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Diabetes and obesity: Managing dual epidemics

Diabetes with obesity—Is there an ideal diet?

The essential role of exercise

Diabetes treatment in the presence of obesity

Antiobesity drugs in the management of diabetes

**Metabolic surgery:
Now supported by diabetes organizations**

BONUS ARTICLE!

Medical treatment of diabetes

**Supplement Editor
M. Cecilia Lansang, MD, MPH**

Diabetes and obesity: Managing dual epidemics

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Cover art: White fat cells contain a large lipid droplet (yellow) and a nucleus (red) located in the periphery. The most prevalent adipose tissue in the body, white fat cells store surplus energy and function as a major secretory and endocrine organ. Excess white fat contributes to metabolic syndrome and diabetes.

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Diabetes and obesity: Managing dual epidemics

The odds are high that practitioners who manage patients with diabetes are also managing patients who are overweight or obese. The numbers are staggering: more than two-thirds of American adults with type 2 diabetes are obese, and the need to address these dual epidemics is clear. Many strategies exist, but how does a practitioner select the best option for an individual patient? This *Cleveland Clinic Journal of Medicine* supplement on diabetes and obesity includes articles by experts who review the evidence on the impact of different diets and exercise and the use of “weight-friendly” diabetes medications, drug therapy, and metabolic surgery in managing obesity in patients with diabetes.

For some patients with type 2 diabetes, changes in diet and exercise are beneficial in managing the disease and can lead to weight loss. Diets abound, but what diets are best, particularly for patients with obesity? Zahrae Sandouk, MD, and I review several popular diets and what is known about their effects on weight loss, glycemic control, and cardiovascular risk.

As for exercise, both aerobic and resistance training are essential to improve glucose regulation and cardiovascular health. John P. Kirwan, PhD, Jessica Sacks, and Stephan Nieuwoudt review exercise recommendations, modalities, and the metabolic benefits of exercise for this patient population.

Drug therapy typically focuses on the diabetes side of the coin and not necessarily the obesity side; however, practitioners are increasingly helping patients establish goals on both fronts. To that end, Mary Angelynne Esquivel, MD, and I discuss medications for treatment of type 2 diabetes that also have weight loss as a side effect, including glucagon-like peptide-1 receptor agonists, sodium-glucose cotransporter-2 inhibitors, neuroendocrine peptide hormones, alpha-glucosidase inhibitors, and metformin.

The heightened focus on addressing obesity warrants consideration of medications for weight loss. Bartolome Burguera, MD, PhD, Khawla F. Ali, MD, and Juan P. Brito, MD, discuss a potential shift in thinking: using antiobesity drugs to manage type 2 diabetes. The authors review pharmacologic therapies approved for managing obesity in the context of diabetes.

While initially used for patients with severe obesity, bariatric surgery is now called *metabolic surgery* when used for type 2 diabetes because of its dramatic impact in reversing type 2 diabetes. Philip R. Schauer, MD, Zubaidah Nor Hanipah, MD, and Francesco Rubino, MD, describe the benefits of metabolic surgery and review the evidence that led diabetes organizations to set new guidelines with a lower body mass index threshold than previously recommended.

The dual epidemics of diabetes and obesity present physicians with a complex set of considerations to help patients achieve their treatment goals on both fronts in the battle. I hope you find this supplement on diabetes and obesity informative and useful to you to enhance patient care.



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Diabetes with obesity—Is there an ideal diet?

■ ABSTRACT

For individuals who are overweight or obese, weight loss is effective in preventing and improving the management of type 2 diabetes. Together with other lifestyle factors like exercise and behavior modification, diet plays a central role in achieving weight loss. Diets vary based on the type and amount of carbohydrate, fat, and protein consumed to meet daily caloric intake goals. A number of popular diets are reviewed as well as studies evaluating the effect of various diets on weight loss, diabetes, and cardiovascular risk factors. Current trends favor the low-carbohydrate, low-glycemic index, Mediterranean, and very-low-calorie diets. However, no optimal dietary strategy exists for patients with obesity and diabetes, and more research is needed. Given the wide range of dietary choices, the best diet is one that achieves the best adherence based on the patient's dietary preferences, energy needs, and health status.

■ KEY POINTS

Weight loss in individuals who are obese has been shown to be effective in the prevention and management of type 2 diabetes.

Diets vary based on the type and amount of carbohydrate, fat, and protein consumed to meet daily caloric intake goals.

Diets of equal caloric intake result in similar weight loss and glucose control regardless of the macronutrient content.

The metabolic status of the patient based on lipid profiles and renal and liver function is the main determinant for the macronutrient composition of the diet.

According to National Health and Nutrition Examination Survey data, more than one-third of adults in the United States are obese and more than two-thirds of adults with type 2 diabetes mellitus (DM) are obese.¹ In light of overall increased life expectancy, the Centers for Disease Control and Prevention estimates that adults in the United States have a 40% lifetime risk of developing diabetes, as diabetes and obesity remain at epidemic levels.²

Weight loss in individuals who are overweight or obese is effective in preventing type 2 DM and improving management of the disease.^{3,4} Dietary changes play a central role in achieving weight loss, as do other important lifestyle interventions such as exercise, behavior modification, and pharmacotherapy. Achieving glycemic goals with diet alone is difficult, and for patients with DM who are also obese, it may be even more challenging.

Medical nutrition therapy, a term coined by the American Dietetic Association, describes an approach to treating medical conditions using specific diets. As developed and monitored by a physician and registered dietitian, diet can result in beneficial outcomes and is a front-line approach for patients with noninsulin-dependent diabetes.⁵ Medical nutrition therapy for patients with type 2 DM is most effective when used within 1 year of diagnosis and is associated with a 0.5% to 2% decrease in hemoglobin A1c (HbA1c) levels.⁶ This article reviews the role of diet in managing patients with both type 2 DM and obesity. Several diets are presented including what is known about their effect on weight loss, glycemic control, and cardiovascular risk prevention in patients with diabetes and obesity.

■ WEIGHT LOSS AND DIET FOR PATIENTS WITH OBESITY AND DIABETES

A person is overweight or obese if he or she weighs more than the ideal weight for their height as calculated by the body mass index (BMI; weight in kg/height in meters squared). A BMI of 25 to 30 is overweight and a BMI of 30 or greater is obese.⁷ The recommended daily caloric intake for adults is based

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on sex, age, and daily activity level and ranges from 1,600 to 2,000 calories per day for women and 2,000 to 2,600 calories per day for men. The lower end of the range is for sedentary adults, and the higher end is for active adults (walking 1.5 to 3 miles per day at 3 to 4 miles per hour, in addition to independent living).⁸

According to the American Diabetes Association (ADA), weight loss requires reducing dietary intake by 500 to 750 calories per day, or roughly 1,200 to 1,500 kcal/day for women and 1,500 to 1,800 kcal/day for men.³ For patients with obesity and type 2 DM, sustained, modest weight loss of 5% of initial body weight improves glycemic control and reduces the need for diabetes medications.⁹ Weight loss of greater than 5% body weight also improves lipid and blood pressure status in patients with obesity and diabetes, though ideally, patients are encouraged to achieve weight reduction of 7% or greater.¹⁰

Evidence of benefits from lifestyle and dietary modifications

The fact that patients with obesity and type 2 DM have increased risk of cardiovascular morbidity and mortality is well established.¹¹ Multiple studies considered the effects of weight loss on cardiovascular morbidity and mortality. Our article focuses on dietary modifications, though most large, multicenter trials used both diet and increased physical activity to achieve weight loss. It is difficult to determine if diet or physical activity had the most effect on outcomes; however, results show that weight loss from dietary and other lifestyle interventions leads to change in outcomes.

Look AHEAD (Action for Health in Diabetes) trial. This large, multicenter, randomized controlled trial evaluated the effect of weight loss on cardiovascular morbidity and mortality in overweight or obese adults with type 2 DM. The 5,145 participants were assigned either to a long-term weight reduction intensive lifestyle intervention of diet, physical activity, and behavior modification or to usual care of support and education. At 1 year, the lifestyle intervention group had greater weight loss, improved fitness, decreased number of diabetes medications, decreased blood pressure, and improved biomarkers of glucose and lipid control compared with the usual care group.¹² No significant reductions in cardiovascular morbidity and mortality were found, though an observational post hoc analysis of the Look AHEAD data suggested an association between the magnitude of weight loss and the incidence of cardiovascular disease.¹³

The diet portion of the intensive lifestyle intervention consisted of self-selected, conventional

foods while recording dietary intake during week 1. In week 2, patients weighing less than 114 kg (250 lbs) restricted their intake to 1,200 to 1,500 kcal/day, and patients weighing 114 kg or more restricted their intake to 1,500 to 1,800 kcal/day. Fewer than 30% of calories were from fat, with less than 10% from saturated fat. During week 3 through week 9, meal replacement options and conventional foods were used to reach caloric goals. Participants then decreased the use of meal replacement and increased the use of conventional foods during week 20 through week 22.¹⁴

The mean weight loss for participants in the intensive lifestyle intervention group was 8.6% compared with 0.7% in the support and education group ($P < .001$). HbA1c decreased by 0.7% in the intervention group compared with 0.1% in the support and education group ($P < .001$).¹²

Finnish Diabetes Prevention Study. This study evaluated lifestyle changes in diet and physical activity in the prevention of type 2 DM in participants with impaired glucose intolerance. Participants ($N = 552$) were randomly assigned to the control group or the intervention group where detailed instruction was provided to achieve weight loss of greater than 5%.¹⁵ The dietary goals included fewer than 30% of total calories from fat, with fewer than 10% from saturated fat, increased fiber consumption (15 g per 1,000 kcal), and physical activity of 30 minutes daily.¹⁵ During the trial (mean duration of follow-up 3.2 years), the risk of type 2 DM was reduced by 58% in the intervention group compared with the control group.¹⁵

Diabetes Prevention Program Research Group. A landmark study by the Diabetes Prevention Program Research Group randomized 3,234 participants with elevated plasma glucose levels to placebo, metformin, and lifestyle intervention arms.⁴ Those in the lifestyle intervention arm were educated about ways to achieve and maintain a 7% or greater reduction in body weight using a low-calorie, low-fat diet and moderate physical activity. Results based on a mean follow-up of 2.8 years found a 58% reduction in the incidence of diabetes for those in the lifestyle intervention arm.⁴

DIETS AND THEIR EFFECTS ON OBESITY, DIABETES, AND CARDIOVASCULAR RISK

When patients seek consultation about diet, they frequently ask about specific types of popular diets, not the very controlled diets employed in research studies. Dietary preferences are personal, so patients may have researched a particular diet or feel that they will

Summary: low-carbohydrate diet

Allows 50 to 100 g/day; < 40% calories from carbohydrates^{18,20}

- Foods: higher in protein (meat, poultry, fish, shellfish, eggs, cheese, nuts, seeds); higher in fat (oils, butter, olives, avocados); low-carbohydrate vegetables (green salad, cucumber, broccoli, squash)
- Avoid: rice, pasta, bread
- Weight loss: rapid, 11.4 kg over 6 months reported²⁴⁻²⁷
- Hemoglobin A1c: reduced 1.4% in 6 months, or 0% to 2.2%^{18,24}
- Cardiovascular: lower triglyceride, higher high-density lipoprotein cholesterol¹⁸
- Weight regain: rapid, 6 months
- Challenges: limits important nutrients; monitor lipids, renal function, protein intake

be more adherent if only 1 or 2 components of their meals are changed. There is no single optimal dietary strategy for patients with both obesity and type 2 DM. In general, diets are categorized based on the 3 basic macronutrients: carbohydrate, fat, and protein. We will review several popular diets, delineating content, effects on weight loss, glycemic control, and cardiovascular factors.

■ LOW-CARBOHYDRATE DIET

Carbohydrates are organic compounds in food that include sugars and starches and are a source of energy for cells in the body and the brain in particular. The US Department of Agriculture Recommended Dietary Allowance of carbohydrate is 130 g per day minimum or 45% to 65% of total daily caloric intake.¹⁶ For a 1,700-calorie diet, 130 g of carbohydrate is 30% of the total caloric intake; in a 1,200-calorie diet, it is 43%.¹⁷

In practice, the median intake of carbohydrates for US adults is much higher, at 220 to 330 g per day for men and 180 to 230 g per day for women.¹⁶ The ADA recommends that all Americans consume fewer refined carbohydrates and added sugars in favor of whole grains, legumes, vegetables, and fruit.¹⁸

Low-carbohydrate diets focus on reducing carbohydrate intake with the thought that fewer carbohydrates are better. However, the definition of a low-carbohydrate diet varies. In most studies, carbohydrate intake was limited to less than 20 g to 120

g daily or fewer than 4% to 45% of the total calories consumed.^{17,19} Intake of fat and total calories is unlimited, though unsaturated fats are preferred over saturated or trans fats.

Limiting the intake of disaccharide sugar in the form of sucrose and high-fructose corn syrup is endorsed because of concerns that these sugars are rapidly digested, absorbed, and fully metabolized. However, several randomized trials showed that substituting sucrose for equal amounts of other types of carbohydrates in individuals with type 2 DM showed no difference in glycemic response.²⁰ The resulting conclusion is that the postprandial glycemic response is mainly driven by the amount rather than the type of carbohydrates. The consumption of sugar-sweetened beverages is associated with obesity and an increased risk of diabetes, attributed to the high caloric intake and decreased insulin sensitivity associated with these beverages.²¹

Of the 2 monosaccharides, glucose and fructose, that make up sucrose, fructose is metabolized in the liver. The rapid metabolism of fructose may lead to alterations in lipid metabolism and affect insulin sensitivity.²² While the ADA does not advise against consuming fructose, it does advise limiting its use due to the caloric density of many foods containing fructose.

Multiple studies have investigated the effect of a low-carbohydrate diet on weight loss, glucose control, and cardiovascular risk, but comparing the results is difficult due to the varying definitions of a low-carbohydrate diet.

Low-carbohydrate diets are associated with rapid weight loss. A 6-month study of 31 patients with obesity and type 2 DM found a mean weight change of -11.4 kg (± 4 kg) in the low-carbohydrate group compared with -1.8 kg (± 3.8 kg) in the high-carbohydrate control group, a loss maintained up to 1 year.²³ Another study of 88 patients with type 2 DM who consumed less than 40 g/day of carbohydrate had a weight loss of 7.2 kg over 12 months.²⁴ Samaha et al²⁵ compared a low-carbohydrate diet with a low-fat diet in 132 participants with obesity (mean BMI 43), of which 39% had diabetes and 43% had metabolic syndrome. Those in the low-carbohydrate diet group had significantly more weight loss over a period of 6 months (-5.8 kg mean, ± 8.6 kg standard deviation [SD] vs -1.9 kg mean ± 4.2 kg SD, $P = .002$). However, at 1 year, there was no significant difference in weight loss between groups. At 36 months, weight regain was 2.2 kg (SD 12.3 kg) less than baseline in the low-carbohydrate group compared with 4.3 kg (SD 12.2 kg) less than baseline in the low-fat group

($P = .071$).^{25,26} On the other hand, a meta-analysis of 23 randomized trials involving 2,788 participants found no difference in weight loss at 6 months between those on a low-carbohydrate diet and those on a low-fat diet.¹⁹

With respect to glucose control, low-carbohydrate diets have been associated with a 1.4% (SD \pm 1.1%) decrease in HbA1c during a 6-month period in 31 patients with obesity and type 2 DM.²³ Another 6-month study of 206 patients with obesity and diabetes comparing a low-carbohydrate diet with a low-calorie diet found no significant difference in HbA1c ($-.48\%$ vs $-.24\%$, respectively) and a weight loss of 1.34 kg vs 3.77 kg, respectively ($P < .001$).²⁷ The change in glycemic control did not persist over time, perhaps due to the weight regain associated with this diet. A meta-analysis concluded that HbA1c was reduced more in patients with type 2 DM randomized to a lower-carbohydrate diet compared with a higher-carbohydrate diet (mean change from baseline 0% to -2.2%).¹⁷

No studies of the effects of a low-carbohydrate diet on overall cardiovascular morbidity or mortality exist. However, Kirk et al¹⁷ reported results of a low-carbohydrate diet on cardiovascular risk factors such as lipid profiles and showed a significant reduction in triglyceride levels but no effect on total cholesterol, high-density lipoprotein cholesterol (HDL-C), or low-density lipoprotein cholesterol (LDL-C) levels.

The ADA has reported that low-carbohydrate diets may be effective in the management of type 2 DM in the short term. Caution is warranted because they could eliminate important sources of energy, fiber, vitamins, and minerals. It is also important to monitor lipid profile, renal function, and protein intake in certain patients, especially those with renal dysfunction.⁶

■ LOW-GLYCEMIC DIET

The glycemic index (GI) is a measure of the rise in plasma glucose 2 hours after ingesting carbohydrate in food compared with a reference food such as glucose that contains an equivalent amount of carbohydrate. The GI measures the postprandial response of different carbohydrates: high-GI foods raise blood glucose more than medium- or low-GI foods.

Various factors affect the GI including the type of carbohydrate, fat content, protein content, and acidity of the food consumed, as well as the rate of intestinal reaction to the food. The faster the digestion of a food, the higher the GI. High-GI foods (> 70), such as those highly processed and with high starch content,

Summary: low-glycemic diet

Foods with glycemic index < 55

- Foods: whole wheat, rye, pita breads; oats, brown rice, couscous; muesli, bulgur; most fruits; nonstarchy vegetables
- Weight loss: none; -0.32 kg³⁰
- Hemoglobin A1c: reduced 0.5%²⁹
- Cardiovascular: undetermined
- Weight regain: undetermined
- Challenges: limits important nutrients; glycemic index varies with preparation and among individuals

produce higher peak glucose levels when compared with low-GI foods (< 55). Low-GI foods include lentils, beans, oats, and nonstarchy vegetables.

Low-GI foods curb the large and rapid rise of blood glucose, insulin response, and glucagon inhibition that occur with high-GI foods. Many low-GI foods have high amounts of fiber, which prolongs distention of the gastrointestinal tract, increases secretion of cholecystokinin and incretins, and extends satiety.²⁸

In a meta-analysis of 19 randomized trials of overweight or obese patients (BMI > 25), a low-glycemic diet did not show weight loss when compared with an isocaloric control diet (mean difference -0.32 kg; 95% confidence interval [CI] -0.86 kg, 0.23 kg).²⁹ On the other hand, the effect on glycemic control is more pronounced. Another meta-analysis that included 11 studies of patients with DM who followed a low-glycemic diet for less than 3 months to over 6 months showed that those who followed a low-glycemic diet had a significant reduction of HbA1c (6 studies had HbA1c as the primary outcome, HbA1c weighted mean difference -0.5% ; 95% CI, -0.8 to -0.2 ; $P = .001$). Five studies reported on parameters related to insulin action, and 1 showed increased sensitivity measured by euglycemic-hyperinsulinemic clamp in a low-glycemic diet (glucose disposal 7.0 ± 1.3 mg glucose/kg/min) vs a high-glycemic diet (4.8 mg glucose/kg/min ± 0.9 , $P < .001$).²⁸

There are no large trials of cardiovascular mortality or morbidity of low-glycemic diets, but some studies have included cardiovascular parameters. A randomized study of 210 patients with type 2 DM evaluated cardiovascular risk factors after 6 months of a low-glycemic diet and high-glycemic diet. The low-glycemic diet group had an increase in HDL-C compared with the high-glycemic diet group (1.7 mg/dL; 95% CI, 0.8

Summary: low-fat diet

Allows < 30% calories from fat

- Foods: whole wheat, rye, pita breads; oats, brown rice, couscous; muesli, bulgur; most fruits; nonstarchy vegetables
- Avoid: saturated and trans fats
- Weight loss: 5.3 kg in 6 months,³⁷ 11% in 1 year³⁸
- Hemoglobin A1c: minimal to none
- Cardiovascular: lower low-density lipoprotein cholesterol and triglyceride, higher high-density lipoprotein cholesterol³⁷
- Weight regain: 4% at 2 years³⁸
- Challenges: differentiating types of fat, avoiding saturated and trans fats

to 2.6 mg/dL vs -0.2 mg/dL; 95% CI, -0.9 to -0.5 mg/dL, $P = .005$).³⁰ Another crossover study of 20 patients with type 2 DM on a low-glycemic diet over 2 consecutive 24-day periods revealed a 53% reduction of the activity of plasminogen activator inhibitor-1, a thrombolytic factor that increases plaque formation.³¹ Most studies were of short duration; thus, weight regain was not clearly established.

The GI of low-GI foods differs based on the cooking method, presence of other macronutrients, and metabolic variations among individuals. Low-glycemic diets can reduce the intake of important dietary nutrients. The ADA notes that low-glycemic diets may provide only modest benefit in controlling postprandial hyperglycemia.³²

■ LOW-FAT DIET

Low-fat diets have 30% or fewer calories from fat, approximately 50 g of fat for a 1,500 kcal/day. The intake of dietary fat and free fatty acids reduces insulin sensitivity and enhances hepatic glucose production contributing to hyperglycemia.³³ The mechanisms by which dietary fat and fatty acids reduce insulin sensitivity include modifications of the cell membrane composition, gene expression, and enzyme activity. Fatty acids also promote inflammatory cytokines and induce endothelial dysfunction. The type of fat rather than its total amount plays a role in glycemic control and cardiovascular disease risk.³²

Different types of fats have different effects on metabolism. LDL-C is mostly derived from saturated fats.³⁴ Consuming 2% of energy intake from trans fat substantially increases the risk of coronary heart dis-

ease.³⁵ Though the ideal total amount of fat for people with diabetes is unknown, the amount consumed still has important consequences, especially since patients with type 2 DM are at risk for coronary artery disease. The Institute of Medicine states that fat intake of 20% to 35% of energy is acceptable for all adults.¹⁶

Low-fat diets along with reduced caloric intake induce weight loss, but this cannot compete with the rapid weight loss that patients experience with the low-carbohydrate diet. This was shown in multiple studies including a meta-analysis of 5 randomized clinical trials of 447 patients with obesity who lost less weight in the low-fat diet group compared with low-carbohydrate diet group (weighted mean difference -3.3 kg; 95% CI, -5.3 to -1.4 kg) at 6 months.³⁶ Interestingly, the difference between diets was nonexistent after 12 months (weighted mean difference -1.0 kg; 95% CI, -3.5 to 1.5 kg), which may be due to weight regain in the low-carbohydrate diet group.³⁶

Foster et al³⁷ studied 307 participants with obesity assigned to a low-fat or low-carbohydrate diet. Both groups lost 11% in 1 year, and with regain, lost 7% from baseline at 2 years. There was no statistically significant difference between groups during the 2 years, but there was a trend for more weight loss in the low-carbohydrate group in the first 3 months ($P = .019$).³⁷

The low-fat diet has no to minimal improvement in glycemic control in patients with diabetes and obesity, regardless of the weight loss achieved. However, a low-fat diet is associated with some beneficial effects on cardiovascular risks. Nordmann et al³⁶ found no difference in blood pressure between low-carbohydrate and low-fat diets. The low-fat diet was associated with lower total cholesterol and LDL-C levels (weighted mean difference 5.4 mg/dL [0.14 mmol/L]; 95% CI, 1.2 mg/dL to 10.1 mg/dL [0.03–0.26 mmol/L]).³⁶ Triglyceride and HDL-C levels were more favorably changed in the low-carbohydrate diet (for triglycerides, weighted mean difference -22.1 mg/dL [-0.25 mmol/L]; 95% CI, -38.1 to -5.3 mg/dL [-0.43 to -0.06 mmol/L]; and for HDL-C, weighted mean difference 4.6 mg/dL [0.12 mmol/L]; 95% CI, 1.5 mg/dL to 8.1 mg/dL [0.04–0.21 mmol/L]).³⁶

■ VERY-LOW-CALORIE DIET

Very-low-calorie diets provide 400 to 800 calories per day of high-quality protein and carbohydrate fortified with vitamins, minerals, and trace elements.³⁸ Very-low-calorie diets promote quick weight loss and use commercial formulas, liquid shakes, and soups to replace all regular meals. This type of diet results

in rapid weight loss without leading to electrolyte imbalances associated with starvation. It was widely promoted in the 1970s, but then lost some of its popularity due to concerns for patients' safety and even death.³⁹ For these reasons, individuals on very-low-calorie diets should be closely monitored by a team of health professionals.

Saris et al³⁸ reported results from 8 randomized clinical trials ranging from 10 to 32 patients with obesity comparing very-low-calorie diets with a low-calorie diet of 800 to 1,200 calories a day. Over the first 4 to 6 weeks, weight loss was between 1.4 kg and 2.5 kg per week and was higher with the very-low-calorie diet when compared with the low-calorie diet though not statistically significant. Interestingly, when followed for 16 to 26 weeks, the difference in weight loss was again not statistically significant with no trend for more weight loss in the very-low-calorie diet group. Another meta-analysis looking at 6 randomized clinical trials in patients with obesity showed that weight loss with very-low-calorie diets was statistically significant when compared with low-calorie diets (16.1% ± 1.6% vs 9.7% ± 2.4% weight loss over a period of 12.7 ± 6.4 weeks).³⁹

In general, it is believed that when individuals lose a large amount of weight in a short period, a larger weight regain will occur, resulting in a higher weight than before the initial loss. This was refuted by Tsai et al,³⁹ who found that long-term data (1 to 5 years) showed the percentage of weight regained is higher with a very-low-calorie diet (62%) vs a low-calorie diet (41%) but the overall weight lost remains superior with the very-low-calorie diet, though not statistically significant (6.3% ± 3.2% and 5.0% ± 4.0% loss of initial weight, respectively).

Toubro et al⁴⁰ looked at 43 obese individuals who followed the very-low-calorie diet for 8 weeks compared with 17 weeks of a conventional diet (1,200 kcal/day) followed by a year of unrestricted calories, low-fat, high-carbohydrate diet or fixed calorie group (1,800 kcal/day). The very-low-calorie diet group lost weight at a more rapid rate, but the rate had no effect on weight maintenance after 6 or 12 months. Interestingly, the group that followed the "unrestricted calories, low-fat, high-carbohydrate diet" for a year maintained 13.2 kg (8.1 kg to 18.3 kg) of the initial 13.8 kg (11.8 kg to 15.7 kg) weight loss, while the fixed-calorie group maintained less weight loss (9.7 kg [6.1 kg to 13.3 kg]). Saris³⁸ concluded that the rapid weight loss by very-low-calorie diet has better long-term results when followed up with a program that includes nutritional education, behavioral therapy,

Summary: very-low-calorie diet

Provides 400 to 800 calories daily with meal replacements³⁹

- Foods: meal replacements such as Optifast, SlimFast shakes
- Weight loss: 1.4 to 2.5 kg/week³⁹; 16.1% over 12.7 weeks⁴⁰
- Hemoglobin A1c: reduced 0.9% over 12 weeks⁴¹
- Cardiovascular: little effect⁴²
- Weight regain: 62% at 5 years⁴⁰
- Challenges: close monitoring by professionals required; requires meal replacements; low adherence rate

and increased physical activity.

Very-low-calorie diets achieve glycemic control by reducing hepatic glucose output, increasing insulin action in the liver and peripheral tissues, and enhancing insulin secretion. These benefits occur soon after starting the diet, which suggests that caloric restriction plays a critical role. A study at the University of Michigan showed that the use of very-low-calorie diets in addition to moderate-intensity exercise resulted in a reduction of HbA1c from 7.4% (± 1.3%) to 6.5% (± 1.2%) in 66 patients with established type 2 DM.⁴¹ HbA1c of less than 7% occurred in 76% of patients with established diabetes and 100% of patients with newly diagnosed diabetes.⁴¹ Improvement in HbA1c over 12 weeks was associated with higher baseline HbA1c and greater reduction in BMI.⁴¹

Long-term cardiovascular risk reduction of very-low-calorie diets is small. One study showed that serum total cholesterol decreased at 2 weeks but did not differ at 3 months from baseline.⁴² A large reduction was observed in serum triglycerides at 3 months (4.57 mmol/L ± 1.0 mmol/L vs 2.18 mmol/L ± .26 mmol/L, $P = .012$) while HDL-C increased (0.96 mmol/L ± .06 mmol/L vs 1.11 mmol/L ± .05 mmol/L, $P = .009$).⁴² Blood pressure was also reduced in both systolic pressure (152 mm Hg ± 6 mm Hg vs 133 mm Hg ± 3 mm Hg, $P = .004$) and diastolic pressure (92 mm Hg ± 3 mm Hg vs 81 mm Hg ± 3 mm Hg, $P = .007$).⁴²

Challenges with this diet include significant weight regain and safety concerns for patients with obesity and type 2 DM, especially those who are taking insulin, since this diet will lead to significant rapid lowering of insulin levels.³⁸ Finally, very-low-calorie diets require a multidisciplinary approach with frequent health professional visits.

Summary: Mediterranean diet

Focuses on 30% to 40% calories from monounsaturated fats

- Foods: olive oil, fresh fruits and vegetables, cereals, beans, nuts, seeds, limited dairy, limited eggs and red meat, wine moderately with meals
- Weight loss: 7.4 kg in 1 year⁴³
- Hemoglobin A1c: reduced 0.4% to 0.6%^{43,47}; lower incidence type 2 diabetes⁴⁶
- Cardiovascular: systolic blood pressure reduced 7.1 mm Hg; reduced high-density lipoprotein cholesterol ratio of .2645
- Weight regain: less, 0.5 kg over 2 years⁴⁴
- Challenges: slower weight loss but higher adherence rate

■ MEDITERRANEAN DIET

The Mediterranean diet focuses on the moderate ingestion of monounsaturated fats such as olive oil (30% to 40% of daily energy intake), legumes, fruits, vegetables, nuts, whole grains, fish, and moderate ingestion of wine. A study of 259 overweight (mean BMI 31.4) patients with diabetes found a mean weight loss of as much as 7.4 kg at a steady state after 12 months.⁴³ A systematic review of 5 randomized clinical trials of obese adults (N = 998) showed that sustained weight loss (up to 12 months) was greater in the Mediterranean diet compared with a low-fat diet (range of mean values: -4.1 to -10.1 kg vs 2.9 to -5.0 kg), but similar to a low-carbohydrate diet (4.1 to -10.1 kg vs -4.7 to -7.7 kg).⁴⁴

This diet also has a positive impact on glycemic control and has been shown to reduce the incidence of diabetes. Estruch et al⁴⁵ conducted a randomized controlled trial on 772 adults at high risk for cardiovascular disease, of which 421 had type 2 DM, assigned to Mediterranean diet supplemented either with extra-virgin olive oil or mixed nuts compared with a control group receiving advice on a low-fat diet. Their primary prevention trial, PREDIMED, looked mainly at the rate of total cardiovascular events (stroke, myocardial infarction, cardiovascular death); however, a subgroup analysis showed that the incidence of new-onset diabetes was reduced by 52% with the Mediterranean diet compared with the control group after 4 years of follow-up. Multivariate-adjusted hazard ratios of diabetes were 0.49 (0.25–0.97) and 0.48 (0.24–0.96) in the Mediterranean diet supplemented with olive oil and nuts

groups, respectively, compared with the control group. Intuitively, they also showed that the higher the adherence, the lower the incidence rate.⁴⁶ This occurred despite no difference in weight loss between the groups and may indicate that the components of the diet itself could have anti-inflammatory and antioxidative effects. Esposito et al⁴⁷ showed that after 1 year of intervention in 215 patients with type 2 DM, HbA1c was lower in those assigned to the Mediterranean diet vs those assigned to a low-fat diet (difference: -0.6%; 95% CI, -0.9 to -0.3). Similarly, in a 12-month trial, Elhayany et al⁴³ found a significant difference in the reduction in HbA1c in those on the Mediterranean diet compared with a low-fat diet (0.4%, *P* = .02).

Many studies have shown a beneficial effect of the Mediterranean diet on cardiovascular health. Estruch et al⁴⁵ showed that 772 patients (143 with type 2 DM) at high risk of cardiovascular disease who followed a Mediterranean diet with nuts for 3 months had a reduced systolic blood pressure of -7.1 mm Hg (CI, -10.0 mm Hg to -4.1 mm Hg) and reduced HDL-C ratio of -0.26 (CI, -0.42 to -0.10) compared with a low-fat diet. There was also a reduction in fasting plasma glucose of -.30 mmol/L (CI, -.58 mmol/L to -.01 mmol/L).⁴⁵

■ PROTEIN-SPARING MODIFIED FAST

The protein-sparing modified fast combines a very-low-carbohydrate ketogenic diet and a very-low-calorie diet. The initial 6-month phase consists of fewer than 800 calories a day followed by a gradual increase in calories over 6 months. Carbohydrate is restricted to 20 to 50 g/day during the initial phase, with protein intake of 1.2 to 1.5 g/kg of ideal body weight per day.⁴⁸

One of the earlier studies on protein-sparing modified fast showed that weight loss was as high as 21 kg ± 13 kg during the initial phase and 19 kg ± 13 kg during the refeeding phase.⁴⁹ Weight regain is high: in the protein-sparing modified fast, most patients return to their baseline weight in 5 years.⁵⁰

A study comparing 6 patients who were put on a protein-sparing modified fast diet with 6 patients who underwent gastric bypass surgery showed that the mean steady-state plasma glucose fell from 377 mg/dL to 208 mg/dL (*P* < .008) and mean fasting insulin values fell from 31.0 to 17.0 μU/mL (*P* < .004).⁵¹ There were also changes in cardiovascular risk factors: mean HDL-C values increased from 33.8 mg/dL to 40.5 mg/dL (*P* < .008), and factor VIII coagulant activity decreased from 194% to 140% (*P* < .005).⁵¹ Total

Summary: protein-sparing modified fast diet

Combines a very-low-carbohydrate ketogenic diet with a very-low-calorie diet

- Foods: low in carbohydrate, high-to-moderate protein intake, minimal fat, includes shakes and meal replacement for low-calorie portion
- Weight loss: 21 kg (\pm 13 kg) initially, 19 kg (\pm 13 kg) refeeding⁴⁹
- Hemoglobin A1c: mean plasma glucose from 377 to 208 mg/dL; mean fasting glucose from 31 to 17 μ U/mL⁵¹
- Cardiovascular: higher high-density lipoprotein cholesterol, lower low-density lipoprotein cholesterol and cholesterol; not maintained at 1 year^{51,52}
- Weight regain: most return to baseline by 5 years⁵⁰
- Challenges: close monitoring by professionals required; requires meal replacements; lower adherence rate

cholesterol and LDL-C levels were also improved, but these changes were not always maintained at follow-up visits.⁵²

■ VEGETARIAN AND VEGAN DIETS

A vegetarian diet consists primarily of cereals, fruits, vegetables, legumes, and nuts and generally excludes animal foods and dairy products. Less restrictive vegetarian diets may include eggs and dairy products. A vegan diet is one of the most restrictive diets and excludes all types of animal products, including honey and processed foods.

In 2013, Mishra et al⁵³ conducted a randomized clinical trial of employees with obesity and type 2 DM (N = 291) assigned to a low-fat vegan diet or no intervention for 18 weeks. Weight decreased in the low-fat vegan diet group compared with the control group (2.9 kg vs 0.06 kg, respectively, $P < .001$). Statistically significant reductions in total cholesterol (8 mg/dL vs 0.01 mg/dL, $P < .01$), LDL-C (8.1 mg/dL vs 0.9 mg/dL, $P < .01$), and HbA1c (0.6% vs 0.08%, $P < .01$) occurred in the intervention group compared with the control group.⁵³

Many studies of vegetarian and vegan diets have been of short duration and used a combination of low-fat and vegetarian or vegan diets on people that were not all considered obese. Research is limited for vegan and vegetarian diets, and not enough informa-

Summary: vegetarian and vegan diets

- Foods: fruits, vegetables, cereals, legumes, whole grains, nuts, soy, fiber; vegan excludes all animal-derived products including dairy, eggs, honey, processed foods
- Weight loss: 2.9-kg decrease⁵³
- Hemoglobin A1c: reduced 0.6% (not statistically significant)⁵³
- Cardiovascular: minimal impact, if any⁵³
- Weight regain: unknown
- Challenges: may lack important nutrients

tion exists about the effects on glycemic control and cardiovascular risk. Vegan and vegetarian diets may reduce the intake of many essential nutrients. Vegans who exclude dairy products, for example, have low bone mineral density and higher risk of fractures due to inadequate intake of calcium.

■ HIGH-PROTEIN DIET

Amino acids contribute to glucose synthesis through gluconeogenesis and play a role in recycling of glucose carbon via the glucose-alanine cycle. High-protein diets include more than 30% of total energy intake from protein (112 g/day assuming 1,500 kcal/day).

Parker et al⁵⁴ reported a weight loss of 5.2 kg \pm 1.8 kg in 12 weeks in 54 patients with obesity and type 2 DM irrespective of a diet with high or low protein content. Women on a high-protein diet lost more total fat and abdominal fat compared with women on a low-protein diet. Total lean mass decreased in all patients irrespective of diet.

Studies have shown that high-protein diets can improve glucose control. Ajala et al⁵⁵ reviewed 20 clinical trials of patients with type 2 DM randomized to various diets for more than 6 months. In the trials that used a high-protein diet as an intervention, HbA1c levels decreased as much as 0.28% compared with the control diets ($P < .001$). A small study of 8 men with untreated type 2 DM compared a high-protein low-carbohydrate diet (nonketogenic, protein 30%, carbohydrate content 20%, fat 50%) with a control diet (protein 15%, carbohydrate 55%, fat 30%).⁵⁶ The high-protein low-carbohydrate diet group had lower HbA1c levels (7.6 mg/dL \pm 0.3 mg/dL vs 9.8 mg/dL \pm 0.5 mg/dL) and mean 24-hour integrated serum glucose (126 mg/dL vs 198 mg/dL) compared with the control diet. Most of the studies

Summary: high-protein diet

Includes > 30% calories from protein sources

- Foods: low-fat cottage cheese, cheese, tofu, red meat, chicken, peanut butter, fish, lentils
- Weight loss: 5.2 kg (± 1.8 kg) in 12 weeks⁵⁴
- Hemoglobin A1c: reduced 0.28%⁵⁵
- Cardiovascular: lower low-density lipoprotein cholesterol, reduction in abdominal fat, no change in high-density lipoprotein cholesterol⁵⁴
- Weight regain: unknown
- Challenges: must be individualized diet accounting for cardiometabolic risk and renal profile

of high-protein diets have been small and of short duration, and have used a combination of macronutrients (high protein and low carbohydrate), limiting the ability to identify the dietary component that had the most effect.

There are no studies evaluating cardiovascular outcomes, but some studies have included cardiovascular risk factors such as LDL-C levels and body fat composition. Parker et al⁵⁴ showed that women on a high-protein diet lost more total fat (5.3 kg vs 2.8 kg, $P = .009$) and abdominal fat (1.3 kg vs 0.7 kg, $P = .006$) compared with a low-protein diet. Interestingly, no difference in total fat and abdominal fat was found in men. LDL-C reduction was greater in a high-protein diet compared with a low-protein diet (5.7% vs 2.7%, $P < .01$).⁵⁴ In a review by Ajala et al,⁵⁵ the high-protein diet was the only diet that did not show a rise in HDL-C levels after interventions of more than 6 months.

The ADA does not recommend high-protein diets as a method for weight loss because the long-term effects are unknown. ADA recommendations include an individualized approach based on a patient's cardiometabolic risk and renal profiles. Protein content should be 0.8 g/kg to 1.0 g/kg of weight per day in patients with early chronic kidney disease, and 0.8 g/kg of weight per day in patients with advanced kidney disease.⁶

COMPARISONS AMONG DIETS

Studies comparing diets have reached varying conclusions and have been limited by inconsistent diet definitions, small sample sizes, and high participant dropout rates. A meta-analysis conducted by Ajala et al⁵⁵ included 20 randomized controlled trials that lasted 6 months or more with 3,073 individuals in

the analysis. Low-carbohydrate, vegetarian, vegan, low-glycemic, high-fiber, Mediterranean, and high-protein diets were compared with low-fat, high-glycemic, ADA, European Association for the Study of Diabetes, and low-protein diets as controls. The greatest weight loss occurred with the low-carbohydrate (-0.69 kg, $P = .21$) and Mediterranean diets (-1.84 kg, $P < .001$). Compared with the control diets, the greatest reductions in HbA1c were with the low-carbohydrate (-0.12% , $P = .04$), low-glycemic (-0.14% , $P = .008$), Mediterranean (-0.47% , $P < .001$), and high-protein diets (-0.28% , $P < .001$). HDL-C levels increased in all the diets except the high-protein diet.⁵⁵

CONCLUSION

The optimal macronutrient intake for patients with obesity and type 2 DM is unknown. Diets with equivalent caloric intakes result in similar weight loss and glucose control regardless of the macronutrient contents. It is important that total caloric intake be appropriate for weight management and glucose control goals. The metabolic status of the patient as determined by lipid profiles, and renal and liver function is the main driver for the macronutrient composition of the diet.

Current trends favor the low-carbohydrate, low-glycemic, Mediterranean, and low-caloric intake diets, though there is no evidence that one is best for weight loss and optimal glycemic control in patients with obesity and type 2 DM. Studies are limited by varying definitions, high dropout rates, and poor adherence. In addition, for many patients, weight regain often follows successful short-term weight loss, indicative of a low durability of results with many diet interventions. Medical nutrition therapy and a multidisciplinary lifestyle approach remain essential components in managing weight and type 2 DM. The ideal diet is one that achieves the best adherence when tailored to a patient's preferences, energy needs, and health status.

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The essential role of exercise in the management of type 2 diabetes

ABSTRACT

Exercise is typically one of the first management strategies advised for patients newly diagnosed with type 2 diabetes. Together with diet and behavior modification, exercise is an essential component of all diabetes and obesity prevention and lifestyle intervention programs. Exercise training, whether aerobic or resistance training or a combination, facilitates improved glucose regulation. High-intensity interval training is also effective and has the added benefit of being very time-efficient. While the efficacy, scalability, and affordability of exercise for the prevention and management of type 2 diabetes are well established, sustainability of exercise recommendations for patients remains elusive.

KEY POINTS

Exercise is often the first lifestyle recommendation made to patients newly diagnosed with type 2 diabetes.

Together with diet and behavior modification, exercise is central to effective lifestyle prevention and management of type 2 diabetes.

All exercise, whether aerobic or resistance training or a combination, facilitates improved glucose regulation.

In addition to the cardiovascular benefits, long-term exercise promotes healthier skeletal muscle, adipose tissue, and liver and pancreas function.

Exercise programs for patients with type 2 diabetes should be of sufficient intensity and volume to maximize the metabolic benefit while avoiding injury and cardiovascular risk.

Type 2 diabetes has emerged as a major public health and economic burden of the 21st century. Recent statistics from the Centers for Disease Control and Prevention suggest that diabetes affects 29.1 million people in the United States,¹ and the International Diabetes Federation estimates diabetes affects 366 million people worldwide.²

As these shocking numbers continue to increase, the cost of caring for patients with diabetes is placing enormous strain on the economies of the US and other countries. In order to manage and treat a disease on the scale of diabetes, the approaches need to be efficacious, sustainable, scalable, and affordable.

Of all the treatment options available, including multiple new medications and bariatric surgery (for patients who meet the criteria, discussed elsewhere in this supplement),³⁻⁵ exercise as part of a lifestyle approach⁶ is a strategy that meets the majority of these criteria.

The health benefits of exercise have a long and storied history. Hippocrates, the father of scientific medicine, was the first physician on record to recognize the value of exercise for a patient with “consumption.”⁷ Today, exercise is recommended as one of the first management strategies for patients newly diagnosed with type 2 diabetes and, together with diet and behavior modification, is a central component of all type 2 diabetes and obesity prevention programs.

The evidence base for the efficacy, scalability, and affordability of exercise includes multiple large randomized controlled trials; and these data were used to create the recently updated exercise guidelines for the prevention and treatment of type 2 diabetes, published by the American Diabetes Association (ADA), American College of Sports Medicine (ACSM), and other national organizations.⁸⁻¹⁰

Herein, we highlight the literature surrounding the metabolic effects and clinical outcomes in patients with type 2 diabetes following exercise intervention, and point to future directions for translational

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TABLE 1
American Diabetes Association recommendations
for exercise in type 2 diabetes

Aerobic exercise: At least 150 minutes/week of moderate to vigorous exercise

- Spread over 3 to 7 days/week, with no more than 2 consecutive days between exercise bouts
- Daily exercise is suggested to maximize insulin action
- Shorter durations (at least 75 minutes/week) of vigorous-intensity or interval training may be sufficient for younger and more physically fit patients
- May be performed continuously, or as high-intensity interval training

Resistance exercise: Progressive moderate to vigorous resistance training should be completed 2 to 3 times/week on nonconsecutive days

- At least 8 to 10 exercises, with completion of 1 to 3 sets of 10 to 15 repetitions

Flexibility and balance training are recommended 2 to 3 times/week for older adults

Participation in supervised training programs is recommended to maximize health benefits of exercise in type 2 diabetes

Data from Colberg et al.¹⁸

research in the field of exercise and diabetes.

It is known that adults who maintain a physically active lifestyle can reduce their risk of developing impaired glucose tolerance, insulin resistance, and type 2 diabetes.⁸ It has also been established that low cardiovascular fitness is a strong and independent predictor of all-cause mortality in patients with type 2 diabetes.^{11,12} Indeed, patients with diabetes are 2 to 4 times more likely than healthy individuals to suffer from cardiovascular disease, due to the metabolic complexity and underlying comorbidities of type 2 diabetes including obesity, insulin resistance, dyslipidemia, hyperglycemia, and hypertension.^{13,14}

Additionally, elevated hemoglobin A1c (HbA1c) levels are predictive of vascular complications in patients with diabetes, and regular exercise has been shown to reduce HbA1c levels, both alone and in conjunction with dietary intervention. In a meta-analysis of 9 randomized trials comprising 266 adults with type 2 diabetes, patients randomized to 20 weeks of regular exercise at 50% to 75% of their maximal

aerobic capacity (VO_{2max}) demonstrated marked improvements in HbA1c and cardiorespiratory fitness.¹¹ Importantly, larger reductions in HbA1c were observed with more intense exercise, reflecting greater improvements in blood glucose control with increasing exercise intensity.

In addition to greater energy expenditure, which aids in reversing obesity-associated type 2 diabetes, exercise also boosts insulin action through short-term effects, mainly via insulin-independent glucose transport. For example, our laboratory and others have shown that as little as 7 days of vigorous aerobic exercise training in adults with type 2 diabetes results in improved glycemic control, without any effect on body weight.^{15,16} Specifically, we observed decreased fasting plasma insulin, a 45% increase in insulin-stimulated glucose disposal, and suppressed hepatic glucose production (HGP) during carefully controlled euglycemic hyperinsulinemic clamps.¹⁵

Although the metabolic benefits of exercise are striking, the effects are short-lived and begin to fade within 48 to 96 hours.¹⁷ Therefore, an ongoing exercise program is required to maintain the favorable metabolic milieu that can be derived through exercise.

EXERCISE MODALITIES

Aerobic exercise

The vast majority of the literature about the effects of exercise on glycemic parameters in type 2 diabetes has been centered on interventions involving aerobic exercise. Aerobic exercise consists of continuous, rhythmic movement of large muscle groups, such as in walking, jogging, and cycling. The most recent ADA guidelines state that individual sessions of aerobic activity should ideally last at least 30 minutes per day and be performed 3 to 7 days of the week (Table 1).¹⁸ Moderate to vigorous (65%–90% of maximum heart rate) aerobic exercise training improves VO_{2max} and cardiac output, which are associated with substantially reduced cardiovascular and overall mortality risk in patients with type 2 diabetes.¹⁹

Notably, aerobic exercise is a well-established way to improve HbA1c, and strong evidence exists with regard to the effects of aerobic activity on weight loss and the enhanced regulation of lipid and lipoprotein metabolism.⁸ For example, in a 2007 report, 6 months of aerobic exercise training in 60 adults with type 2 diabetes led to reductions in HbA1c ($-0.63\% \pm 0.41$ vs $0.31\% \pm 0.10$, $P < .001$), fasting plasma glucose (-18.6 mg/dL ± 4.4 vs 4.28 mg/dL ± 2.57 , $P < .001$), insulin resistance (-1.52 ± 0.6 vs 0.56 ± 0.44 , $P = .023$; as measured by homeostatic model assessment),

fasting insulin (-2.91 mU/L \pm 0.4 vs 0.94 mU/L \pm 0.21 , $P = .031$), and systolic blood pressure (-6.9 mm Hg \pm 5.19 vs 1.22 mm Hg \pm 1.09 , $P = .010$) compared with the control group.¹⁴

Furthermore, meta-analyses reviewing the benefits of aerobic activity for patients with type 2 diabetes have repeatedly confirmed that compared with patients in sedentary control groups, aerobic exercise improves glycemic control, insulin sensitivity, oxidative capacity, and important related metabolic parameters.¹¹ Taken together, there is ample evidence that aerobic exercise is a tried-and-true exercise modality for managing and preventing type 2 diabetes.

Resistance training

During the last 2 decades, resistance training has gained considerable recognition as a viable exercise training option for patients with type 2 diabetes. Synonymous with strength training, resistance exercise involves movements utilizing free weights, weight machines, body weight exercises, or elastic resistance bands.

Primary outcomes in studies evaluating the effects of resistance training in type 2 diabetes have found improvements that range from 10% to 15% in strength, bone mineral density, blood pressure, lipid profiles, cardiovascular health, insulin sensitivity, and muscle mass.^{18,20} Furthermore, because of the increased prevalence of type 2 diabetes with aging, coupled with age-related decline in muscle mass, known as sarcopenia,²¹ resistance training can provide additional health benefits in older adults.

Dunstan et al²¹ reported a threefold greater reduction in HbA1c in patients with type 2 diabetes ages 60 to 80 compared with nonexercising patients in a control group. They also noted an increase in lean body mass in the resistance-training group, while those in the nonexercising control group lost lean mass after 6 months. In a shorter, 8-week circuit weight training study performed by the same research group, patients with type 2 diabetes had improved glucose and insulin responses during an oral glucose tolerance test.²²

These findings support the use of resistance training as part of a diabetes management plan. In addition, key opinion leaders advocate that the resistance-training-induced increase in skeletal muscle mass and the associated reductions in HbA1c may indicate that skeletal muscle is a “sink” for glucose; thus, the improved glycemic control in response to resistance training may be at least in part the result of enhanced muscle glycogen storage.^{21,23}

Based on increasing evidence supporting the role of resistance training in glycemic control, the ADA

and ACSM recently updated their exercise guidelines for treatment and prevention of type 2 diabetes to include resistance training.⁹

Combining aerobic and resistance training

The combination of aerobic and resistance training, as recommended by current ADA guidelines, may be the most effective exercise modality for controlling glucose and lipids in type 2 diabetes.

Cuff et al²⁴ evaluated whether a combined training program could improve insulin sensitivity beyond that of aerobic exercise alone in 28 postmenopausal women with type 2 diabetes. Indeed, 16 weeks of combined training led to significantly increased insulin-mediated glucose uptake compared with a group performing only aerobic exercise, reflecting greater insulin sensitivity.

Balducci et al²⁵ demonstrated that combined aerobic and resistance training markedly improved HbA1c (from $8.31\% \pm 1.73$ to $7.1\% \pm 1.16$, $P < .001$) compared with the control group and globally improved risk factors for cardiovascular disease, supporting the notion that combined training for patients with type 2 diabetes may have additive benefits.

Of note, Snowling and Hopkins²⁶ performed a head-to-head meta-analysis of 27 controlled trials on the metabolic effects of aerobic, resistance, and combination training in a total of 1,003 patients with diabetes. All 3 exercise modes provided favorable effects on HbA1c, fasting and postprandial glucose levels, insulin sensitivity, and fasting insulin levels, and the differences between exercise modalities were trivial.

In contrast, Schwingshackl and colleagues²⁷ performed a systematic review of 14 randomized controlled trials for the same 3 exercise modalities in 915 adults with diabetes and reported that combined training produced a significantly greater reduction in HbA1c than aerobic or resistance training alone.

Future research is necessary to quantify the additive and synergistic clinical benefits of combined exercise compared with aerobic or resistance training regimens alone; however, evidence suggests that combination exercise may be the optimal strategy for managing diabetes.

High-intensity interval training

High-intensity interval training (HIIT) has emerged as one of the fastest growing exercise programs in recent years. HIIT consists of 4 to 6 repeated, short (30-second) bouts of maximal effort interspersed with brief periods (30 to 60 seconds) of rest or active recovery. Exercise is typically performed on a stationary bike, and a single session lasts about 10 minutes.

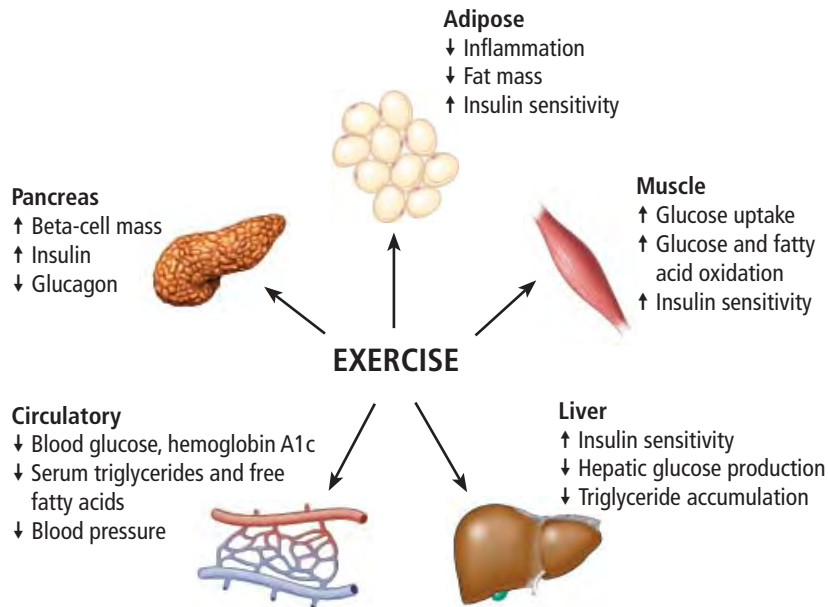


FIGURE 1. Tissue-specific metabolic effects of exercise in patients with type 2 diabetes.

HIIT increases skeletal muscle oxidative capacity, glycemic control, and insulin sensitivity in adults with type 2 diabetes.^{28,29} A recent meta-analysis that quantified the effects of HIIT programs on glucose regulation and insulin resistance reported superior effects for HIIT compared with aerobic training or no exercise as a control.²⁸ Specifically, in 50 trials with interventions lasting at least 2 weeks, participants in HIIT groups had a 0.19% decrease in HbA1c and a 1.3-kg decrease in body weight compared with control groups.

Alternative high-intensity exercise programs have also emerged in recent years such as CrossFit, which we evaluated in a group of 12 patients with type 2 diabetes. Our proof-of-concept study found that a 6-week CrossFit program reduced body fat, diastolic blood pressure, lipids, and metabolic syndrome Z-score, and increased insulin sensitivity to glucose, basal fat oxidation, VO_{2max} , and high-molecular-weight adiponectin.³⁰ HIIT appears to be another effective way to improve metabolic health; and for patients with type 2 diabetes who can tolerate HIIT, it may be a time-efficient, alternative approach to continuous aerobic exercise.

■ BENEFITS OF EXERCISE FOR SPECIFIC METABOLIC TISSUES

Within 5 years of the discovery of insulin by Banting and Best in 1921, the first report of exercise-induced improvements in insulin action was published, though the specific cellular and molecular mecha-

nisms that underpin these effects remain unknown.³¹

There is general agreement that the acute or short-term exercise effects are the result of insulin-dependent and insulin-independent mechanisms, while longer-term effects also involve “organ crosstalk,” such as from skeletal muscle to adipose tissue, the liver, and the pancreas, all of which mediate favorable systemic effects on HbA1c, blood glucose levels, blood pressure, and serum lipid profiles (**Figure 1**).

Skeletal muscle

Following a meal, skeletal muscle is the primary site for glucose disposal and uptake. Peripheral insulin resistance originating in skeletal muscle is a major driver for the development and progression of type 2 diabetes.

Exercise enhances skeletal muscle glucose uptake using both insulin-dependent and insulin-independent mechanisms, and regular exercise results in sustained improvements in insulin sensitivity and glucose disposal.³²

Of note, acute bouts of exercise can also temporarily enhance glucose uptake by the skeletal muscle up to fivefold via increased (insulin-independent) glucose transport.³³ As this transient effect fades, it is replaced by increased insulin sensitivity, and over time, these 2 adaptations to exercise result in improvements in both the insulin responsiveness and insulin sensitivity of skeletal muscle.³⁴

The fuel-sensing enzyme adenosine monophosphate-activated protein kinase (AMPK) is the major insulin-independent regulator of glucose uptake, and its activation in skeletal muscle by exercise induces glucose transport, lipid and protein synthesis, and nutrient metabolism.³⁵ AMPK remains transiently activated after exercise and regulates several downstream targets involved in mitochondrial biogenesis and function and oxidative capacity.³⁶

In this regard, aerobic training has been shown to increase skeletal muscle mitochondrial content and oxidative enzymes, resulting in dramatic improvements in glucose and fatty acid oxidation¹⁰ and increased expression of proteins involved in insulin signaling.³⁷

Adipose tissue

Exercise confers numerous positive effects in adipose tissue, namely, reduced fat mass, enhanced insulin

sensitivity, and decreased inflammation. Chronic low-grade inflammation has been integrally linked to type 2 diabetes and increases the risk of cardiovascular disease.³⁸

Several inflammatory adipokines have emerged as novel predictors for the development of atherosclerosis,³⁹ and fat-cell enlargement from excessive caloric intake leads to increased production of pro-inflammatory cytokines, altered adipokine secretion, increased circulating fatty acids, and lipotoxicity concomitant with insulin resistance.⁴⁰

It has been suggested that exercise may suppress cytokine production through reduced inflammatory cell infiltration and improved adipocyte function.⁴¹ Levels of the key pro-inflammatory marker C-reactive protein is markedly reduced by exercise,^{14,42} and normalization of adipokine signaling and related cytokine secretion has been validated for multiple exercise modalities.⁴²

Moreover, Ibañez et al⁴³ demonstrated that in addition to significant improvements in insulin sensitivity, resistance exercise training reduced visceral and subcutaneous fat mass in patients with type 2 diabetes.

Liver

The liver regulates fasting glucose through gluconeogenesis and glycogen storage. The liver is also the primary site of action for pancreatic hormones during the transition from pre- to postprandial states.

As with skeletal muscle and adipose tissue, insulin resistance is also present within the liver in patients with type 2 diabetes. Specifically, impaired suppression of HGP by insulin is a hallmark of type 2 diabetes, leading to sustained hyperglycemia.⁴⁴

Approaches using fasting measures of glucose and insulin do not distinguish between peripheral and hepatic insulin resistance.⁴⁵ Instead, hepatic insulin sensitivity and HGP are best assessed by the hyperinsulinemic-euglycemic clamp technique, along with isotopic glucose tracers.¹⁵

Although more elaborate, magnetic resonance spectroscopy may also be used to assess intrahepatic lipid content, as its accumulation has been shown to drive hepatic insulin resistance.⁴⁶ Indirect measures of hepatic dysfunction may be made from increased levels of the circulating hepatic enzymes alkaline phosphatase, alanine transaminase, and aspartate transaminase.¹⁶

From an exercise perspective, we have shown that 7 days of aerobic training, in the absence of weight loss, improves hepatic insulin sensitivity.¹⁵ It has also been shown that hepatic AMPK is stimulated during

exercise, suggesting that an AMPK-induced adaptive response to exercise may facilitate improved suppression of HGP.⁴⁷ We have also shown that a longer 12-week aerobic exercise intervention reduces hepatic insulin resistance, with and without restricted caloric intake.⁴⁸ Further, HGP correlated with reduced visceral fat, suggesting that this fat depot may play an important mechanistic role in improved hepatic function.

Pancreas

Insulin resistance in adipose tissue, muscle, or the liver places greater demand on insulin secretion from pancreatic beta cells. For many, this hypersecretory state is unsustainable, and the subsequent loss of beta-cell function marks the onset of type 2 diabetes.⁴⁹ Fasting plasma glucose, insulin, and glucagon levels are generally poor indicators of beta-cell function.

Clinical research studies typically use the oral glucose tolerance test and hyperglycemic clamp technique to more accurately measure the dynamic regulation of glucose homeostasis by the pancreas.⁵⁰ However, few studies have examined the effects of exercise on beta-cell function in type 2 diabetes.

Dela and colleagues⁵¹ showed that 3 months of aerobic training improved beta-cell function in type 2 diabetes, but only in those who had some residual function and were less severely diabetic. We have shown that a 12-week aerobic exercise intervention improves beta-cell function in older obese adults and in patients with type 2 diabetes.^{52,53} We have also found that improvements in glycemic control that occur with exercise are better predicted by changes in insulin secretion as opposed to peripheral insulin sensitivity.⁵⁴ It has also been shown that a relatively short (8-week) HIIT program improved beta-cell function in patients with type 2 diabetes.⁵⁵ And we recently found that a 6-week CrossFit training program improved beta-cell function in adults with type 2 diabetes.³⁰

■ SUMMARY, CONCLUSIONS, AND FUTURE DIRECTIONS

Regular exercise produces health benefits beyond improvements in cardiovascular fitness. These include enhanced glycemic control, insulin signaling, and blood lipids, as well as reduced low-grade inflammation, improved vascular function, and weight loss.

Both aerobic and resistance training programs promote healthier skeletal muscle, adipose tissue, liver, and pancreatic function.¹⁸ Greater whole-body insulin sensitivity is seen immediately after exercise

and persists for up to 96 hours. While a discrete bout of exercise provides substantial metabolic benefits in diabetic cohorts, maintenance of glucose control and insulin sensitivity are maximized by physiologic adaptations that only occur with weeks, months, and years of exercise training.^{15,33}

Exercise intensity,¹¹ volume, and frequency⁵⁶ are associated with reductions in HbA1c; however, a consensus has not been reached on whether one is a better determinant than the other.

The most important consideration when recommending exercise to patients with type 2 diabetes is that the intensity and volume be optimized for the greatest metabolic benefit while avoiding injury or cardiovascular risk. In general, the risk of exercise-induced adverse events is low, even in adults with type 2 diabetes, and there is no current evidence that screening procedures beyond usual diabetes care are needed to safely prescribe exercise in asymptomatic patients in this population.¹⁸

Future clinical research in this area will provide a broader appreciation for the interactions (positive and negative) between exercise and diabetes medications, the synergy between exercise and bariatric surgery, and the potential to use exercise to reduce the health burden of diabetes complications, including nephropathy, retinopathy, neuropathy, and peripheral arterial disease.

Moreover, basic research will likely identify the detailed molecular defects that contribute to diabetes in insulin-targeted tissues. The emerging science surrounding cytokines, adipokines, myokines, and, most recently, exerkines is likely to deepen our understanding of the mechanistic links between exercise and diabetes management.

Finally, although we have ample evidence that exercise is an effective, scalable, and affordable approach to prevent and manage type 2 diabetes, we still need to overcome the challenge of discovering how to make exercise sustainable for patients.

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Optimizing diabetes treatment in the presence of obesity

■ ABSTRACT

Evidence of a neurophysiologic mechanism that involves hormones from adipocytes, pancreatic islet cells, and the gastrointestinal tract implicated in both obesity and diabetes has led to a search for drugs that not only either target obesity and diabetes or reduce hemoglobin A1c, but also have weight loss as a potential side effect. The authors review medications approved for the treatment of type 2 diabetes mellitus (including pramlintide, also approved for type 1 diabetes) that also have weight loss as a side effect. Drugs discussed include glucagon-like peptide-1 (GLP-1) receptor agonists, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, neuroendocrine peptide hormones, alpha-glucosidase inhibitors, and metformin. Where appropriate, the authors comment on the cardiovascular effects of these drugs.

■ KEY POINTS

The rationale for GLP-1 receptor agonists is that peripheral GLP-1 activates a cascade of centrally mediated signals that ultimately result in secretion of insulin by the pancreas and slowing of gastrointestinal motility. It also exerts an anorexic effect by acting on central pathways that mediate satiation.

SGLT-2 inhibitors have relatively weak glycemic efficacy. Inhibition of SGLT-2 alleviates hyperglycemia by decreasing glucose reabsorption in the kidneys and by increasing excretion in the urine, suggesting urinary loss of glucose (and hence caloric loss). This is thought to contribute to weight reduction in addition to initial weight loss from fluid loss due to osmotic diuresis.

Meta-analyses so far have shown that alpha-glucosidase inhibitors have either a neutral or a beneficial effect on body weight.

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D iabetes was a term coined by Sims et al¹ in the 1970s to describe diabetes occurring in the setting of obesity. Today, the link between type 2 diabetes mellitus (DM), obesity, and insulin resistance is well recognized, and 80% of people with type 2 DM are overweight or obese.^{2,3} Unfortunately, weight gain is a known side effect of most agents used to treat type 2 DM (eg, insulin, sulfonylureas, thiazolidinediones), and this often leads to nonadherence, poor glycemic control, and further weight gain.

During the past several years, evidence has emerged of a neurophysiologic mechanism that involves hormones from adipocytes, pancreatic islet cells, and the gastrointestinal tract implicated in both obesity and diabetes.² This has led to research for drugs that not only either target obesity and diabetes or reduce hemoglobin A1c (HbA1c), but also have weight loss as a potential side effect.

In this paper, we review medications approved for the treatment of type 2 DM (including pramlintide, also approved for type 1 DM) that also have weight loss as a side effect. Drugs we will discuss include glucagon-like peptide-1 (GLP-1) receptor agonists, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, neuroendocrine peptide hormones, alpha-glucosidase inhibitors, and metformin. Where appropriate, we also comment on the effects of the drugs on cardiovascular outcomes.

■ GLP-1 RECEPTOR AGONISTS

Mechanism of action

GLP-1 is a hormone produced from the proglucagon gene in the alpha cells of the pancreas, in the L cells of intestinal mucosa (predominantly in the ileum and distal colon), and in structures of the nervous system including the brainstem, hypothalamus, and vagal afferent nerves.⁴ Food in the gastrointestinal tract, especially if high in fats and carbohydrates, stimulates secretion of GLP-1 in the L cells, which in turn amplifies insulin secretion in a glucose-dependent

manner (the incretin effect).⁴ Glucagon secretion is inhibited by GLP-1 during times of hyperglycemia but not hypoglycemia, thereby preventing inappropriately high levels of the hormone.⁵ Peripheral GLP-1 activates a cascade of centrally mediated signals that ultimately result in secretion of insulin by the pancreas and slowing of gastrointestinal motility.⁵ Lastly, GLP-1 exerts an anorexic effect by acting on central pathways that mediate satiation.⁶

Recent studies suggest that GLP-1 receptor agonist drugs have proliferative, anti-apoptotic, and differentiation effects on pancreatic beta cells, thereby leading to improved glycemic control.⁷ Table 1 summarizes the sites of action and physiologic effects of GLP-1.⁷

Bioactive forms of GLP-1 are rapidly degraded in the circulation by the dipeptidyl peptidase-4 enzyme. GLP-1 receptor agonists have slightly altered molecular structure and longer duration of action than native GLP-1. Short-acting GLP-1 agonists (eg, exenatide, lixisenatide) have more effect on gastric emptying and lower postprandial blood glucose levels, whereas long-acting GLP-1 agonists (eg, liraglutide, albiglutide, dulaglutide, semaglutide, exenatide) have a greater effect on fasting glucose levels.⁴

Effects on HbA1c and weight loss

As a class, GLP-1 receptor agonists have been proven to cause significant reduction in HbA1c levels. In a meta-analysis of 17 randomized controlled trials involving patients with type 2 DM with suboptimal control on 1 or 2 oral agents, GLP-1 agonists decreased HbA1c levels by 1% (treatment difference 0.5% to 1.6%) compared with placebo.⁸ HbA1c reductions from each GLP-1 agonist along with dosing, administration, and weight loss benefit are shown in Table 2.⁹⁻¹⁴

Of the current GLP-1 agonists, exenatide and liraglutide have been on the market the longest, thus studied more in terms of weight reduction.

Exenatide. Exenatide BID was the first GLP-1 agonist, approved by the US Food and Drug Administration (FDA) in 2005 for the treatment of type 2 DM. In a 30-week triple-blind, placebo-controlled study of 336 patients already on background therapy with metformin, progressive weight loss was noted with exenatide 5 μ g (-1.6 ± 0.4 kg) and exenatide 10 μ g

TABLE 1
Sites of action and physiologic effects of glucagon-like peptide-1

Site of action	Physiologic effects	Remarks
Pancreas	Stimulates insulin secretion Inhibits glucagon secretion	These actions are glucose-dependent
Vagal afferent neurons	Slows gastric emptying Decreases gastric acid secretion Stimulates pancreatic insulin secretion	Effects mediated via vagal signaling to the gastrointestinal tract and the pancreas
Central nervous system	Suppresses appetite and reduces food intake	Satiety and reward centers of the brain

Based on data from lepsen et al.⁷

(-2.8 ± 0.5 kg) compared with placebo (-0.3 ± 0.3 kg; $P < .001$).¹⁵ A meta-analysis of 14 trials with 2,583 patients showed significant weight reduction with both exenatide 5 μ g twice daily (a difference of -0.56 kg, 95% confidence interval [CI] -1.07 to -0.06 , $P = .0002$) in 8 trials and exenatide 10 μ g twice daily (a difference of -1.24 kg, 95% CI -1.69 to -0.78 , $P < .001$) in 12 trials, after treatment for more than 16 weeks.¹⁶

Liraglutide. Liraglutide has a longer half-life than exenatide and is administered once daily. It is not a first-line therapy for type 2 DM and is recommended as an add-on. Approved daily doses for type 2 DM are 1.2 mg and 1.8 mg.

Multiple studies of glycemic control and weight loss with liraglutide have been conducted since its introduction to the US market in 2010. In the Liraglutide Effect and Action in Diabetes (LEAD) series of trials, liraglutide use as monotherapy or in combination with oral agents was associated with significant dose-dependent weight loss.¹⁷ Liraglutide monotherapy (at 1.2 mg and 1.8 mg) compared with glimepiride in the LEAD-3 trial led to significant weight reduction (2.1 kg and 2.5 kg, respectively, $P < .001$) after 16 weeks, and was sustained up to 52 weeks.¹⁸ Addition of liraglutide (at 1.2 mg and 1.8 mg) to metformin plus rosiglitazone resulted in significant weight loss (1.02 kg and 2.02 kg, respectively) whereas the addition of placebo caused a 0.6-kg weight gain ($P < .001$).¹⁹ The SCALE study randomized 846 adults with type 2 DM who were overweight to obese (body mass index [BMI] ≥ 27 kg/m²), were taking 0 to 3 oral antihyperglycemic agents (metformin, thiazolidinedione, and a sulfonylurea), and had stable body weight and an HbA1c of 7% to 10% to liraglutide 1.8 mg, liraglutide

TABLE 2
Currently approved glucagon-like peptide-1 receptor agonists for diabetes mellitus

Generic name (Brand name)	Administration ^a	Dose	Hemoglobin A1c reduction (%)	Weight change (kg)
Exenatide BID (Byetta) ⁹	Within 60 minutes before breakfast and dinner	5 µg BID	0.5 to 0.7	-1.1 to -2.7
		10 µg BID	0.7 to -1.7	-1.5 to -2.9
Liraglutide (Victoza) ¹⁰	Once daily at any time of day	0.6 mg QD		
		1.2 mg QD	0.8 to 1.1	+0.3 to -2.6
		1.8 mg QD	0.5 to 1.5	-0.2 to -2.8
Exenatide QW (Bydureon) ¹¹	Once every 7 days at any time of day	2 mg QW	1.3 to 1.6	-2.0 to -2.7
Albiglutide (Tanzeum) ¹²	Once every 7 days at any time of day	30 mg QW	0.7 to 0.8	-0.4 to -1.2
		50 mg QW	0.6 to 0.9	
Dulaglutide (Trulicity) ¹³	Once weekly at any time of day	0.75 mg QW	0.7 to 1.6	+0.2 to -2.8
		1.5 mg QW	0.8 to 1.6	-0.9 to -3.1
Lixisenatide (Adlyxin) ¹⁴	Within 60 minutes before main meal	10 µg QD	0.6 to 0.9	+0.31 to -2.7
		20 µg QD		

^a All drugs administered by subcutaneous injection.

BID = twice daily; QD = once daily; QW = once every 7 days

Data based on package inserts.⁹⁻¹⁴

3.0 mg, or placebo. Mean weight loss after 56 weeks was 6.0% (6.4 kg) with liraglutide 1.8 mg, 4.7% (5.0 kg) with liraglutide 3.0 mg, and 2.0% (2.2 kg) with placebo.²⁰

In 2016, high-dose once-daily liraglutide 3.0 mg (Saxenda) was approved by the FDA for weight loss. In a double-blind randomized trial of liraglutide 3.0 mg vs placebo in patients who had a BMI of at least 30 or who had a BMI of at least 27 plus treated or untreated dyslipidemia or hypertension, Pi-Sunyer et al²¹ reported a mean weight reduction of 8.4 ± 7.3 kg with liraglutide vs 2.8 ± 6.5 kg with placebo (a difference of -5.6 kg, 95% CI -6.0 to -5.1, *P* < .001) after 56 weeks. Furthermore, 63.2% of patients in the liraglutide group lost at least 5% of body weight vs 27.1% with placebo, and 33.1% in the liraglutide group lost 10% or more of body weight vs 10.6% in the placebo group (*P* < .001).²¹ Of note, liraglutide 3.0 mg is not indicated for type 2 DM per se.

In a 2012 meta-analysis of randomized controlled trials of adults with and without type 2 DM, with a BMI of 25 or greater, and who received GLP-1 receptor agonists at clinically relevant doses (exenatide ≥ 10 µg/day, exenatide ≥ 2 mg/week, or liraglutide ≥ 1.2 mg/day), those taking GLP-1 receptor agonists had more weight loss than those on a control intervention (oral antihyperglycemic, insulin, or placebo) at a

minimum of 20 weeks, with a weighted mean difference -2.9 kg (95% CI -3.6 to -2.2) in 21 trials and 6,411 participants.²²

GLP-1 agonists currently being investigated for obesity treatment are lixisenatide, albiglutide, taspoglutide, and oxyntomodulin.²³

Cardiovascular outcomes

The presence of GLP-1 receptors in blood vessels and myocardium has led to the hypothesis that GLP-1 receptor agonists can improve cardiovascular disease outcomes.²⁴ In the pivotal Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, 9,340 patients with type 2 DM and increased cardiovascular disease risk were randomized to liraglutide vs placebo.²⁵ The hazard ratio (HR) for time to the primary end point of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke was 0.87 (*P* = .01 for superiority, *P* < .001 for noninferiority) for liraglutide compared with placebo after 3.8 years. The incidence of death from any cause or cardiovascular cause was also lower with liraglutide.²⁵

Adverse effects

Tolerable transient nausea and vomiting are reported adverse effects; these symptoms occur early in therapy, usually resolve in 4 to 8 weeks, and appear to

be associated with greater weight loss.²⁶ Although no causal relationship between GLP-1 receptor agonist use and pancreatitis or pancreatic cancer has been established to date, several cases of acute pancreatitis have been reported.²⁵ Alternative therapies should be considered in patients with a history of or risk factors for pancreatitis.

Combined with insulin

A product that combines insulin glargine and lixisenatide (Soliqua) is FDA-approved for patients with type 2 DM. In a 30-week randomized controlled trial of the combination product vs insulin glargine alone in patients with type 2 DM not controlled on basal insulin with or without up to 2 oral agents, the combination product resulted in an HbA1c reduction from baseline of 1.1% vs 0.6% for insulin glargine alone ($P < .001$).²⁷ Mean body weight decreased by 0.7 kg with the combination product and increased by 0.7 kg with insulin glargine ($P < .001$).²⁷ In a 24-week study of a lixisenatide-insulin glargine combination vs insulin glargine in insulin-naïve patients taking metformin, there was a reduction in HbA1c of about -1.7% from baseline in both groups, while the combination group had a 1-kg weight reduction compared with a 0.5-kg weight increase in the insulin glargine group ($P < .001$).²⁸

■ SGLT-2 INHIBITORS

Mechanism of action

In a healthy normoglycemic person, about 180 g of glucose per day is filtered into the glomerular filtrate and reabsorbed into the circulation.²⁹ SGLT-2 facilitates the reabsorption of glucose in the proximal convoluted tubule of the kidneys. Approximately 90% of glucose reabsorption is mediated by SGLT-2 found in the S1 and S2 segments of the proximal convoluted tubule, and the remaining 10% by SGLT-1 in the S3 segment. At serum glucose levels above 180 g, the reabsorptive capacity of the nephron is overwhelmed, resulting in glycosuria.³⁰ SGLT-2 expression is also increased in patients with diabetes, thus leading to increased glucose reabsorption into the circulation, further contributing to hyperglycemia.³⁰ Inhibition of SGLT-2 alleviates hyperglycemia by decreasing glucose reabsorption (30% to 50% of filtered glucose) in the kidneys and by increasing excretion (50 mg to 80 mg of glucose) in the urine.³¹ SGLT-2 inhibitors currently FDA-approved are canagliflozin (Invokana), dapagliflozin (Farxiga), and empagliflozin (Jardiance).

HbA1c

SGLT-2 inhibitors have relatively weak glycemic efficacy. A meta-analysis of SGLT-2 inhibitors vs other antidiabetic medications or placebo found that SGLT-2 inhibitors appeared to have a “favorable effect” on HbA1c, with a mean difference vs placebo of -0.66% (95% CI -0.73% to -0.58%) and a mean difference vs other antihyperglycemic medications of -0.06% (95% CI 0.18% to 0.05%).³²

Weight loss

The same meta-analysis found that SGLT-2 inhibitors reduced body weight (mean difference -1.8 kg, 95% CI -3.50 kg to -0.11 kg).³² And in a randomized controlled trial, monotherapy with canagliflozin 100 mg/day and 300 mg/day resulted in body weight reduction of 2.2% (1.9 kg) and 3.3% (-2.9 kg), respectively, after 26 weeks.³³ A Japanese study showed a dose-related total body weight loss with empagliflozin vs placebo ranging from 2.5 ± 0.2 kg (5-mg dose) to 3.1 ± 0.2 kg (50-mg dose) after 12 weeks.³⁴ Bolinder et al³⁵ reported that adding dapagliflozin 10 mg to metformin in patients with type 2 DM reduced total body weight by -2.96 kg (95% CI -3.51 to -2.41 , $P < .001$) at week 24. Whole-body dual-energy x-ray absorptiometry and magnetic resonance imaging findings in this study revealed a decrease in fat mass and visceral and subcutaneous adipose tissue after treatment with dapagliflozin, thus suggesting urinary loss of glucose (and hence caloric loss) contributing to weight reduction in addition to initial weight loss from fluid loss due to osmotic diuresis.³⁵ A continuous decline in total body weight was observed in a 78-week extension study resulting in -4.54 kg (95% CI -5.43 to -3.66 kg) at week 102, along with further reduction in total body fat mass as measured by dual-energy x-ray absorptiometry.³⁶

Cardiovascular outcomes

The landmark study Empagliflozin, Cardiovascular Outcomes and Mortality in Type 2 Diabetes (EMPA-REG) involving 7,020 patients was the first large cardiovascular outcomes trial in patients with type 2 DM and overt cardiovascular disease. A relative risk reduction of 14% (12.1% to 10.5%, HR 0.86, 95% CI 0.74 to 0.99) in major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) was observed with empagliflozin.³⁷ Rates of all-cause mortality and hospitalization for heart failure relative risk reductions were 32% (8.3% to 5.7%; HR 0.68 [0.57, 0.8]) and 35% (4.1% to 2.7%; HR 0.65 [0.50, 0.85]), respectively, with empagliflozin. The mechanism behind this cardiovascular benefit is unknown but is currently being explored.³⁷

Adverse effects

Increased risk of urinary tract and genital infections are known adverse effects of SGLT-2s. Other effects noted include postural hypotension from volume depletion and a transient increase in serum creatinine and decrease in glomerular filtration.²⁹

■ NEUROENDOCRINE PEPTIDE HORMONE: AMYLIN ANALOGUES

Mechanism of action

Amylin is a 37-amino-acid neuroendocrine peptide hormone secreted primarily by pancreatic beta cells. It promotes early satiety, and its anorexigenic effects are mediated by its action on the neurons of the area postrema in the brain.³⁸ After a meal, amylin decreases gastric acid secretion and slows gastric emptying. It is co-secreted with insulin in a 1:20 amylin-to-insulin ratio and inhibits glucagon secretion via a centrally mediated mechanism.³⁹

Pramlintide (Symlin) is an amylin analogue administered subcutaneously immediately before major meals. It decreases postprandial glucose levels and has been approved by the FDA as an adjunct to prandial insulin in patients with type 1 and type 2 DM.⁴⁰

HbA1c

Amylin secretion is impaired in type 1 and type 2 DM, and small but significant reductions in HbA1c have been observed with addition of pramlintide to usual insulin regimens. In patients with type 1 DM, HbA1c levels were reduced by 0.4% to 0.6% after 26 weeks on 30 µg 3 times daily to 60 µg 4 times daily of pramlintide added to insulin.^{41,42} And pramlintide 120 µg added to usual antihyperglycemic therapy in patients with type 2 DM has been reported to decrease HbA1c by 0.7% at week 16 or 26.^{43,44}

Weight loss

A meta-analysis of 8 randomized controlled trials assessed the effects of pramlintide on glycemic control and weight in patients with type 2 DM treated with insulin and in obese patients without diabetes.⁴⁵ In these trials, patients took at least 120 µg of pramlintide before 2 to 3 meals for at least 12 weeks; a total of 1,616 participants were included. In the type 2 DM group, pramlintide reduced body weight by 2.57 kg (95% CI -3.44 to -1.70 kg, $P < .001$) vs control, over 16 to 52 weeks.⁴⁵ The nondiabetic obese group had a weight loss of -2.27 kg (95%CI -2.88 to -1.66 kg, $P < .001$) vs control.⁴⁵

Pramlintide and a pramlintide-phentermine combination are currently under investigation for treatment of obesity.²³

Cardiovascular outcomes

Cardiovascular outcomes in patients treated with pramlintide have not been studied to date, but reductions have been observed in markers of cardiovascular risk including high-sensitivity C-reactive protein and triglycerides.⁴⁶

Adverse effects

Transient mild-to-moderate nausea is the most common adverse effect of pramlintide. Hypoglycemia has also been reported, more frequently in patients with type 1 DM, which is possibly associated with inadequate reduction in insulin.

■ ALPHA-GLUCOSIDASE INHIBITORS

Mechanism of action

Alpha-glucosidase inhibitors competitively inhibit the alpha-glucosidase enzymes at the brush border of the small intestine. Taken orally before meals, these drugs mitigate postprandial hyperglycemia by preventing the breakdown of complex carbohydrates into simpler monosaccharides, thus delaying their absorption.⁴⁷ These agents may be used as monotherapy or in combination with other antihyperglycemic agents. They work independently from insulin, although they have been shown to potentiate GLP-1 secretion.⁴⁸ Acarbose and miglitol are currently approved in the United States. Acarbose has been more extensively studied worldwide.

HbA1c

Alpha-glucosidase inhibitors have been reported to reduce mean HbA1c by 0.8% (95% CI -0.9% to -0.7%), as well as fasting and postprandial glucose, and postprandial insulin levels.⁴⁹

Weight loss

There is conflicting evidence on whether alpha-glucosidase inhibitor therapy has a neutral or beneficial effect on body weight. A Cochrane meta-analysis observed significant BMI reduction with acarbose, although no effect on body weight was noted,⁴⁹ whereas in another meta-analysis, body weight was significantly reduced by 0.96 kg (95% CI -1.80 to -0.12 kg) when acarbose was added to metformin.⁵⁰ A review of pooled data from worldwide post-marketing studies for acarbose reported a weight reduction after 3 months of 0.98 ± 2.11 kg in overweight patients and 1.67 ± 3.02 kg in obese patients.⁵¹

Cardiovascular outcomes

In the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM), when compared with

placebo, treatment of patients with impaired glucose tolerance with acarbose significantly reduced the incidence of cardiovascular events (HR 0.51, 95% CI 0.28 to 0.95, $P = .03$), myocardial infarction (HR 0.09, 95% CI 0.01 to 0.72, $P = .02$), and newly diagnosed hypertension (HR 0.66, 95% CI 0.49 to 0.89, $P = .006$).⁵²

Adverse effects

Although mild, gastrointestinal effects of flatulence and diarrhea can be bothersome and result in discontinuation of the drug in most patients.

METFORMIN

Mechanism of action

Metformin is the first-line antihyperglycemic agent for type 2 DM recommended by the American Diabetes Association and European Association for the Study of Diabetes.^{53,54} The main action of metformin is to decrease glucose production in the liver. In the small intestine, metformin stimulates the L cells to produce GLP-1, and in skeletal muscle, it increases glucose uptake and disposal.⁵⁵

HbA1c

As monotherapy, metformin has resulted in HbA1c reductions of 0.88% to 1.2%.⁵⁵

Weight loss

Reduced food intake^{56,57} and gastrointestinal intolerance⁵⁸ occurring early in therapy have been noted to account for weight loss in short-term studies of non-diabetic obese patients treated with metformin.⁵⁹ Long-term trials of patients with and without diabetes have yielded mixed results on weight reduction from metformin as monotherapy or adjunct therapy. In the United Kingdom Prospective Diabetes Study (UKPDS), metformin had resulted in approximately 1.5 kg of weight gain (slightly less than the 4-kg weight gain in the glibenclamide group).⁶⁰ Improved antihyperglycemic efficacy of other antihyperglycemic agents (insulin, sulfonylureas, and thiazolidinediones) with addition of metformin led to dose-lowering of the antihyperglycemic agents, ultimately resulting in amelioration of weight gain; this has also led to small weight reductions in some studies.⁵⁹ In the Diabetes Prevention Program study of patients with impaired glucose tolerance, metformin treatment resulted in an average weight loss of 2.1 kg compared with placebo (−0.1 kg) and lifestyle intervention (−5.6 kg; $P < .001$).⁶¹

Cardiovascular outcomes

Metformin has been observed to decrease micro- and macrovascular complications. Compared with diet

alone, metformin was associated with a 39% reduction in the risk of myocardial infarction, and a 30% lower risk of a composite of macrovascular diseases (myocardial infarction, sudden death, angina, stroke, and peripheral disease).⁶⁰

Adverse effects

The most common adverse effect of metformin is gastrointestinal intolerance from abdominal pain, flatulence, and diarrhea.⁶² Metformin-associated lactic acidosis is a serious and potentially life-threatening effect; and vitamin B₁₂ deficiency may occur with long-term treatment.⁶²

TAKE-HOME POINTS

As more medications and interventions are being developed to counter obesity, it also makes sense to select diabetes medications that do not contribute to weight gain in patients who are already overweight or obese. The effects of available medications can be maximized and treatment regimens individualized (based on patients' needs and preferences, within the limitations of drug costs and side effects), along with lifestyle modification, to target diabetes.

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Antiobesity drugs in the management of type 2 diabetes: A shift in thinking?

■ ABSTRACT

Antiobesity medications can improve metabolic control for patients with type 2 diabetes mellitus (DM) and obesity, but are underutilized. In this review, we describe the role of antiobesity drugs in the context of medically supervised and comprehensive weight-loss interventions and propose a pragmatic therapeutic algorithm for patients with type 2 DM and obesity that incorporates the use of antiobesity drugs early in the course of management.

■ KEY POINTS

Obesity contributes to type 2 DM and worsens its control. Yet insulin therapy and most first-line diabetes drugs cause weight gain as a side effect.

We believe that physicians should include body weight along with blood glucose levels as targets of therapy in patients with type 2 DM.

Several drugs are approved for weight loss, and although their effect on weight tends to be moderate, some have been shown to reduce the incidence of type 2 DM and improve diabetic control.

A stepwise approach to managing type 2 DM and obesity starts with lifestyle interventions and advances to adding (1) metformin, (2) a glucagon-like peptide-1 receptor agonist or a sodium-glucose cotransporter-2 inhibitor, and (3) one of the approved weight-loss drugs.

Obesity is a leading public health concern, affecting nearly 60 million adult Americans.¹ It is a major risk factor for the development of insulin resistance and type 2 diabetes mellitus (DM).² More than 90% of patients with type 2 DM have obesity, and obesity is a major obstacle to achieving long-term glycemic control.³

Clinical studies have demonstrated that a 6- to 7-kg increase in body weight increases the risk of developing type 2 DM by 50%, while a 5-kg loss reduces the risk by a similar amount.⁴ As a result, most patients who have a body mass index greater than 40 kg/m² suffer from type 2 DM.⁵ Strong evidence exists that bariatric surgery and its resulting weight loss has positive effects on fasting blood sugar, hemoglobin A1c (HbA1c), lipid profiles, and other metabolic variables.⁶

When combined, obesity and type 2 DM carry a significant burden of micro- and macrovascular complications such as retinopathy, nephropathy, neuropathy, and cardiovascular disease. As a result, a high prevalence of morbidity and mortality is seen among patients with obesity and type 2 DM; those between the ages of 51 and 61 have a 7-times higher mortality rate compared with nonobese normoglycemic people, and patients with diabetes alone have a 2.6-times higher mortality rate.⁷

■ A DILEMMA IN THE CLINIC: FOCUS ON THE SUGAR OR THE WEIGHT?

Although type 2 DM and obesity go hand in hand, clinicians tend to focus on the sugar and neglect the weight, concentrating their efforts on improving blood glucose indices, and prescribing in many instances medications that cause weight gain. As a result, we are faced with a rising epidemic of obesity, perpetuating a preexisting epidemic of diabetes.

An optimal, comprehensive approach to managing patients with type 2 DM should encompass both the control of dysglycemia and its associated comorbidities, obesity being the key player.⁸ However, clinical

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practice is often misaligned with the evidence. For instance, many of our first-line oral treatments for type 2 DM (except for metformin) are associated with weight gain.⁹ With time, control of glycemia becomes more and more ineffective, at which point therapy is intensified with insulin, further exacerbating the weight gain.¹⁰

Therefore, it seems counterintuitive to treat a disease for which obesity is one of the main risk factors with medications that promote weight gain. Yet healthcare providers are faced with a therapeutic dilemma: should they focus their efforts on improving patients' glycemic control, or should they invest in helping these patients lose weight? Although an ideal approach would incorporate both aspects, the reality is that it is far from practical.

A few issues impinge on integrating weight loss in the care of type 2 DM. Although the American Medical Association recognized obesity as a disease in 2013,¹¹ some providers still perceive obesity as a self-inflicted condition that is due to bad lifestyle and behavior.¹¹ Many clinicians may also have low expectations for patients' success, and often lack the time and knowledge to intervene regarding nutrition, physical activity, and psychological issues pertinent to the management of obesity in type 2 DM. Therefore, in many cases, it seems less complicated and more rewarding for both patients and physicians to concentrate on improving the HbA1c value rather than investing efforts in weight loss. For diabetic patients with obesity, this could mean that clinicians may prescribe glucose-lowering therapies, such as insulin and sulfonylureas, at the expense of weight gain. Additionally, clinicians often experience the need to provide recommendations more aligned with metrics that dictate reimbursement (eg, HbA1c targets) within healthcare systems that still raise concerns regarding obesity visit reimbursements.

Lastly, the lack of trustworthy or pertinent evidence (lack of comparative effectiveness research) for antiobesity medications may limit their use in daily practice. Physicians have had little confidence in the efficacy of antiobesity drugs, and often raise significant safety concerns, especially after witnessing important fiascos in this field, eg, dexfenfluramine, rimonabant, and sibutramine.^{2,12,13}

As a result, many of our patients with obesity and type 2 DM may not consider the need for weight loss, and may not even be aware that type 2 DM is caused by obesity and physical inactivity in the first place. Others have accumulated a significant degree of frus-

tration, and have "thrown in the towel" already after unsuccessful weight-loss efforts, many of which were not medically supervised.

For all of the above reasons, both clinicians and patients often concentrate their efforts on treating blood glucose numbers rather than the "obesity-diabetes" as a whole.¹⁴ And as a result, our practices are slowly filling up with patients with obesity and type 2 DM who are treated primarily with insulin, resulting in a progressive (and untreated) obesity and diabetes epidemic.

■ DRUGS FOR TREATING OBESITY AND TYPE 2 DM

Because the body strongly defends its fat cells, the common advice to simply "eat less, move more" cannot be expected to bring about meaningful and lasting weight reduction or control of HbA1c. However, weight-loss drugs (**Table 1**),¹⁵ used in conjunction with an interdisciplinary lifestyle intervention program, may provide more success regarding both issues. Here we discuss a few pharmacologic therapies approved for the management of obesity in the context of type 2 DM, and vice versa. Taking into account that dosages of these medications should be individualized to achieve a weight-loss goal with the lowest effective dose possible.

Orlistat

Orlistat (Xenical) is the only weight-loss drug approved by the US Food and Drug Administration (FDA) that acts outside the brain. It inhibits pancreatic lipases, resulting in up to 30% less fat absorption in the gut. Orlistat has been approved for long-term use by the FDA.

Benefits. In the XENical in the Prevention of Diabetes in Obese Subjects study, treatment with orlistat resulted in a significant reduction in the cumulative incidence of type 2 DM after 4 years of treatment (9.0% with placebo vs 6.2% with orlistat), corresponding to a risk reduction of 37.3%.¹⁶ Mean weight loss after 4 years was significantly greater in the orlistat group (5.8 vs 3.0 kg with placebo; $P < .001$).¹⁶ Other benefits of orlistat included a reduction in low-density lipoprotein cholesterol independent of that expected from change in body weight.¹⁶

Adverse effects include flatulence with discharge and fecal urgency after high-fat dietary indiscretions. Serum levels of fat-soluble vitamins (A, D, E, and K) were lower with orlistat than with placebo,¹⁶ and a fat-soluble vitamin supplement should be taken 2 hours before or after taking orlistat. Serious but very uncommon adverse events such as kidney dam-

TABLE 1
Drugs approved by the US Food and Drug Administration for treatment of obesity^a

Drug	Mechanism of action	Effect	Daily dosage ^b
Orlistat (Xenical)	Inhibits pancreatic and gastric lipase	Decreases fat absorption	120 mg 3 times a day with each main meal containing fat
Phentermine (Adipex-P, Lomaira)	Augments central norepinephrine release	Decreases appetite	8 mg to 37.5 mg once daily
Phentermine and topiramate extended-release (Qsymia)	Augments central norepinephrine and gamma-amino butyric acid release	Decreases appetite	Phentermine 3.75 mg/topiramate 23 mg once daily (initial); phentermine 7.5 mg/topiramate 46 mg once daily (maintenance)
Bupropion and naltrexone sustained-release (Contrave)	Inhibits dopamine and norepinephrine reuptake; blocks opioid receptor	Decreases appetite	1 tablet (bupropion 90 mg/naltrexone 8 mg) once daily in morning (initial); 2 tablets (bupropion 180 mg/naltrexone 16 mg) twice daily (usual); maximum daily dose: bupropion 360 mg/naltrexone 32 mg
Diethylpropion (Tenuate, Tenuate Dospa)	Augments central norepinephrine release	Decreases appetite	25 mg 3 times a day (immediate release); 75 mg once daily, midmorning (controlled release)
Lorcaserin (Belviq)	Activates serotonin 5-HT _{2c} receptor	Decreases appetite	10 mg twice a day (immediate release)
Liraglutide (Saxenda)	Activates glucagon-like peptide 1 receptor	Decreases appetite	3 mg subcutaneously once a day

^a Average weight loss is about 5 to 10 kg by 1 year.

^b By mouth, except for liraglutide.

Based on data from Lexicomp Online.¹⁵

age have been reported.¹⁷ Kidney and liver function should be monitored while taking orlistat.

Phentermine

Phentermine (Adipex-P, Lomaira), a sympathomimetic amine, is the most commonly prescribed antiobesity drug in the United States. A schedule IV controlled substance, it is FDA-approved for short-term use (up to 12 weeks). Its primary mechanism of action is mediated by reduction in hunger perception. It was first developed in the 1970s and is available in doses ranging from 8 mg to 37.5 mg daily.¹⁸

Benefits. In a randomized trial, at 28 weeks, weight loss was 1.5 kg with placebo and 5.3 kg with phentermine.¹⁹ No long-term (> 1 year) randomized controlled trials of the effectiveness of phentermine monotherapy in weight loss have been conducted.

Adverse effects. Dizziness, dry mouth, insomnia, constipation, and increase in heart rate were most common.¹⁹

Phentermine is contraindicated in patients with coronary artery disease, congestive heart failure, stroke, and uncontrolled hypertension. Currently, no data exist on the long-term cardiovascular effects of phentermine. We believe phentermine, used in

patients at low to intermediate cardiovascular risk, is a useful “jumpstart” tool, in combination with lifestyle changes, to achieve weight loss and improve metabolic values for those with type 2 DM and obesity.

Phentermine is a controlled substance per Ohio law. Patients must be seen once a month by the prescribing provider and prescriptions are limited to a 30-day supply, which must be filled within 7 days of the date of the prescription. Phentermine can only be prescribed for a maximum of 3 months and must be discontinued for 6 months before patients are eligible for a new prescription.

Phentermine and topiramate extended-release

Obesity is a product of complex interactions between several neurohormonal pathways. Approaches simultaneously targeting more than one regulatory pathway have become popular and quite efficient strategies in treating patients with obesity.²⁰ Stemming from such approaches, antiobesity drug combinations such as phentermine and topiramate extended-release (Qsymia) have become increasingly recognized and used in clinical practice. The combination of these 2 medications has been approved for long-term use by the FDA.

Phentermine and topiramate extended-release is a fixed-dose combination that was approved for weight loss in 2012. Topiramate, an anticonvulsant, and phentermine exert their anorexigenic effects through regulating various brain neurotransmitters and result in more weight loss when used together than when either is used alone. Several clinical trials evaluated the efficacy of low doses of this combination in weight loss.

Benefits. In a randomized trial in patients with obesity and cardiometabolic diseases, at 56 weeks, the mean weight loss was:

- 1.2% in the placebo group
- 7.8% in the group receiving phentermine 7.5 mg and topiramate 46 mg
- 9.8% in the group receiving phentermine 15 mg and topiramate 92 mg.²¹

Patients in the active treatment groups also had significant improvements in cardiovascular and metabolic risk factors such as waist circumference, systolic blood pressure, and total cholesterol/high-density lipoprotein cholesterol ratio. At 56 weeks, patients with diabetes and prediabetes taking this preparation had greater reductions in HbA1c values, and fewer prediabetes patients progressed to type 2 DM.²¹

Adverse effects most commonly seen were dry mouth, paresthesia, and constipation.²¹

This combination is contraindicated in pregnancy, patients with recent stroke, uncontrolled hypertension, coronary artery disease, glaucoma, hyperthyroidism, or in patients taking monoamine oxidase inhibitors. Women of childbearing age should be tested for pregnancy before starting therapy, and monthly thereafter, and also be advised to use effective methods of contraception while taking the medication. Topiramate has been associated with the development of renal stones and thus should be used with caution in patients with a history of kidney stones.

Bupropion and naltrexone sustained-release

Bupropion and naltrexone sustained-release (Contrave) is another FDA-approved combination drug for chronic weight management. Bupropion is a dopamine and norepinephrine reuptake inhibitor approved for depression and smoking cessation, and naltrexone is an opioid receptor antagonist approved for treating alcohol and opioid dependence. The combination of these 2 medications has been approved for long-term use by the FDA.

Benefits. In a randomized trial in patients with obesity and type 2 DM, weight loss at 56 weeks was:

- 1.8% with placebo
- 5.0% with naltrexone 32 mg and bupropion 360 mg daily.

Absolute reductions in HbA1c were:

- 0.1% with placebo
- 0.6% with naltrexone-bupropion.

Improvements were also seen in other cardiometabolic risk factors such as triglyceride and high-density lipoprotein cholesterol levels.²²

Adverse effects. The most common adverse effect leading to drug discontinuation was nausea. Other adverse effects reported were constipation, headache, vomiting, and dizziness.²²

Naltrexone-bupropion is contraindicated in patients with a history of seizure disorder or a diagnosis of anorexia nervosa or bulimia, or who are on chronic opioid therapy.

Diethylpropion

Diethylpropion (Tenuate, Tenuate Dospan) is a central nervous system stimulant similar to bupropion in its structure. It was approved by the FDA for treating obesity in 1959. It should be used as part of a short-term weight-loss plan, along with a low-calorie diet. Diethylpropion is also a controlled substance and, as with phentermine therapy, patients are required to be seen once a month by their prescriber. Diethylpropion cannot be prescribed for more than 3 months.

Benefits. Weight loss in a randomized trial at 6 months:

- 3.2% with placebo
- 9.8% with diethylpropion 50 mg twice a day.²³

After 6 months, all participants received diethylpropion in an open-label extension for an additional 6 months. At 12 months, the mean weight loss produced by diethylpropion was 10.6%.²³ No differences in heart rate, blood pressure, electrocardiographic results, or psychiatric evaluations were observed.

Adverse effects. As with phentermine, common side effects of diethylpropion include insomnia, dry mouth, dizziness, headache, mild increases in blood pressure, and palpitations.²³

Lorcaserin

Lorcaserin (Belviq) was approved by the FDA for chronic weight management in June 2012. It exerts its effects through binding selectively to central 5-HT_{2C} serotonin receptors, with poor affinity for 5-HT_{2A} and 5-HT_{2B} receptors. Nonselective serotonergic agents, including fenfluramine and dexfenfluramine, were withdrawn from the market in 1997 after being reported to be associated with valvular heart abnormalities.²⁴ Lorcaserin has been approved for long-term use by the FDA.

Benefits. Mean weight loss at 1 year in the Behav-

ioral Modification and Lorcaserin for Overweight and Obesity Management in Diabetes Mellitus trial²⁵ was:

- 1.5% with placebo
- 5.0% with lorcaserin 10 mg once daily
- 4.5% with lorcaserin 10 mg twice daily.

Absolute reductions in HbA1c values were:

- 0.4% with placebo
- 0.9% with lorcaserin 10 mg once daily
- 1.0% with lorcaserin 10 mg twice daily.

Absolute reductions in fasting plasma glucose values were:

- 11.9 mg/dL with placebo
- 27.4 mg/dL with lorcaserin 10 mg once daily
- 28.4 mg/dL with lorcaserin 10 mg twice daily.²⁵

Adverse effects. The most common adverse effects were headache, dizziness, and fatigue. There was no significant increase in valvulopathy on echocardiography of participants receiving lorcaserin compared with placebo.²⁵

Liraglutide

Liraglutide (Saxenda, Victoza) is a glucagon-like peptide-1 (GLP-1) receptor agonist. Native GLP-1 is a hormone secreted by intestinal L cells in response to consumption of fat and carbohydrate-rich foods. It stimulates the release of insulin and suppresses any inappropriately elevated postprandial glucagon levels. In addition to its effect on glucose metabolism, GLP-1 also reduces appetite and delays gastric emptying in humans.²⁶ Unlike the extremely short half-life of native GLP-1 (estimated at 1 to 2 minutes), liraglutide has a half-life of 13 hours, allowing it to be given once daily.²⁶ Liraglutide medication has been approved for long-term use by the FDA.

Benefits. The Liraglutide Effect and Action in Diabetes 1–5 studies compared the effects of liraglutide monotherapy with antidiabetic oral medications or insulin, as well as in combination with antidiabetic oral agents. Liraglutide (Victoza) at doses approved for type 2 DM of 1.2 mg and 1.8 mg daily had significant effects in reducing HbA1c by 0.48% to 1.84% and weight by 2.5 kg to 4 kg.^{27,28} At a dose of 3.0 mg, liraglutide (Saxenda) is approved for chronic weight management. This dose of liraglutide has been shown to be effective and safe in patients with type 2 DM and obesity.

In the 56-week SCALE Diabetes trial,²⁹ liraglutide at a dose of 3.0 mg resulted in 6.0% weight reduction, compared with 2.0% in the placebo group. Of participants receiving 3.0 mg of liraglutide, 54.3% achieved more than 5% weight loss at 56 weeks compared with 21.4% with placebo. Liraglutide also resulted in significant improvements in HbA1c (mean change

–1.3% vs –0.3% with placebo), fasting and postprandial glucose levels, and fasting glucagon levels.²⁹

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results trial has shown liraglutide to significantly reduce rates of major cardiovascular events (first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) in patients with elevated cardiovascular risk factors.³⁰ These findings make liraglutide a favorable choice for high-risk patients with type 2 DM, obesity, and cardiovascular disease.

It is important to indicate that if a 5% weight loss is not achieved by 3 months with any of these weight-loss medications, it would be reasonable to stop the medication and consider switching to a different medication. These medications work best when combined with diet and increased physical activity. Weight-loss medications should never be used during pregnancy.

Women of childbearing age should be advised to use effective contraception methods while taking any of the above antiobesity medications.

Diabetes medications associated with weight loss: Metformin and SGLT-2 inhibitors

Although not FDA-approved for weight management, metformin has anorexigenic effects that aid in weight loss. It also inhibits hepatic glucose production and improves peripheral insulin sensitivity, making it a useful agent in patients with type 2 DM and obesity.

A meta-analysis of 31 trials showed that metformin reduced body mass index by 5.3% compared with placebo.³¹ Metformin should be considered as a first-line agent in obese patients with type 2 DM.

In healthy people, nearly all glucose is filtered in the glomerulus, but then 98% of it is reabsorbed in the proximal tubule by sodium-glucose cotransporter-2 (SGLT-2). Drugs that inhibit SGLT-2 increase urinary glucose excretion and, as a result, help control hyperglycemia. Another, off-label effect of excreting more glucose is weight loss: a sustained weight loss of about 3 kg to 5 kg in clinical studies.³² Although they can be used as monotherapies, SGLT-2 inhibitors are usually used as add-on therapies in patients with type 2 DM.

■ AN ALGORITHM FOR TREATMENT

In an ever-changing field of antiobesity medicines, practitioners are challenged daily with the “when’s and how’s” of prescribing antiobesity drugs. The addition of type 2 DM to the picture makes the choice of drug therapy even more challenging. Here, we pro-

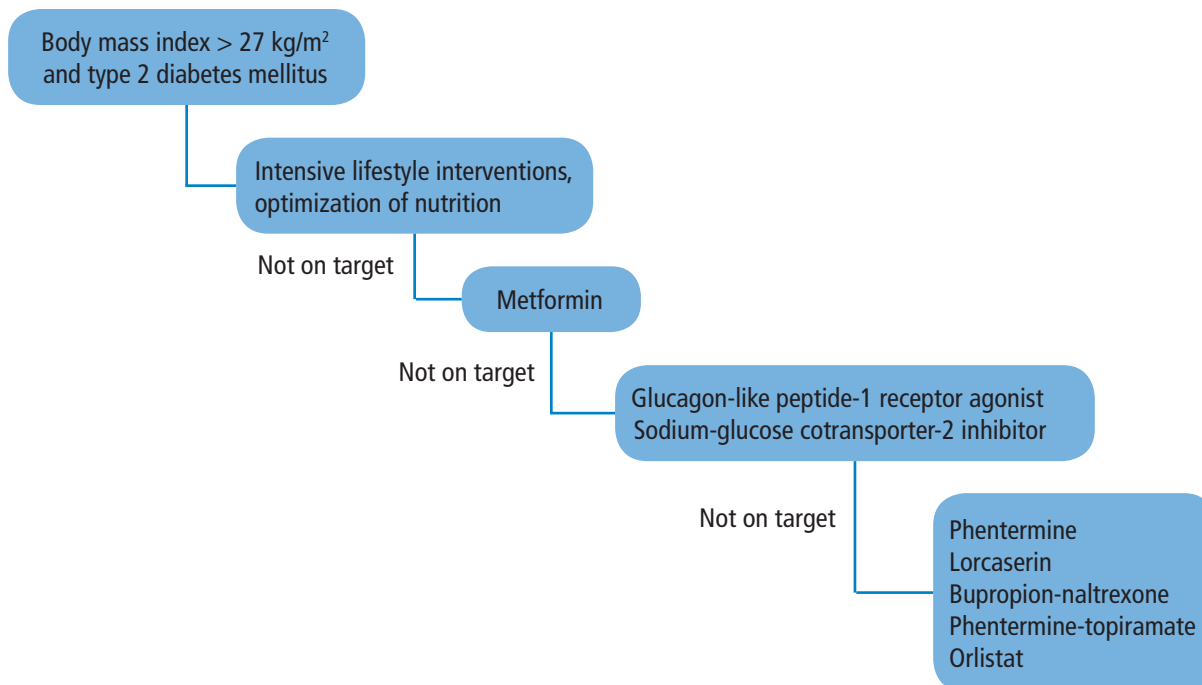


FIGURE 1. Therapeutic algorithm for patients with obesity and type 2 diabetes mellitus.

pose a practical therapeutic algorithm (**Figure 1**) that incorporates antiobesity drugs in the management of patients with type 2 DM and obesity.

First, we believe that lifestyle interventions by optimization of nutrition and physical activity should be the cornerstone therapy in the management plan of any patient with type 2 DM and obesity. These interventions are best implemented through a comprehensive, multidisciplinary approach that integrates the care of dietitians, physical therapists, exercise physiologists, psychologists, and social workers.³³ Patients need also to be seen frequently, ie, at least once every 3 months. The possibility of seeing patients in group-shared medical appointments on a monthly basis could also be considered.

We also believe that metformin should be added early in the course of treatment for its known benefits of improving insulin sensitivity and suppressing appetite. Target HbA1c goals and body weight in patients with type 2 diabetes and obesity should be tailored to the individual based on age, general health status, risk of hypoglycemia, capacity to do physical activity, and associated comorbidities. If no improvements are seen (HbA1c > 7% and < 3% weight loss) despite lifestyle changes and the addition of metformin, the possibility of adding a GLP-1 receptor agonist or an

SGLT-2 inhibitor as a second-line therapy should be considered. Both classes of medications aid in lowering HbA1c and promote further weight loss.

If no clinical progress is achieved at 3 months, the possibility of adding an FDA-approved weight-loss medication, as discussed above, should be strongly considered. Of note, this algorithm targets different endogenous pathways for weight loss and thus minimizes weight regain through compensatory mechanisms.

■ THE NEED FOR PATIENT-CENTERED WEIGHT-LOSS CONVERSATIONS

Patient-centered care has become a core quality measure in our healthcare systems and a key to our patients' success. The decision to start an antiobesity drug should therefore reflect careful consideration of medical and personal patient issues, all of which are valued differently by patients.³⁴

Individualized therapy is even more relevant among patients suffering from a significant burden of disease. About 80% of patients with diabetes live with at least 1 other medical condition,³⁵ and each of these patients spends over 2 hours a day, on average, following doctors' recommendations.³⁶ If antiobesity medications are prescribed without careful consid-

eration of the patient's preexisting workload, they will be destined to fail. Therefore, it becomes crucial to first account for the patient's ability to cope with therapy intensification. This requires careful deliberation between healthcare providers and patients, in aims of targeting a weight-loss plan that fits patients' goals and is aligned with providers' expectations.

Healthcare systems also play a key role in supporting better conversations about obesity in type 2 DM patients. They could implement multifaceted initiatives to promote shared decision-making and the use of decision aids to advance patient-centered obesity practices.³⁷ Policymakers could redesign quality measures aimed at capturing the quality of obesity conversations, and develop policies that support better education for clinicians regarding the importance of addressing obesity with adequate communication and patient-centered skills. Guidelines are often too disease-specific and do not consider comorbidities in their context when providing recommendations.³⁸ Thus, diabetes societies should respond to the need to guide care for patients with diabetes and its comorbidities, particularly obesity.

CONCLUSIONS

Obesity is a serious global health issue and a leading risk factor for type 2 DM. Lifestyle measures are the cornerstone of preventing and treating obesity and type 2 DM. Emerging data support the effectiveness of intensive, interdisciplinary weight-loss programs in patients with diabetes. The use of antiobesity drugs should be considered in patients who have not achieved adequate responses to lifestyle interventions. Medications should be tailored to the individual's health risks and metabolic and psychobehavioral characteristics. In many cases, the addition of weight-loss drugs will help accomplish and maintain the recommended 10% weight reduction, resulting in improvement in glycemic control and significant reduction in cardiovascular risk factors. New studies combining antiobesity and antidiabetes medications in the context of lifestyle interventions will help define the optimal therapeutic approach for patients with type 2 DM and obesity.

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Metabolic surgery for treating type 2 diabetes mellitus:

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■ ABSTRACT

The term *metabolic surgery* describes bariatric surgical procedures used primarily to treat type 2 diabetes and related metabolic conditions. Originally, bariatric surgery was used as an alternative weight-loss therapy for patients with severe obesity, but clinical data revealed its metabolic benefits in patients with type 2 diabetes. Metabolic surgery is more effective than lifestyle or medical management in achieving glycemic control, sustained weight loss, and reducing diabetes comorbidities. Perioperative adverse events are similar to other gastrointestinal surgeries. New guidelines for type 2 diabetes expand use of metabolic surgery to patients with a lower body mass index.

■ KEY POINTS

Randomized clinical trials have shown that metabolic surgery is statistically superior to medical treatment in achieving targeted glycemic levels along with improvements in weight loss, remission of metabolic syndrome, reduction in medications, and improvements in lipid levels.

The safety of metabolic and bariatric surgery has significantly improved with the advent of laparoscopic surgery, resulting in complication profiles similar to those of cholecystectomy and appendectomy.

Metabolic surgery is now recommended as standard treatment option for type 2 diabetes in patients with body mass index levels as low as 30 kg/m².

Type 2 diabetes mellitus (DM) and obesity are chronic diseases that often coexist. Combined, they account for tremendous morbidity and mortality. Approximately 85% of all patients with type 2 DM have a body mass index (BMI) categorizing them as overweight (BMI 25.0–29.9 kg/m²) or obese (BMI > 30.0 kg/m²) (Figure 1).¹ Obesity is strongly associated with diabetes and is a major cause of insulin resistance that leads to the cascade of hyperglycemia, glucotoxicity, and beta-cell failure, which ultimately leads to the development of microvascular (neuropathy, nephropathy, retinopathy) and macrovascular (myocardial infarction, stroke) complications. Treatment guidelines emphasize that both diabetes and obesity should be treated to optimize long-term outcomes.^{2–5} Metabolic surgery is the only diabetes treatment proven to result in long-term remission in 23% to 60% of patients depending upon preoperative duration of diabetes and disease severity. This review presents the evidence supporting use of metabolic surgery as a primary treatment for type 2 DM, potential mechanisms for its effects, associated complications, and recommendations for its use in expanded patient populations.

■ LIMITATIONS OF LIFESTYLE MANAGEMENT AND MEDICATIONS

First-line therapy with lifestyle management and second-line therapy with medications, including oral agents and insulin, are the mainstays of type 2 DM therapy. Although these approaches have reduced hyperglycemia and cardiovascular mortality, many patients have poor glycemic control and develop severe diabetes-related complications. A study using data from the National Health and Nutrition Examination Survey (N = 4,926) to evaluate success rates of lifestyle management plus drug therapy found that just 53% of patients with type 2 DM maintained a hemoglobin A1c (HbA1c) below 7%.⁶ Similarly,

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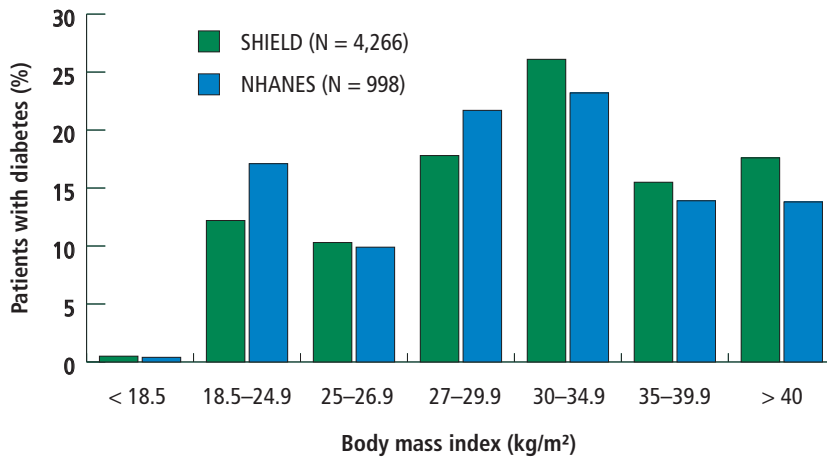


FIGURE 1. Relative distribution of body mass index of patients with diabetes. SHIELD = Study to Help Improve Early Evaluation and Management of Risk Factors Leading to Diabetes (2004); 4,266 of 127,420 survey respondents with diabetes (type 1 = 368; type 2 = 3,898). NHANES = National Health and Nutrition Examination Survey (1999–2002); 998 of 11,441 survey respondents with diabetes (type 1 and 2).

Data from Bays et al.¹

only 51% of those patients achieved a systolic and diastolic blood pressure less than 130/80 mm Hg, and only 56% achieved a low-density lipoprotein cholesterol level less than 100 mg/dL. Altogether, only 19% of the study cohort achieved all 3 therapy targets. Documented limitations of lifestyle counseling and drug therapy include behavior maladaptation, limitations in drug potency, nonadherence to medications, adverse effects, and economic deterrents.⁷

■ METABOLIC SURGERY FOR TYPE 2 DM

For patients with obesity and type 2 DM in whom lifestyle management and medications do not achieve desired treatment goals, bariatric surgery has emerged as the most effective treatment for attaining significant and durable weight loss. These gastrointestinal (GI) procedures, which reduce gastric volume with or without rerouting nutrient flow through the small intestine, were developed to yield long-term weight loss in patients with severe obesity. It is now known that they also cause dramatic improvement or remission of obesity-related comorbidities, especially type 2 DM. Research has shown that these effects are not only secondary to weight loss but also depend on neuroendocrine mechanisms secondary to changes in GI physiology. For these reasons, bariatric surgery is increasingly used with the primary intent to treat type 2 DM or metabolic disease, a practice referred to as *metabolic surgery*.

Between 150,000 and 200,000 bariatric procedures are performed annually in the United States,

and nearly 500,000 worldwide.⁸ The most common procedures are sleeve gastrectomy (SG, 49%), Roux-en-Y gastric bypass (RYGB, 43%), laparoscopic adjustable gastric banding (LAGB, 6%), and biliopancreatic diversion with duodenal switch (BPD-DS, 2%) (Figure 2).^{9,10} The development of laparoscopic, minimally invasive approaches to these procedures, starting in the mid-1990s, has significantly reduced rates of perioperative morbidity and mortality.

For more than 2 decades, indications for metabolic surgery reflected guidelines from a 1991 National Institutes of Health (NIH) consensus conference, which suggested considering surgery only in patients with a BMI of 40 kg/m² or greater or a BMI of 35 kg/m² or greater and significant obesity-

related comorbidities.¹¹ Guidelines published in 2013 expanded the recommendations to include adults with a BMI of at least 35 kg/m² and an obesity-related comorbidity, such as diabetes, who are motivated to lose weight.⁴ These recommendations were primarily designed to guide the use of surgery as a weight-loss intervention for severe obesity. However, guidelines published in 2016 support use of metabolic surgery as a specific treatment for type 2 DM.⁵

Potential mechanisms resolving type 2 DM: More than weight loss

Bariatric surgery has been shown to have profound glucoregulatory effects. These include rapid improvement in hyperglycemia and reduction in exogenous insulin requirements that occur early after surgery and before the patient has any significant weight loss.^{12,13} Additionally, experiments in rodents showed that changes to GI anatomy can directly influence glucose homeostasis, independently of weight loss and caloric restriction.¹⁴

Although the exact molecular mechanisms underlying the effects of metabolic surgery on diabetes are not fully understood, many factors appear to play a role, including changes in bile acid metabolism, GI tract nutrient sensing, glucose utilization, insulin resistance, and intestinal microbiomes.¹⁵ These changes, acting through peripheral or central pathways, or perhaps both, lead to reduced hepatic glucose production, increased tissue glucose uptake, improved insulin sensitivity, and enhanced beta-

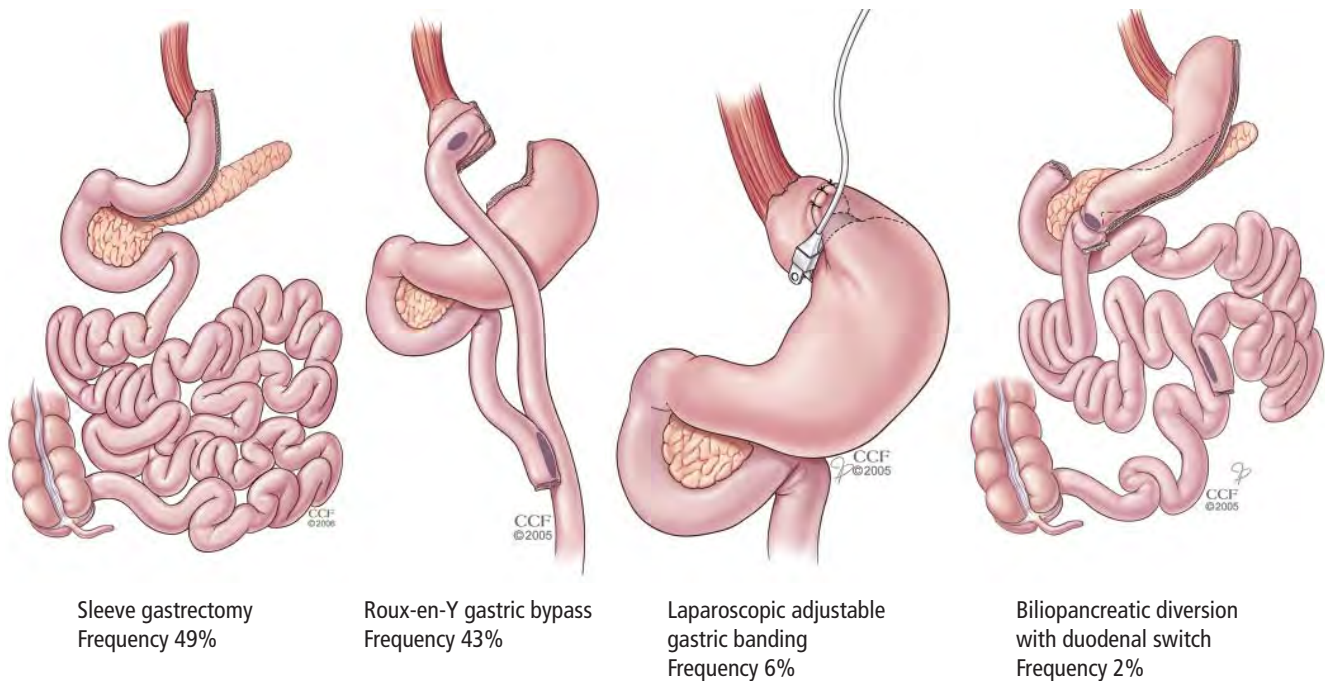


FIGURE 2. Most common metabolic surgical procedures.

cell function. A constellation of gut-derived neuroendocrine changes, rather than a single overarching mechanism, is the likely mediator of postoperative glycemic improvement, with the contributing factors varying according to the surgical procedure.

■ METABOLIC SURGERY OUTCOMES

Weight loss

Long-term reduction of excess body fat is a major goal of metabolic and bariatric surgery. Weight loss is usually expressed as either the percent of weight loss or the percent of excess weight loss (ie, weight loss above ideal weight). A meta-analysis of mostly short-term weight-loss outcomes (ie, < 5 years) from more than 22,000 procedures found an overall mean excess weight loss of 47.5% for patients who underwent LAGB, 61.6% for RYGB, 68.2% for vertical-banded gastroplasty, and 70.1% for BPD-DS.¹⁶ Vertical-banded gastroplasty differs from LAGB in that both a band and staples are used to create a small stomach pouch. Excess weight loss for SG generally averages 50% to 55%, which is intermediate between LAGB and RYGB.^{17,18}

The Swedish Obese Subjects study (N = 4,047), a prospective study of bariatric surgery vs nonsurgical weight management of severely obese patients (BMI > 34), is the largest weight-loss study with the longest follow-up.¹⁹ At 20 years, the mean weight loss was

26% for gastric bypass, 18% for vertical-banded gastroplasty, 13% for gastric banding, and 1% for controls. A 10-year study in 1,787 severely obese patients (BMI ≥ 35) who underwent RYGB had 21% more weight loss from their baseline weight than the nonsurgical match.²⁰ At 4-year follow-up in 2,410 patients, there were significant variations in weight loss depending on the procedure: 27.5% for RYGB, 17.8% for SG, and 10.6% in LAGB. Between 2% and 31% regained weight back to baseline: 30.5% for LAGB, 14.6% for SG, and 2.5% for RYGB.²⁰ In contrast, long-term medical (nonsurgical) weight loss rarely exceeds 5%, even with intensive lifestyle intervention.²¹

Diabetes remission, cardiovascular risk factors, glycemic control

A meta-analysis of 19 mostly observational studies (N = 4,070 patients) reported an overall type 2 DM remission rate of 78% after bariatric surgery with 1 to 3 years of follow-up.²² Resolution or remission was typically defined as becoming “nondiabetic” with normal HbA1c without medications. In the Swedish Obese Subjects study, the remission rate was 72% at 2 years and 36% at 10 years compared with 21% and 13%, respectively, for the nonsurgical controls ($P < .001$).²³ Bariatric surgery was also markedly more effective than nonsurgical treatment in preventing type 2 DM, with a relative risk reduction of 78%.

TABLE 1
Metabolic surgery for type 2 diabetes mellitus: Randomized controlled clinical trials

Study	Pts with BMI < 35 kg/m ²	Study design	No. pts	Follow-up (mo)	Remission criteria	Remission ^a or change in HbA1c (%)	P value
Dixon ²⁸	22%	LAGB vs control	60	24	HbA1c < 6.2%	73 vs 13	< .001
Schauer ^{29,30,43}	36%	RYGB vs SG vs control	150	60	HbA1c ≤ 6.0%	22 vs 15 vs 0	< .05
Mingrone ^{31,32}	0%	RYGB vs BPD vs control	60	60	HbA1c ≤ 6.5%	42 vs 68 vs 0	.003
Ikramuddin ^{33,34}	59%	RYGB vs control	120	24	HbA1c < 6.0%	44 vs 9	< .001
Liang ³⁵	100%	RYGB vs control	101	12	HbA1c < 6.5%	90 vs 0 vs 0 ^b	< .0001
Halperin ³⁶	34%	RYGB vs control	38	12	HbA1c < 6.5%	58 vs 16	.03
Courcoulas ^{37,38}	43%	RYGB vs LAGB vs control	69	36	HbA1c < 6.5%	40 vs 29 vs 0	.004
Wentworth ³⁹	100%	LAGB vs control	51	24	FBG < 7.0 mmol/L	52 vs 8	.001
Parikh ⁴⁰	100%	RYGB/LAGB/SG vs control	57	6	HbA1c < 6.5%	65 vs 0	.0001
Ding ⁴¹	34%	LAGB vs control	45	12	HbA1c < 6.5%	33 vs 23 ^c	.46
Cummings ⁴²	25%	RYGB vs control	43	12	HbA1c < 6.0%	60 vs 5.9	.002
Shah ⁴⁴	85	RYGB vs control	80	24	HbA1c < 6.5%	60 vs 2.5	< .001

Remission criteria:

^a Remission was primary or secondary end point; HbA1c value without diabetes medications, unless otherwise specific.

^b Remission was not precisely defined; HbA1c < 6.5% by extrapolation.

^c Intermittent diabetes medications.

BMI = body mass index; BPD = biliopancreatic diversion; FBG = fasting blood glucose; HbA1c = glycated hemoglobin; LAGB = laparoscopic adjustable gastric band; RYGB = Roux-en-Y gastric bypass; SG = sleeve gastrectomy

Modified from Schauer PR, et al. Clinical outcomes of metabolic surgery: efficacy of glycemic control, weight loss, and remission of diabetes. *Diabetes Care* 2016; 39:908–911. ©2016 American Diabetes Association. All rights reserved. Material from this publication is used with the permission of American Diabetes Association.

A systematic review published in 2012 evaluated long-term cardiovascular risk reduction after bariatric surgery in 73 studies and 19,543 patients.²⁴ At a mean follow-up of 57.8 months, the average excess weight loss for all procedures was 54% and rates of remission or improvement were 63% for hypertension, 73% for type 2 DM, and 65% for hyperlipidemia. Results from 12 cohort-matched, nonrandomized studies comparing bariatric surgery vs nonsurgical controls suggest that improvements in surrogate disease markers such as HbA1c, blood pressure, lipids, and body weight after surgery translate to reduced macrovascular and microvascular events and death.²⁵ One of these studies involving male veterans who were mostly at high cardiovascular risk reported a 42% reduction in mortality at 10 years compared with medical therapy.²⁶

In the Swedish Obese Subjects study, the mortality rate from cardiovascular disease in the bariatric surgical group was lower than for control patients (adjusted hazard ratio, 0.47; *P* = .002) despite a greater prevalence of smoking and higher baseline weights and blood pressures in the surgical cohort.¹⁹ For patients with type 2 DM in this study, surgery was associated

with a 50% reduction in microvascular complications.²⁷ After 15 years of follow-up, the cumulative incidence of microvascular complications was 41.8 per 1,000 person-years for control patients and 20.6 per 1,000 person-years in the surgery group (hazard ratio, 0.44; *P* < .001).

These observational, nonrandomized study data suggest that in patients with type 2 DM, bariatric surgery is significantly better than medical management alone in improving glycemic control, reducing cardiovascular risk factors, and lowering long-term morbidity and mortality associated with type 2 DM.

■ METABOLIC SURGERY: CLINICAL TRIALS

During the past 10 years, 12 randomized controlled trials (RCTs) have compared metabolic surgery vs medical treatment for type 2 DM (Table 1).^{28–44} All the trials included obese patients with type 2 DM (N = 874; range 38–150 patients per study) with follow-up from 6 months to 5 years. Surgeries were RYGB (9 studies), LAGB (5 studies), SG (2 studies), and BPD-DS (1 study); some studies had multiple surgery types. The severity of type 2 DM varied significantly from mild

(mean HbA1c 7.7%, < 2-year onset, no insulin)²⁸ to advanced (mean HbA1c 9.3%, duration 8.3 years, 48% on insulin).²⁹ The BMI ranged from 25 to 53 kg/m², with 11 of 12 studies including patients with BMI less than 35 kg/m². Demographics of age, sex, and ethnic background were similar, although 3 studies^{33–35,44} included a significant number of Asian patients. For most studies, the primary end point was the success rate of reaching remission, defined as an HbA1c target at or below 6.0% to 6.5% without a need for diabetes medications.

Collectively, these RCTs showed that surgery was significantly superior to medical treatment in reaching the designated glycemic target (*P* < .05 for all). The one exception showed that diabetes remission for LAGB vs medical treatment was 33% and 23%, respectively.⁴¹ This result might be due to patients in this study having advanced type 2 DM (HbA1c 8.2% ± 1.2%, with 40% on insulin), and they likely had reduced beta-cell function. Overall, surgery decreased HbA1c by 2% to 3.5%, whereas medical treatment lowered it by only 1% to 1.5%. Most of these studies also showed superiority of surgery over medical treatment in achieving secondary end points such as weight loss, remission of metabolic syndrome, reduction in diabetes and cardiovascular medications, and improvement in triglycerides, lipids, and quality of life. Results were mixed in terms of improvements in systolic and diastolic blood pressure or low-density lipoproteins after surgery vs medical treatment, but many studies did show a corresponding reduction in medication usage.

Durability of the effects of surgery was demonstrated in a 5-year study that showed superior and durable weight loss and glycemic control (remission) with both RYGB and BPD in severely obese patients (BMI ≥ 35) vs medical therapy.³² Similarly, Schauer et al⁴³ showed that RYGB and SG were more effective than intensive medical therapy in improving or, in some cases, resolving hyperglycemia for 5 years. In the RCTs, patients who preoperatively had shorter duration of diabetes, lower HbA1c levels, no insulin requirement, and more postoperative weight loss were more likely to achieve diabetes remission.

Although previous guidelines and payer coverage policies had limited metabolic surgery to severely obese patients (BMI ≥ 35 kg/m²), nearly all RCTs

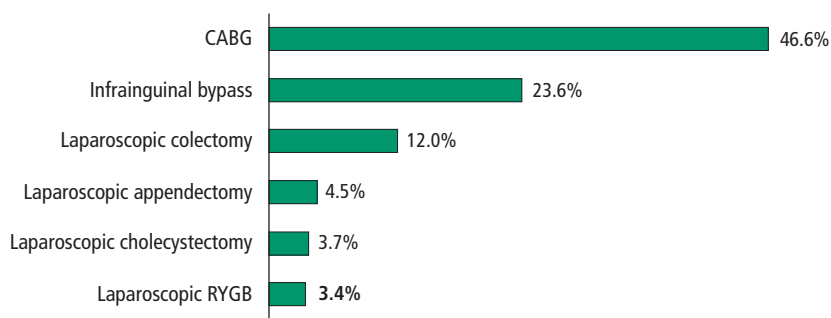


FIGURE 3. Postoperative complication rates of surgical procedures in patients with type 2 diabetes mellitus: US data.

CABG = coronary artery bypass graft; RYGB = Roux-en-Y gastric bypass

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showed that the surgical procedures, especially RYGB and SG, were equally effective in patients with BMI 30 to 35 kg/m². This is particularly important given that most patients with type 2 DM have a BMI less than 35 kg/m². The effect of surgery in these patients with mild obesity is also durable out to at least 5 years.⁴³

No RCT was sufficiently powered to detect differences in macrovascular or microvascular complications or death, especially at the relatively short follow-up, and no such differences have been detected thus far. The STAMPEDE (Surgical Therapy and Medications Potentially Eradicate Diabetes Efficiently) trial⁴³ showed that bariatric surgery (RYGB or SG) did not appear to worsen or improve retinopathy outcomes at 5 years compared with intensive medical management.

■ METABOLIC SURGERY: ADVERSE EVENTS

Surgical complications

Overall, rates of perioperative morbidity and mortality of bariatric surgery are similar to those of common, relatively low-risk abdominal procedures such as cholecystectomy and appendectomy. The NIH-supported Longitudinal Assessment of Bariatric Surgery study reported a low 30-day mortality rate of 0.3% in 4,776 patients and a 4.3% incidence of major adverse events in the early postoperative period.⁴⁵ A study from the American College of Surgeons (> 65,000 patients) showed that laparoscopic RYGB had perioperative morbidity and mortality rates of 3.4% and 0.3%, respectively, similar to those for laparoscopic cholecystectomy (3.7% and 0.7%) and appendectomy (4.5% and 0.5%) (Figures 3 and 4) and much lower

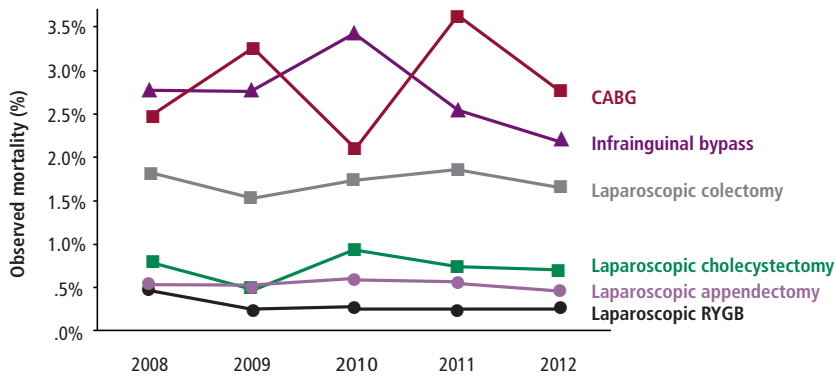


FIGURE 4. Mortality rates of 8 procedures in patients with diabetes (2008–2012).

CABG = coronary artery bypass grafting; RYGB = Roux-en-Y gastric bypass

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than for laparoscopic colectomy (12.0% and 1.7%).⁴⁶

Table 2 summarizes early and late postoperative complications of metabolic surgery. Although rare (< 1%), cardiopulmonary complications such as myocardial infarction and pulmonary embolism are the major causes of mortality, representing 70% of all perioperative deaths.⁴⁵ Intestinal leakage at the anastomosis or staple line is the most serious early surgical complication after RYGB (0.1%–5.6%) and may potentially lead to peritonitis. Bowel obstruction (0.5%–2%) and marginal ulcers (1%–5%) may also occur months to years after RYGB.^{47,48} Staple-line leakage (1%–5%) and gastric stenosis (1%–5%) are the most common surgical complications of SG.¹⁷

For BPD-DS, perioperative complications are similar to those for RYGB. Although LAGB is safe, with a very low mortality rate (< 0.3%), late complications such as band slippage, erosion, migration, and surgical port infection occur in about 20% of patients.⁴⁹ Reoperation for poor weight loss or complications after LAGB is common, occurring in approximately 50% of patients.⁵⁰ In general, patients at higher risk of complications after bariatric surgery are those with high BMI, older age, multiple comorbidities, smoking, or previous revisional operations; men are also at higher risk.⁴⁵

Nutritional deficiencies

Postoperative nutritional deficiencies are typically associated with diminished nutrient intake or the malabsorptive effect of bariatric procedures. They are more common after RYGB and BPD-DS and less common after SG and LAGB. In addition, there is a high prevalence of nutritional deficiencies (35%–80%)

in patients seeking bariatric surgery; thus, poor preoperative nutrition may be a factor in the development of postoperative deficiencies. Common preoperative nutrient deficiencies are vitamin A (11%), vitamin B₁₂ (13%), vitamin D (40%), zinc (30%), iron (16%), ferritin (9%), selenium (58%), and folate (6%).⁵¹ Recommendations are to assess for these deficiencies and correct any identified before surgery.

Mild anemia after bariatric procedures is common, occurring in 15% to 20% of cases, and it is believed to result from reduced absorption of iron and B₁₂, as well from pre-existing iron deficiency anemia in premenopausal patients.⁵² Deficiencies in trace minerals

(selenium, zinc, and copper) and vitamins (B₁₂, B₁, A, E, D, and K) can occur after bariatric procedures, especially after BPD-DS.⁵³ Nutrient deficiencies can be prevented or corrected with appropriate vitamin, iron, and calcium supplementation.⁵⁴

Bone mineral density may decrease after bariatric surgery (14% in the proximal femur).⁵⁵ Reduced mechanical loading after weight loss, reduced consumption and malabsorption of micronutrients (calcium, vitamin D), and neurohormonal alterations are potential underlying mechanisms of bone mineral density reduction after bariatric surgery. Rates of bone fracture and osteoporosis are not well delineated, raising questions about whether bone loss after bariatric surgery is clinically relevant or a functional adaptation to skeletal unloading. However, the extreme malabsorptive procedures of BPD-DS have been associated with severe calcium and vitamin D deficiencies, leading to decreased bone mineral density and osteoporosis.

Protein malnutrition also can occur after these extreme malabsorptive procedures. Patients require postoperative oral protein supplementation (80–100 g/day) and lifelong monitoring for nutritional complications after these procedures.⁵⁶

Additional complications

Other late complications of bariatric surgery that are less clear in incidence and cause include kidney stones, alcohol abuse, depression, and suicide. One study of patients after RYGB (N = 4,690) reported a significantly higher prevalence of kidney stones than in obese controls: 7.5% vs 4.6%, respectively.⁵⁷

Proposed causes of kidney stone formation following bariatric surgery include hyperoxaluria, hypocitraturia, and elevated urine acidity.⁵⁸

The prevalence of alcohol-use disorder after bariatric surgery ranges from 7.6% to 11.8% and appears to be higher in patients with a history of alcohol use.⁵⁹ Paradoxically, while bariatric surgery has been shown to significantly decrease depression,⁶⁰ some studies suggest that a slight increase in the risk of suicide may occur,⁶¹ while others do not.⁶² A recent review concluded that accurate rates of suicide after bariatric surgery are not known, but practitioners should be aware of this concern and appropriately screen and counsel their patients.⁶³

Although the 12 RCTs reported in **Table 1** were not powered to detect differences in treatment-related complications, the overall rates of complications were consistent with those in observational studies.⁹ The most common surgical complications were anemia (15%), need for reoperation (8%), and GI (5%–10%). The 30-day surgical mortality rate was 0.2% (1 death) among the 465 surgical patients. Complications were not limited to the surgical patients. In the medical-treatment control group of the STAMPEDE trial,³⁰ anemia (16%) and weight gain (16%) were common. Investigators reported challenges with medication compliance, including adverse effects leading to discontinuation of medications. Mild hypoglycemia was common, with no significant differences between the surgical and medical treatment groups.

METABOLIC SURGERY: COST EFFECTIVENESS

The cost of bariatric procedures varies considerably but, in general, ranges from \$20,000 to \$30,000, similar to the cost of cholecystectomy, hysterectomy, and colectomy. Retrospective analyses and modeling studies indicate that metabolic surgery is cost-effective and may present a cost savings in patients with type 2 DM, with a break-even time between 5 and 10 years.^{64,65} The cost savings, largely based on assumptions of long-term effectiveness and safety, result from reductions in medication use, outpatient care costs, and long-term complications of type 2 DM.

WHO SHOULD HAVE METABOLIC SURGERY?

Until recently, there was no clear national or international consensus on the role of metabolic surgery in treating type 2 DM. In 2015, the 2nd Diabetes Surgery Summit (DSS-II) Consensus Conference published guidelines that were endorsed by more than 50 diabetes and medical organizations.⁵ The recommendations cover many clinically relevant issues, including patient

TABLE 2
Complications after metabolic surgery

Complications	Frequency (%)
Sepsis from anastomotic leak	0.1–5.6
Hemorrhage	1–4
Cardiopulmonary events	< 1
Thromboembolic disease	0.34
Death	0.1–0.3
Late complications for LAGB	
Band slippage	15
Leakage	2–5
Erosion	1–2
Late complications of bypass procedures	
Anastomotic stricture	1–5
Marginal ulcer	1–5
Bowel obstruction	0.5–2
Micronutrient and macronutrient deficiencies from RYGB 2–3 years postoperatively	
Iron deficiency	45–52
Vitamin B ₁₂ deficiency	8–37
Calcium deficiency	10
Vitamin D deficiency	51
Fat-soluble vitamin deficiencies (A, D, E, and K) and protein calorie malnutrition from BPD-DS procedures	1–5

BPD-DS = biliopancreatic diversion with duodenal switch; LAGB = laparoscopic adjustable gastric banding

From Schauer PR, et al. Clinical outcomes of metabolic surgery: efficacy of glycemic control, weight loss, and remission of diabetes. *Diabetes Care* 2016; 39:908–911. ©2016 American Diabetes Association. All rights reserved. Material from this publication is used with the permission of American Diabetes Association.

selection, preoperative evaluation, choice of procedure, and postoperative follow-up. The consensus conference delegates concluded that there is sufficient evidence demonstrating that metabolic surgery achieves excellent glycemic control and reduces cardiovascular risk factors.

According to the DSS-II guidelines, metabolic surgery should be recommended to treat type 2 DM in patients with class III obesity (BMI ≥ 40 kg/m²) regardless of glycemic control and in those with class II obesity (BMI 35.0–39.9 kg/m²) when hyperglycemia is inadequately controlled by lifestyle and optimal medical therapy. Surgery should also be considered for patients with type 2 DM and BMI 30.0 to 34.9 kg/m² if hyperglycemia is inadequately controlled despite optimal treatment with either oral or injectable medications. These BMI thresholds should be reduced by 2.5 kg/m² for Asian patients.

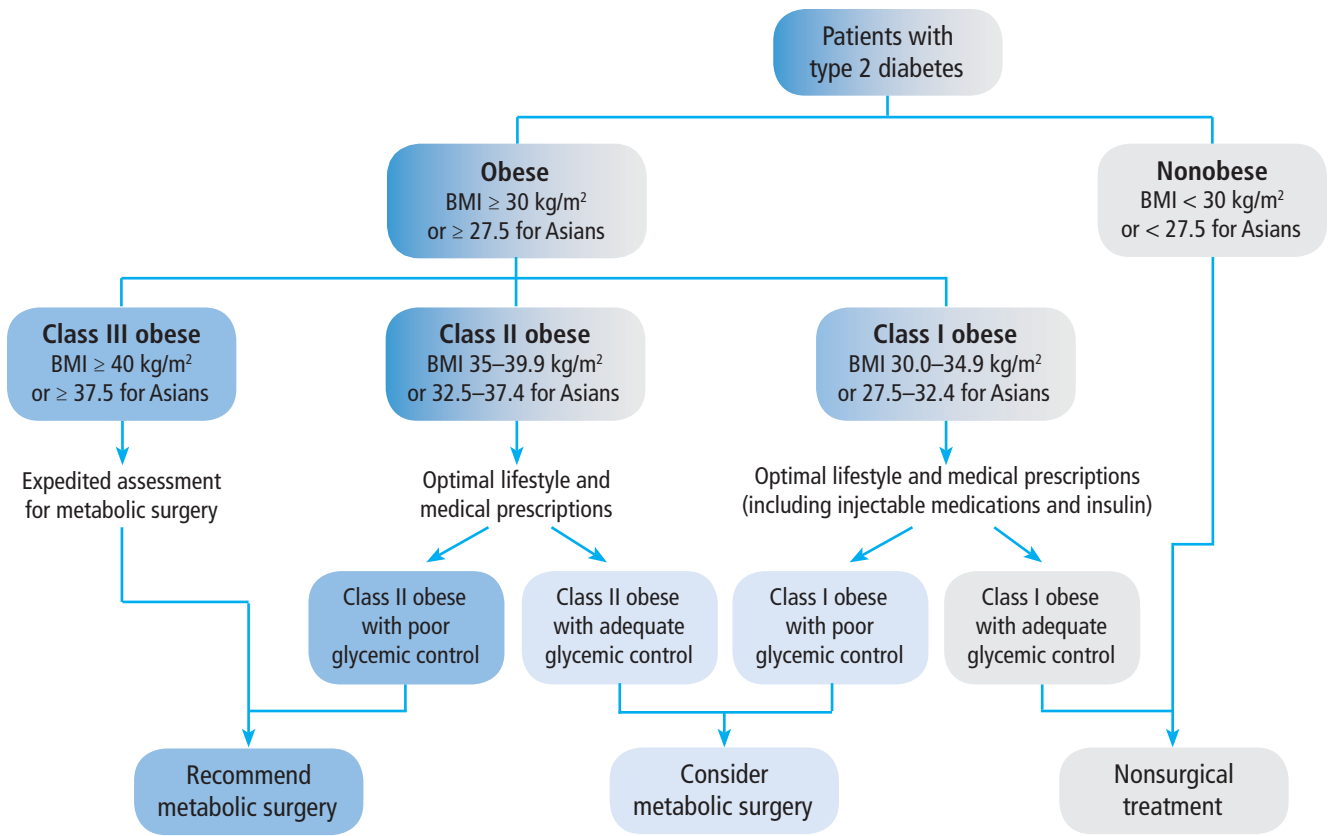


FIGURE 5. Algorithm for the treatment of type 2 diabetes, as recommended by the 2nd Diabetes Surgery Summit's voting delegates.

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TABLE 3
American Diabetes Association's recommendations for the treatment of type 2 diabetes mellitus

Treatment	Body mass index category (kg/m ²)				
	23.0 ^a or 25.0–26.9	27.0–29.9	27.5 ^a or 30.0–34.9	35.0–39.9	≥ 40
Diet, physical activity, and behavioral therapy	†	†	†	†	†
Pharmacotherapy		†	†	†	†
Metabolic surgery			†	†	†

^a Cutoff points for Asian American individuals.

† Treatment may be indicated for selected motivated patients.

From American Diabetes Association. Obesity management for the treatment of type 2 diabetes. Sec. 7. In: *Standards of Medical Care in Diabetes—2017*. *Diabetes Care* 2017; 40(suppl 1):S57–S63. ©2017 American Diabetes Association. All rights reserved. Material from this publication is used with the permission of American Diabetes Association.

The treatment algorithm from DSS-II incorporates appropriate use of all 3 treatment modalities: lifestyle intervention, drug therapy, and surgery (Figure 5).⁵ The 2017 Standards of Care for Diabetes from the American Diabetes Association include those key indications in the recommendations for metabolic surgery (Table 3).²

SUMMARY

Recent evidence from multiple RCTs has provided level 1a evidence supporting metabolic surgery as an effective treatment for type 2 DM. These studies have shown the superiority of surgery vs medical therapy in achieving excellent and durable glycemic control as well as benefits in long-

term weight loss, medication reduction, dyslipidemia, overall quality of life, and other cardiovascular risk factor reductions. Metabolic surgery is the only diabetes treatment proven to result in long-term remission in 23% to 60% of patients.

The safety of metabolic surgery has significantly improved with the advent of laparoscopic surgery and recent national quality improvement initiatives that have made gastric bypass and SG as safe as cholecystectomy and appendectomy. Although observational studies suggest that metabolic surgery is associated with a reduction in cardiovascular and diabetes complications and mortality, these observations have not been confirmed in long-term RCTs.

Based on the published evidence, metabolic surgery is now endorsed as a standard treatment option, which provides patients and practitioners with a powerful tool to help combat the life-impairing effects of type 2 DM.

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Medical Treatment of Diabetes Mellitus

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In the United States, 57.9% of patients with diabetes mellitus (DM) have at least 1 diabetes-related complication and 14.3% of patients with diabetes have 3 or more diabetes-related complications.¹ Achieving glycemic control in patients with DM reduces the development and progression of retinopathy, nephropathy, and neuropathy. Aggressive treatment of dyslipidemia and hypertension decreases macrovascular complications.²⁻⁴ The techniques for monitoring blood glucose and the various treatment options available to manage glycemic control in patients with diabetes are reviewed below.

Measuring Glycemic Control

The primary techniques available to assess the quality of a patient's glycemic control are self-monitoring of blood glucose and interval measurement of hemoglobin A1c (HbA1c). Continuous glucose monitoring is also available and may be appropriate for select patients, such as patients with brittle diabetes and those using insulin pumps.

Self-monitoring of blood glucose

For patients with type 1 DM and patients with insulin-dependent type 2 DM, self-monitoring of blood glucose allows patients to adjust insulin dosing to prevent hypoglycemia and hyperglycemia.^{2,5-7} The American Diabetes Association (ADA) guidelines recommend that patients with type 1 DM self-monitor their glucose:

- Before eating
- At bedtime
- Before exercise
- If hypoglycemia is suspected
- Until hypoglycemia is corrected

- Postprandially upon occasion
- And before critical tasks (ie, driving).⁸

Patients should be educated about how to use real-time blood glucose values to adjust their food intake and medical therapy.

It is commonly recommended that patients with type 2 DM self-monitor their blood glucose levels, but the evidence to support the effectiveness of this practice is inconclusive. Initial studies showed reductions in HbA1c with self-monitoring; however, the inclusion of beneficial health behaviors such as diet and exercise in the analyses makes it difficult to assess the effectiveness of self-monitor blood glucose alone.^{2,9}

The ADA recommends that nonpregnant adults maintain blood glucose levels of 80 mg/dL to 130 mg/dL preprandial and less than 180 mg/dL postprandial.⁸ The blood glucose goals for patients with gestational diabetes are 95 mg/dL or less preprandial and either 140 mg/dL or less 1-hour postprandial or 120 mg/dL or less 2-hours postprandial.

HbA1c

HbA1c tests reflect the mean blood glucose values over a 3-month period and can predict patients' risk of microvascular complications.^{10,11} The ADA recommends that patients with stable glycemic control have an HbA1c test at least twice a year. Quarterly HbA1c testing is suggested for patients with a recent change in therapy or for patients not meeting their glycemic goals.⁸

Measurement of HbA1c is influenced by the red blood cell turnover rate; therefore, anemia, transfusions, and hemoglobinopathies can cause inaccurate test values. The ADA recommends that nonpregnant adults maintain HbA1c levels near 7%. For patients with diabetes who become pregnant, the goal is HbA1c levels less than 6.0%.⁸ The ADA also recommends that select patients, especially those with a long life expectancy and little comorbidity, adopt glycemic targets near normal levels (HbA1c < 6.5%), providing the target can be achieved without significant hypoglycemia.⁸

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TABLE 1
Glycemic treatments by therapeutic category

Insulin sensitizers

Biguanide: metformin (Fortamet, Glucophage, Glumetza, Riomet)
Thiazolidinedione: pioglitazone (Actos), rosiglitazone (Avandia)

Insulin secretagogues

Sulfonylureas: chlorpropamide (Diabinese), glimepiride (Amaryl), glipizide (Glucotrol), glyburide (Micronase, Glynase)
Glinides: repaglinide (Prandin), nateglinide (Starlix)

Alpha-glucosidase inhibitors

Acarbose (Precose), miglitol (Glyset), voglibose

Incretin-based therapies

Glucagon-like peptide-1 agonists: albiglutide (Tanzeum), dulaglutide (Trulicity), exenatide (Bydureon, Byetta), liraglutide (Saxenda, Victoza), lixisenatide (Adlyxin)
Dipeptidyl peptidase-4 inhibitors: alogliptin (Nesina), linagliptin (Tradjenta), saxagliptin (Onglyza), sitagliptin (Januvia)

Sodium-glucose transporter-2 inhibitors

Canagliflozin (Invokana), dapagliflozin (Farxiga), empagliflozin (Jardiance)

Amylinomimetic

Pramlintide (SymlinPen 120, SymlinPen 60)

Dopamine agonist

Bromocriptine (Cycloset)

Insulin

Rapid-acting

Aspart insulin (Novolog)
Gulisine insulin (Apidra)
Lispro insulin (Humalog)

Short-acting

Regular insulin (Humulin R, Humulin R U-500 KwikPen, NovoLIN R, NovoLIN R ReliOn)

Intermediate-acting

Isophane insulin, NPH insulin (Humulin N, Novolin N)

Long-acting

Detemir insulin (Levemir)
Glargine insulin (Basaglar KwikPen, Lantus, Lantus SoloStar, Toujeo SoloStar)
Degludec insulin (Tresiba)

Premixed

Several types intermediate-acting and short-acting insulin combined are available

Based on information from the American Diabetes Association⁹ and Inzucchi et al.¹²

Glycemic Treatment

Treatment options to control blood glucose include insulin sensitizers, insulin secretagogues, alpha-glucosidase inhibitors, incretin-based therapies, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, amylinomimetics (pramlintide), dopamine-receptor agonists (bromocriptine), and insulin (Table 1).^{8,12}

Insulin sensitizers

Biguanides (metformin)

Metformin is the only available biguanide. Metformin should be used as a first-line therapy in patients with type 2 DM whenever possible.¹³ Metformin suppresses hepatic glucose output and primarily affects fasting glycemia; however, reduced postprandial glucose concentrations also occur.

The most common side effects of metformin are diarrhea, nausea, and abdominal discomfort. Metformin has the potential to produce very rare but life-threatening lactic acidosis

(< 1 in 100,000). The use of metformin is contraindicated in patients with a glomerular filtration rate less than 30 mL/min, with acidosis, hypoxia, or dehydration.⁸

Metformin usually does not lead to hypoglycemia when used as monotherapy. It can lead to weight loss (3%–5% of body weight), and it has been shown to decrease plasma triglyceride concentrations (10%–20%).^{8,14,15}

Thiazolidinediones

Thiazolidinediones (TZDs) primarily enhance the insulin sensitivity of muscle and fat tissue and mildly enhance insulin sensitivity of the liver. TZDs lower fasting and postprandial blood glucose levels.

Major side effects of TZDs include weight gain, with an increase in subcutaneous adiposity, and fluid retention. Fluid retention typically manifests as peripheral edema, but heart failure can occur on occasion. These agents should be avoided in patients with functional class III or IV heart failure. The PRO-active trial of the TZD pioglitazone found that pioglitazone did

not increase cardiovascular risk compared with placebo.¹⁶ TZDs have been associated with an increased risk of fractures, particularly in women. When used as monotherapy, TZDs do not cause hypoglycemia. Pioglitazone lowers triglyceride levels, increases high-density lipoprotein cholesterol, and increases the low-density lipoprotein cholesterol particle size.^{8,16–18}

Insulin secretagogues

Insulin secretagogues such as sulfonylureas and glinides stimulate secretion of insulin from the pancreas regardless of the ambient glucose concentration.

Sulfonylureas

Sulfonylureas lower fasting and postprandial glucose levels. The main side effects include weight gain (about 2 kg upon initiation) and hypoglycemia. The UK Prospective Diabetes Study (UKPDS) trial showed a decrease in microvascular complications with the use of sulfonylureas.¹⁹ Caution should be used in patients with liver or kidney dysfunction or patients who frequently skip meals. Newer, second-generation sulfonylureas (ie, glipizide and glimepiride) may have less risk of hypoglycemia because their action is somewhat glucose dependent.^{8,17,19}

Glinides

Glinides, which include repaglinide and nateglenide, have a rapid onset of action and a short duration of action, so they are a good option for patients with erratically timed meals. Glinides have a lower risk of hypoglycemia than sulfonylureas. Caution must be used with glinides in patients with liver dysfunction. Dosing is immediately before meals.^{8,17}

Alpha-glucosidase inhibitors

Alpha-glucosidase inhibitors such as acarbose, miglitol, and voglibose block the enzyme alpha-glucosidase in the cells of the brush border of the small intestine, which delays absorption of carbohydrates. Alpha-glucosidase inhibitors primarily affect postprandial hyperglycemia without causing hypoglycemia. Abdominal cramps, bloating, flatulence, and diarrhea are the most common side effects. Use of alpha-glucosidase inhibitors should be avoided in patients with severe hepatic or renal impairment. Dosing is prior to carbohydrate-containing meals.^{8,20}

Incretin-based therapies

Therapies that target the incretin hormones to increase insulin production include glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors.

GLP-1 agonists

Exenatide, liraglutide, albiglutide, and dulaglutide are synthetic analogs of the GLP-1 hormone. GLP-1 is produced in the small

intestine; it stimulates insulin secretion and inhibits glucagon secretion in a glucose-dependent manner. It also delays gastric emptying and suppresses appetite through central pathways. GLP-1 agonists primarily decrease postprandial blood glucose levels; however, a moderate reduction in fasting blood glucose and some weight loss can also occur.

The major side effects are gastrointestinal complaints such as nausea, vomiting, and diarrhea. Hypoglycemia does not occur unless GLP-1 analogues are combined with a sulfonylurea or insulin. There is a slightly increased risk of acute pancreatitis in patients using GLP-1 agonist medications, and patients must be warned to discontinue use of these medications if abdominal pain occurs.

Dosing of GLP-1 agonist medications is either twice daily, daily, or weekly by subcutaneous injection.^{8,21}

DPP-4 inhibitors

DPP-4 is an enzyme that rapidly degrades GLP-1. Suppression of DPP-4 leads to higher levels of insulin secretion and suppression of glucagon secretion in a glucose-dependent manner.

The DPP-4 inhibitors such as linagliptin, sitagliptin, saxagliptin, and alogliptin are given orally once daily. An increased risk of acute pancreatitis has been reported in some patients. Dose reduction is needed in patients with renal impairment for most of these medications.^{8,22}

SLGT-2 inhibitors

SGLT-2 inhibitors include canagliflozin, dapagliflozin, and empagliflozin and are the newest group of antidiabetic medications. These medications inhibit glucose reabsorption in proximal tubule of the kidney leading to glycosuria, which lowers the blood glucose concentration, lowers blood pressure, and leads to some weight loss. Empagliflozin was shown to be cardioprotective in some patients.²³

SGLT-2 inhibitors are given once a day in the morning and the primary side effects are polyuria and genital yeast infections. These medications are contraindicated in patients with severe end-stage renal disease and those who are on dialysis.^{8,24}

Pramlintide (amylinomimetics)

Pramlintide, an amylinomimetic, is a synthetic drug that acts like amylin, a hormone secreted by beta cells that suppresses glucagon secretion, slows gastric emptying, and suppresses appetite through central pathways. Pramlintide acts primarily on postprandial blood glucose levels.

The side effects of pramlintide are gastrointestinal complaints, especially nausea. Currently, pramlintide is approved only as an adjunctive therapy with insulin, and it can be used in patients with type 1 DM or type 2 DM. The dose for type 1

DM is 15 μg before each meal subcutaneously, and for type 2 DM it is generally 60 μg before meals.²⁵

Dopamine-receptor agonist (bromocriptine)

Bromocriptine is a central dopamine-receptor agonist, and when given in rapid-release form within 2 hours of awakening in the morning, it improves glycemic control for patients with type 2 DM. The mechanism of action resulting in improved glycemic control is unknown. Studies have demonstrated the cardiovascular safety of bromocriptine.²⁶

Side effects of bromocriptine include hypotension, somnolence, and nausea. Individuals with psychiatric disorders may experience exacerbation while taking bromocriptine. Bromocriptine is taken with food to diminish nausea.²⁷

Insulin

Insulin and insulin analogues remain the most direct method of reducing hyperglycemia. There is no upper limit in dosing for therapeutic effect, so it can be used to bring any HbA1c down to near-normal levels. Other benefits of insulin include reducing triglyceride levels and increasing high-density lipoprotein cholesterol.

Hypoglycemia is a concern with use of insulin, and studies have shown that episodes for which the patient required assistance due to the hypoglycemia occurred between 1 and 3 times per 100 patient-years.¹³ Weight gain can occur after initiation of insulin therapy, and patients typically gain 2 kg to 4 kg.⁸

Initiation and Titration of Therapy

All patients with type 1 DM require insulin therapy. There are 2 regimens available: basal-bolus and insulin-pump therapy. Patients with type 2 DM often require insulin, which can be combined with oral hypoglycemic agents. Regimens include basal insulin only, twice-daily premixed insulin, basal-bolus therapy, and insulin-pump therapy.²⁸

Basal-bolus therapy

The basal-bolus regimen combines a long-acting agent for basal-insulin needs that is used once or twice daily and a rapid-acting agent for prandial coverage. Traditionally, 50% of the total daily dose is given as basal insulin (detemir, glargine, degludec) and the remaining dose as prandial insulin divided equally before meals (regular, lispro, glulisine, or aspart).

The meal dose of insulin can be fixed, but it is better to determine the dose based on the carbohydrate content of the meal. To do so, patients should be educated about carbohydrate counting and the dose of insulin required to cover the carbohydrate content of the meal. Consultation with a diabe-

tes educator is needed for patients to effectively dose insulin based on the carbohydrate content of meals. Patients are also provided with a sliding scale of supplemental insulin to use as a third component of therapy when the blood glucose level is higher than desired.

The starting total daily insulin dose is typically 0.3 U/kg for patients with type 1 DM and 0.5 U/kg for patients with type 2 DM if no other medications are used. The ADA recommends adding basal insulin at 0.1 to 0.2 U/kg for patients with type 2 DM once they need it. The key to good glycemic control is self-monitoring of blood glucose by the patient and frequent adjustment of the regimen until control is achieved.⁸

Insulin-pump therapy

The insulin pump allows the use of different basal insulin rates at different periods of the day for greater flexibility with daily dosing. The insulin pump also allows administration of the meal bolus as a single discrete bolus or as an extended bolus (square bolus) over a certain period of time, which allows a better match between insulin delivery and glucose absorption from the meal in patients with abnormalities of gastric emptying. Use of an insulin pump should be considered in the following patients:

- Patients unable to achieve target goals with basal-bolus regimens
- Patients with frequent hypoglycemia, dawn phenomenon, or brittle diabetes
- Pregnant patients
- Patients with insulin sensitivity or those requiring more intense monitoring due to complications.

Recently, continuous glucose monitors have been developed that measure interstitial glucose levels. Continuous glucose monitoring has been shown to lower HbA1c in adult patients with type 1 DM.²⁹

Gestational diabetes

In patients with gestational diabetes, insulin therapy is indicated when exercise and nutritional therapy are ineffective in controlling prandial and fasting blood glucose levels. Basal therapy alone may be sufficient, but a basal-bolus regimen is often required.⁸

Summary

- Glycemic control reduces the development and progression of complications of diabetes such as retinopathy, nephropathy, and neuropathy.
- The primary techniques available to assess the quality of a patient's glycemic control are self-monitoring of blood

glucose and interval measurement of HbA1c.

- Available treatment options to control blood glucose include insulin sensitizers, insulin secretagogues, alpha-glucosidase inhibitors, incretin-based therapies, SGLT-2 inhibitors, amylinomimetics (pramlintide), dopamine-receptor agonist (bromocriptine), and insulin.

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