clinical trials with the phentermine/topiramate combination have demonstrated up to an 11% decrease in body weight when administered to obese patients.¹¹⁰ In October 2010, however, the FDA rejected the combination and required

the manufacturer, VIVUS, Inc, (Mountain View, CA) to provide more evidence regarding the elevation of heart rate associated with phentermine, including the likelihood that it increases the risk for major adverse cardiovascular events, as well as mandating a comprehensive assessment of the product's potential to cause birth defects associated with topiramate.¹¹¹ A study published in 2008 reported that although the number of adverse outcomes was low among pregnant individuals exposed to topiramate, the overall rate of oral clefts in newborns was eleven times the background rate, raising concerns about congenital malformation among those receiving topiramate polytherapy.¹¹² In March 2011, the FDA informed the public that new data revealed an increased risk for development of cleft lip and/or cleft palate (oral clefts) among infants born to women who were treated with topiramate.¹¹³

Neurohormonal approaches have demonstrated efficacy in the treatment of obesity and may have less risk for significant toxicity than agents aimed primarily at the central nervous system. Leptin is a neurohormone secreted by adipocytes, and leptin-deficient humans exhibit severe hyperphagia and profound obesity. Amylin is another peptide hormone that is secreted with insulin from pancreatic β -cells and the amylin analog pramlintide increases satiation and reduces food intake.¹¹⁴ The combination of pramlintide and metreleptin is being developed as a treatment for obesity. A 24-week, randomized, double-blind trial included 177 obese or overweight subjects (mean baseline BMI 32.0 kg/m²) who received pramlintide (180 μ g twice daily for 2 weeks, and 360 μ g twice daily thereafter) and diet (40% calorie deficit) for 4 weeks. Those who achieved 2%–8% weight loss over 4 weeks were randomized to 20 weeks of treatment with metreleptin (5 mg twice daily), pramlintide (360 μ g twice daily), or combination of the two agents at the stated doses. Weight reductions with the three treatments were –8.2%, –8.4%, and –12.7%, respectively. Combination treatment was significantly more effective than either metreleptin ($P < 0.01$) or pramlintide ($P < 0.001$) monotherapy.¹¹⁴

The beneficial effects of liraglutide on body weight (see incretin-based treatments section) have prompted its development for the treatment of obesity. A double-blind, placebo-controlled 20-week trial included 564 obese individuals (mean baseline BMI 30–40 kg/m²) who were randomized to liraglutide doses of 1.2 mg, 1.8 mg, 2.4 mg, or 3.0 mg/day, placebo, or orlistat (120 mg/day). All subjects also had an energy-deficit diet and increased their physical activity. Mean weight losses with liraglutide 1.2 mg, 1.8 mg, 2.4 mg, and 3.0 mg were 4.8 kg, 5.5 kg, 6.3 kg, and 7.2 kg,

respectively compared to 2.8 kg with placebo and 4.1 kg with orlistat.¹¹⁵

Bariatric surgery

Four types of bariatric surgery are used most often in the US. These include adjustable gastric band, Roux-en-Y gastric bypass (RYGB), biliopancreatic diversion with a duodenal switch, and vertical sleeve gastrectomy (Figure 3).¹¹⁶ The adjustable gastric band limits food intake by placing a small band around the top of the stomach to produce a small pouch. The outlet size is controlled by a circular balloon inside the band that can be inflated or deflated with saline solution. The RYGB restricts food intake and also reduces absorption. Food intake is limited by a small pouch and absorption of food is reduced by routing food directly from the pouch into the small intestine and thus bypassing most of the stomach, duodenum, and upper intestine. The biliopancreatic diversion with a duodenal switch removes a large portion of the stomach to promote smaller meal sizes and decreases absorption by rerouting food away from much of the small intestine and by rerouting bile and other digestive juices. The vertical sleeve gastrectomy involves removing a large portion of the stomach to create a gastric sleeve that remains connected to a very short segment of the duodenum, which is then directly connected to a lower part of the small intestine. This operation makes the distance between the stomach and colon much shorter after this operation, thus promoting malabsorption.¹¹⁶

Eight clinical trials of patients who have undergone gastric bypass surgery have shown that this intervention is associated with a 99% to 100% prevention of diabetes in individuals with IGT and an 80% to 90% clinical resolution of diagnosed T2DM.¹¹⁷ A systematic review and meta-analysis summarizing 136 studies published in English between 1990 and 2003 that included >22,000 patients who underwent bariatric surgery (73% women; mean BMI 47 kg/m²) indicated complete resolution of T2DM (defined as discontinuation of all diabetes-related medications and blood glucose levels within the normal range) in 77% of cases. An average weight loss of 41 kg (approximately 65% of the excess weight) was recorded among patients with resolution of diabetes.¹¹⁸ The effectiveness of bariatric surgery in decreasing body weight and returning patients to euglycemia and normal insulin levels has prompted the suggestion that the small bowel may play a key role in the pathophysiology of T2DM.¹¹⁹

The ADA 2011 Standards of Medical Care in Diabetes support gastric reduction surgery, stating that it can be effective for inducing weight loss among individuals with severe obesity.²⁶

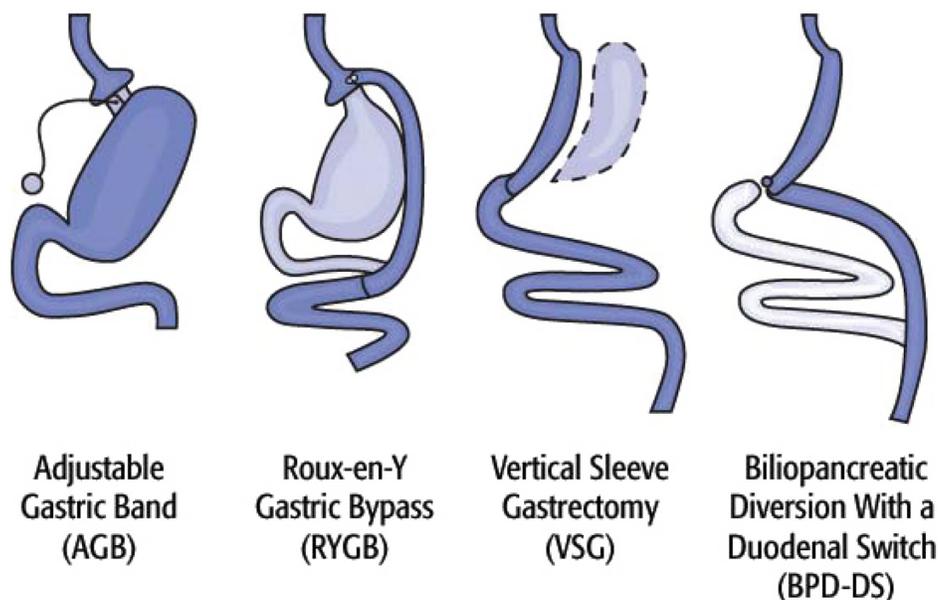


Figure 3 Commonly used bariatric surgery procedures.

Notes: From Weight Control Information Network and National Institute of Diabetes and Digestive and Kidney Diseases.¹¹⁶ Image used with permission from Walter Pories, MD, FACS. ©Copyright University of North Carolina.

A Diabetes Surgery Summit Position Statement likewise recognizes the legitimacy of surgical procedures such as gastric bypass for treatment of diabetes among certain patients, and notes that clinical trials aimed at determining the role of surgery for those with less severe obesity and diabetes should be a priority.¹²⁰

Several new devices have been developed (and adapted) to facilitate the endoluminal approach to bariatric procedures. An endoluminal bariatric sleeve that is open at both ends and is intended to mimic the duodenal and proximal jejunal bypass impact of an RYGB produced an average weight loss of 23.6% in a group of 10 patients followed for 12 weeks.¹²¹ In December 2010 the FDA approved a gastric band (LAP-BAND® Adjustable Gastric Banding System; BioEnterics Corporation, Carpinteria, CA; initially approved in 2001) for weight reduction in obese patients with a BMI ≥ 35 kg/m² and in those with BMI > 30 kg/m² who have one or more comorbid conditions, finding that benefits of such procedures outweigh the risks.¹²² The effectiveness of the LAP-BAND® in patients with T2DM is supported by results from 413 patients who were followed for ≥ 1 year postsurgery. Resolution of diabetes was observed in 66% at 1-year and 80% at 2-year follow-up. The mean HbA_{1c} value declined from 7.25% preoperatively to 5.58% at 2 years after surgery. The reduction in excess weight was 39.2% at 1 year and 52.6% at 2 years.¹²³

Results from the Swedish Obese Subjects study of 4047 obese patients has provided insight into the long-term effects

of bariatric surgery. Ten-year follow-up of these patients showed weight losses from baseline of 25%, 16%, and 14%, respectively for patients treated with gastric bypass, vertical-banded gastroplasty (stapling), and banding. Study results also indicated significantly decreased mortality risk for patients who underwent surgery versus controls (HR 0.76; $P = 0.04$).¹²⁴

The benefits of bariatric surgery on glycemic control may result, at least in part, from their effects on the incretin system. Results from a study of 41 obese patients with T2DM undergoing either bypass, banding, or very-low-calorie diet who were followed for up to 42 days indicated that patients who underwent bypass surgery had increased GLP-1 responses to meals ($P < 0.05$).¹²⁵ Similarly, a study of 16 obese patients with T2DM who received either RYGB or gastric-restrictive surgery (laparoscopic adjustable gastric band or laparoscopic sleeve gastrectomy) indicated that those treated with RYGB had significant increases in insulin secretion, GLP-1 levels, and β -cell sensitivity to glucose ($P < 0.05$).¹²⁶ It has been suggested that RYGB and other malabsorptive procedures, such as biliopancreatic diversion, improve glucose homeostasis by increasing delivery of unabsorbed nutrients to the distal gut and thus increasing secretion of GLP-1.¹²⁷ Further support for the view that hormonal effects, independent of weight loss, may underlie improvements in glycemic control in patients undergoing bariatric surgery is that this effect is observed in days to weeks after surgery, prior to the occurrence of significant weight loss.¹²⁸ The suggestion that hormonal effects

associated with nutrient delivery to the distal gut and elevated GLP-1 secretion contributes to improved glycemic control is supported by results of studies which have shown that RYGB improved glucose control versus restrictive procedures despite equivalent weight loss. Results from a comparison of RYGB versus adjustable gastric banding indicated better higher post-meal GLP-1 and glucose control with the former procedure despite equivalent postsurgical BMI in the two groups of patients.¹²⁹ Other gastrointestinal hormones may also play a role in the weight loss associated with bariatric surgery. Peptide YY₃₋₃₆ is involved in food intake and clinical trial results have indicated that gastric bypass surgery, but not gastric banding, increases levels of this peptide.¹³⁰ It has also been shown that gastric bypass surgery, but not diet-induced weight loss, increases levels of oxyntomodulin, and it has been suggested that elevation of this hormone may be necessary for the improved glucose control associated with bariatric surgery.¹³¹

Economic considerations

Use of nonpharmacologic interventions and newer therapies (eg, incretin-based treatments, insulin detemir) and surgical intervention in an effort to lower body weight or prevent weight gain in patients with diabetes has the potential to increase the cost of care, although results from pharmacoeconomic studies have indicated long-term economic benefit of these approaches. It has been noted that dietary programs aimed at decreasing obesity, such as the Dietary Approaches to Stop Hypertension program, are effective for lowering weight and improving other cardiovascular risk factors and have low cost.¹³² Projection of long-term treatment outcomes supports the cost-effectiveness of both liraglutide and exenatide for the treatment of T2DM.^{133,134} Pharmacoeconomic analysis has also indicated that treatment of patients with T2DM using insulin detemir is cost-effective versus NPH insulin.¹³⁵ Bariatric surgery has been reported to be cost-effective versus nonsurgical interventions in severely obese patients.¹³⁶

Conclusion

Overweight and obesity are common in the US population. Obesity increases the risk for T2DM as well as that for complications in people with the disease. Close attention to diet and lifestyle can significantly decrease the frequency of T2DM in high-risk patients and help control blood glucose in patients with the disease. These interventions have also been shown to be effective for reversing T2DM in patients diagnosed with this disease. Treatment for diabetes evolves with disease progression, and clinicians must consider effects on weight when selecting medications. Among older agents,

metformin and acarbose have the lowest risk for weight gain. Clinical trial results have also consistently demonstrated that treatment with GLP-1 receptor agonists lowers weight, and DPP-4 inhibitors are weight-neutral in patients with T2DM. Most patients with T2DM ultimately require insulin treatment, and insulin analogs have lower liability for weight gain than human insulin. This benefit has been demonstrated most consistently for insulin detemir and is less clear for insulin glargine and the rapid-acting insulin analogs. Surgical therapies aimed at treating obesity can improve metabolic control and can even prevent T2DM in some individuals. Bariatric surgery remains the most effective treatment for obesity, and research is elucidating its unique effectiveness and it can also reverse diabetes in patients with T2DM. The factors responsible for this resolution before actual weight loss may lie in the secretion of incretin hormones. Overall, results summarized in this review underscore the point that changes in lifestyle and diet are highly effective for controlling body weight and reversing T2DM and should be emphasized as first steps in patient management. For patients who cannot achieve significant and sustained weight loss with these approaches, careful selection of antidiabetes therapy and additional surgical intervention, if necessary, can assist in the control of body weight.

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