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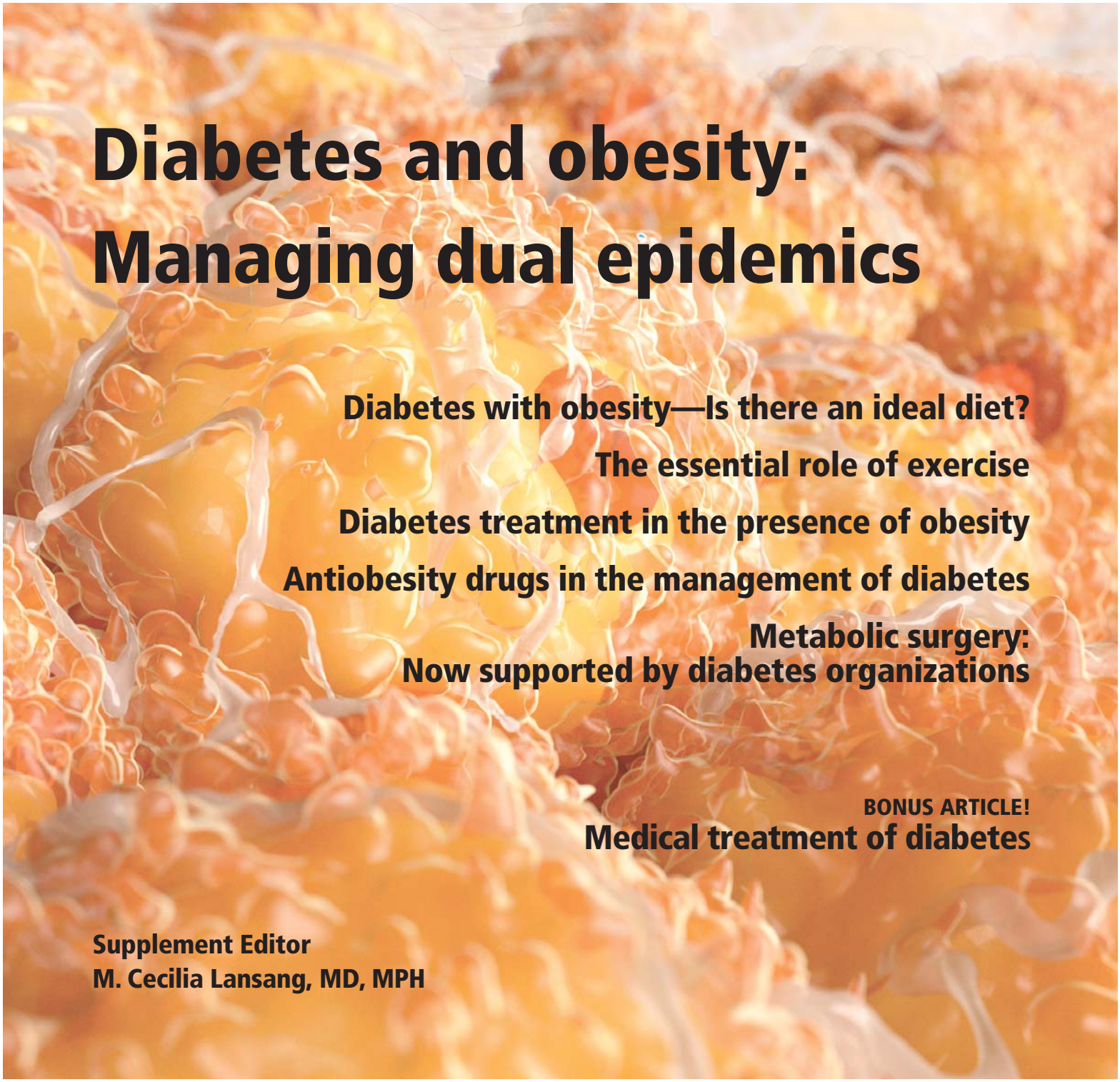

Diabetes and obesity: Managing dual epidemics

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

With type 2 diabetes, life can change in a heartbeat

THE MORNING ON THE BEACH WAS PERFECT…

Reference: 1. Shepherd J, Barter P, Carmena R, et al. Effect of lowering LDL cholesterol substantially below currently recommended levels in patients with coronary heart disease and diabetes. *Diabetes Care.* 2006;29:1220-1226.

[a]The Treating to New Targets (TNT) study included 1501 patients with diabetes and CHD, with LDL cholesterol levels <130 mg/dL. Patients were randomized to receive either atorvastatin 10 mg/day (n=753) or 80 mg/day (n=748) and were followed for a median of 4.9 years. The primary endpoint was the time to first major cardiovascular event.

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Diabetes and obesity: Managing dual epidemics

Supplement Editor

M. Cecilia Lansang, MD, MPH
Endocrinology & Metabolism Institute
Cleveland Clinic

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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.

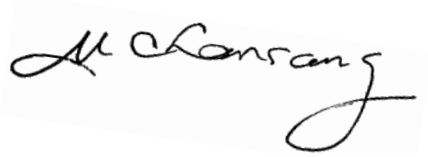
As for exercise, both aerobic and resistance training are essential to improve glucose regulation and cardiovascular health. John P. Kirwan, PhD, Jessica Sacks, and Stephan Nieuwoudt review exercise recommendations, modalities, and the metabolic benefits of exercise for this patient population.

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 macronutient composition of the diet.

Both authors reported no financial interests or relationships that pose a potential conflict of interest with this article.

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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

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% 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 participates 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 reported[24–27]
- Hemoglobin A1c: reduced 1.4% in 6 months, or 0% to 2.2%[18,24]
- Cardiovascular: lower triglyceride, higher high-density lipoprotein cholesterol[18]
- 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 al[25] 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 ± 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 al[17] 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, produce higher peak glucose levels when compared with low-GI foods (< 55). Low-GI foods include lentils, beans, oats, and nonstarchy vegetables.

Summary: low-glycemic diet

Foods with glycemic index < 55

- Foods: whole wheat, rye, pita breads; oats, brown rice, couscous; muesli, bulgur; most fruits; nonstarchy vegatables
- Weight loss: none; −0.32 kg[30]
- Hemoglobin A1c: reduced 0.5%[29]
- Cardiovascular: undetermined
- Weight regain: undetermined
- Challenges: limits important nutrients; glycemic index varies with preparation and among individuals

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 statiety.[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 vegatables
- Avoid: saturated and trans fats
- Weight loss: 5.3 kg in 6 months,[37] 11% in 1 year[38]
- Hemoglobin A1c: minimal to none
- Cardiovascular: lower low-density lipoprotein cholesterol and triglyceride, higher high-density lipoprotein cholesterol[37]
- Weight regain: 4% at 2 years[38]
- 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 disease.[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 al[37] 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 al[36] 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 al[38] 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 al[40] 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]). Saris[38] 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, and increased physical activity.

Summary: very-low-calorie diet

Provides 400 to 800 calories daily with meal replacements[39]

- Foods: meal replacements such as Optifast, SlimFast shakes
- Weight loss: 1.4 to 2.5 kg/week[39]; 16.1% over 12.7 weeks[40]
- Hemoglobin A1c: reduced 0.9% over 12 weeks[41]
- Cardiovascular: little effect[42]
- Weight regain: 62% at 5 years[40]
- Challenges: close monitoring by professionals required; requires meal replacements; low adherence rate

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 year[43]
- Hemoglobin A1c: reduced 0.4% to 0.6%[43,47]; lower incidence type 2 diabetes[46]
- Cardiovascular: systolic blood pressure reduced 7.1 mm Hg; reduced high-density lipoprotein cholesterol ration of .2645
- Weight regain: less, 0.5 kg over 2 years[44]
- 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 al[45] 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 al[47] 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 al[43] 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 al[45] 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 (± 13 kg) initially, 19 kg (± 13 kg) refeeding[49]
- Hemoglobin A1c: mean plasma glucose from 377 to 208 mg/dL; mean fasting glucose from 31 to 17 μU/mL[51]
- 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 years[50]
- Challenges: close monitoring by professionals required; requires meal replacements; lower adherence rate

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 decrease[53]
- Hemoglobin A1c: reduced 0.6% (not statistically significant)[53]
- Cardiovascular: minimal impact, if any[53]
- Weight regain: unknown
- Challenges: may lack important nutrients

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 al[53] 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 information 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 al[54] reported a weight loss of 5.2 kg ± 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 al[55] 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 ± 0.3 mg/dL vs 9.8 mg/dL ± 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 weeks[54]
- Hemoglobin A1c: reduced 0.28%[55]
- Cardiovascular: lower low-density lipoprotein cholesterol, reduction in abdominal fat, no change in high-density lipoprotein cholesterol[54]
- 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 al[54] 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 al[55] 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.

REFERENCES

1. **Kramer H, Cao G, Dugas L, Luke A, Cooper R, Durazo-Arvizu R.** Increasing BMI and waist circumference and prevalence of obesity among adults with type 2 diabetes: The National Health and Nutrition Examination Surveys. J Diabetes Complications 2010; 24:368–374.
2. **Centers for Disease Control and Prevention.** Diabetes Report Card 2014. Atlanta, GA: Centers for Disease Control and Prevention, US Dept of Health and Human Services; 2015.
3. **American Diabetes Association.** Obesity management for the treatment of type 2 diabetes. Sec. 6. In: Standards of Medical Care in Diabetes—2016. Diabetes Care 2016; 39(suppl 1):S47–S51.
4. **Knowler WC, Barrett-Connor E, Fowler SE; Diabetes Prevention Program Research Group.** Reduction in the incidence of type

2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002; 346:393–403.
5. **Franz MJ, Powers MA, Leontos C, et al.** The evidence for medical nutrition therapy for type 1 and type 2 diabetes in adults. J Am Diet Assoc 2010; 110:1852–1889.
6. **American Diabetes Association.** Introduction. In: Standards of Medical Care in Diabetes—2017. Diabetes Care 2017; 40(suppl 1):S1–S2.
7. Defining adult overweight and obesity. Centers for Disease Control and Prevention website. https://www.cdc.gov/obesity/adult/defining.html. Updated June 16, 2016. Accessed June 26, 2017.
8. **Institute of Medicine.** Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty acids, Cholesterol, Protein, and Amino Acids. Washington, DC: National Academy Press; 2002.
9. **American Diabetes Association.** Lifestyle management. Sec. 4. In: Standards of Medical Care in Diabetes—2017. Diabetes Care 2017; 40(suppl 1):S33–S43.
10. **American Diabetes Association.** Obesity management for treatment of type 2 diabetes. Sec. 7. In: Standards of Medical Care in Diabetes—2017. Diabetes Care 2017; 40(suppl 1):S57–S63.
11. **National Institutes of Health.** Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults—the evidence report. Obes Res 1998; 6(suppl 2):51S–209S.
12. **Look AHEAD Research Group; Pi-Sunyer X, Blackburn G, Brancati FL, et al.** Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. Diabetes Care 2007; 30:1374–1383.
13. **Look AHEAD Research Group; Gregg EW, Jakicic JM, Blackburn G, et al.** Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the look AHEAD randomised clinical trial. Lancet Diabetes Endocrinol 2016; 4:913–921.
14. **Look AHEAD Research Group; Wadden TA, West DS, Delahanty L, et al.** The Look AHEAD Study: a description of the lifestyle intervention and the evidence supporting it. Obesity (Silver Spring) 2006; 14:737–752.
15. **Tuomilehto J, Lindstrom J, Eriksson JG, et al; Finnish Diabetes Prevention Study Group.** Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001; 344:1343–1350.
16. **Institute of Medicine.** Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients). Washington, DC: The National Academies Press; 2005. doi:https://doi.org/10.17226/10490.
17. **Kirk JK, Graves DE, Craven TE, Lipkin EW, Austin M, Margolis KL.** Restricted-carbohydrate diets in patients with type 2 diabetes: a meta-analysis. J Am Diet Assoc 2008; 108:91–100.
18. **Franz MJ, Monk A, Barry B, et al.** Effectiveness of medical nutrition therapy provided by dietitians in the management of non-insulin-dependent diabetes mellitus: a randomized, controlled clinical trial. J Am Diet Assoc 1995; 95:1009–1017.
19. **Hu T, Mills KT, Yao L, et al.** Effects of low-carbohydrate diets versus low-fat diets on metabolic risk factors: a meta-analysis of randomized controlled clinical trials. Am J Epidemiol 2012; 176(suppl 7):S44–S54.
20. **Bantle JP, Swanson JE, Thomas W, Laine DC.** Metabolic effects of dietary sucrose in type II diabetic subjects. Diabetes Care 1993; 16:1301–1305.
21. **Malik VS, Popkin BM, Bray GA, Despres JP, Willett WC, Hu FB.** Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes: a meta-analysis. Diabetes Care 2010; 33:2477–2483.
22. **Stanhope KL, Schwarz JM, Havel PJ.** Adverse metabolic effects of dietary fructose: results from the recent epidemiological, clinical, and mechanistic studies. Curr Opin Lipidol 2013; 24:198–206.
23. **Nielsen JV, Jonsson E, Nilsson AK.** Lasting improvement of hyperglycaemia and bodyweight: low-carbohydrate diet in type 2 diabetes. A brief report. Ups J Med Sci 2005; 110:69–73; 179–183.
24. **Robertson AM, Broom J, McRobbie LJ, MacLennan GS.** Low carbohydrate diets in the treatment of resistant overweight patients with type 2 diabetes. Diabet Med 2002; 19(suppl 2):24 [Abstract 94].
25. **Samaha FF, Iqbal N, Seshadri P, et al.** A low-carbohydrate as compared with a low-fat diet in severe obesity. N Engl J Med 2003; 348:2074–2081.
26. **Vetter ML, Iqbal N, Dalton-Bakes C, Volger S, Wadden TA.** Long-term effects of low-carbohydrate versus low-fat diets in obese persons. Ann Intern Med 2010; 152:334–335.
27. **Daly ME, Piper J, Paisey R, et al.** Efficacy of carbohydrate restriction in obese type 2 diabetes patients. Diabet Med 2006; 23(suppl 2):26–27 [Abstract 98].
28. **Thomas D, Elliott EJ.** Low glycaemic index, or low glycaemic load, diets for diabetes mellitus. Cochrane Database Syst Rev 2009; (1):CD006296.
29. **Braunstein CR, Mejia SB, Stoiko E, et al.** Effect of low-glycemic index/load diets on body weight: a systematic review and meta-analysis. FASEB 2016; 30:906.9.
30. **Jenkins DJ, Kendall CW, McKeown-Eyssen G, et al.** Effect of a low-glycemic index or a high-cereal fiber diet on type 2 diabetes: a randomized trial. JAMA 2008; 300:2742–2753.
31. **Järvi AE, Karlstrom BE, Granfeldt YE, Bjorck IE, Asp NG, Vessby BO.** Improved glycaemic control and lipid profile and normalized fibrinolytic activity on a low-glycaemic index diet in type 2 diabetes patients. Diabetes Care 1999; 22:10–18.
32. **Evert AB, Boucher JL, Cypress M, et al.** Nutrition therapy recommendations for the management of adults with diabetes. Diabetes Care 2014; 37(suppl 1):S120–S143.
33. **Savage DB, Petersen KF, Shulman GI.** Disordered lipid metabolism and the pathogenesis of insulin resistance. Physiol Rev 2007; 87:507–520.
34. **Risérus U.** Fatty acids and insulin sensitivity. Curr Opin Clin Nutr Metab Care 2008; 11:100–105.
35. **Oomen CM, Ocke MC, Feskens EJ, van Erp-Baart MA, Kok FJ, Kromhout D.** Association between trans fatty acid intake and 10-year risk of coronary heart disease in the Zutphen Elderly Study: a prospective population-based study. Lancet 2001; 357:746–751.
36. **Nordmann AJ, Nordmann A, Briel M, et al.** Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. Arch Intern Med 2006; 166:285–293.
37. **Foster GD, Wyatt HR, Hill JO, et al.** Weight and metabolic outcomes after 2 years on a low-carbohydrate versus low-fat diet: a randomized trial. Ann Intern Med 2010; 153:147–157.
38. **Saris WH.** Very-low-calorie diets and sustained weight loss. Obes Res 2001; 9(suppl 4):295S–301S.
39. **Tsai A, Wadden TA.** The evolution of very-low-calorie diets: an update and meta-analysis. Obesity 2006; 14:1283–1293.
40. **Toubro S, Astrup A.** Randomised comparison of diets for maintaining obese subjects' weight after major weight loss: ad lib, low fat, high carbohydrate diet v fixed energy intake. BMJ 1997; 314:29–34.
41. **Rothberg AE, McEwen LN, Kraftson AT, Fowler CE, Herman WH.** Very-low-energy diet for type 2 diabetes: an underutilized therapy? J Diabetes Complications 2014; 28:506–510.
42. **Uusitupa MI, Laakso M, Sarlund H, Majander H, Takala J, Penttilä I.** Effects of a very-low-calorie diet on metabolic control and cardiovascular risk factors in the treatment of obese non-insulin-dependent diabetics. Am J Clin Nutr 1990; 51:768–773.
43. **Elhayany A, Lustman A, Abel R, Attal-Singer J, Vinker S.** A low carbohydrate Mediterranean diet improves cardiovascular risk factors and diabetes control among overweight patients with type 2 diabetes mellitus: a 1-year prospective randomized intervention study. Diabetes Obes Metab 2010; 12:204–209.
44. **Mancini JG, Filion KB, Atallah R, Eisenberg MJ.** Systematic review of the Mediterranean diet for long-term weight loss. Am J Med 2016; 129:407–415.e4.
45. **Estruch R, Martinez-González MA, Corella D, et al; PREDIMED Study Investigators.** Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. Ann Intern Med 2006; 145:1–11.
46. **Salas-Salvadó J, Bulló M, Babio N, et al; PREDIMED Study**

Investigators. Reduction in the incidence of type 2 diabetes with the Mediterranean diet: results of the PREDIMED-Reus nutrition intervention randomized trial. Diabetes Care 2011; 34:14–19.
47. **Esposito K, Maiorino MI, Ciotola M, et al.** Effects of a Mediterranean-style diet on the need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes: a randomized trial. Ann Intern Med 2009; 151:306–314.
48. **Chang J, Kashyap SR.** The protein-sparing modified fast for obese patients with type 2 diabetes: what to expect. Cleve Clin J Med 2014; 81:557–565.
49. **Palgi A, Read JL, Greenberg I, Hoefer MA, Bistrian BR, Blackburn GL.** Multidisciplinary treatment of obesity with a protein-sparing modified fast: results in 668 outpatients. Am J Public Health 1985; 75:1190–1194.
50. **Paisey RB, Frost J, Harvey P, et al.** Five year results of a prospective very low calorie diet or conventional weight loss programme in type 2 diabetes. J Hum Nutr Diet 2002; 15:121–127.
51. **Hughes TA, Gwynne JT, Switzer BR, Herbst C, White G.** Effects of caloric restriction and weight loss on glycemic control, insulin release and resistance, and atherosclerotic risk in obese patients with type II diabetes mellitus. Am J Med 1984; 77:7–17.
52. **Li Z, Tseng CH, Li Q, Deng ML, Wang M, Heber D.** Clinical efficacy of a medically supervised outpatient high-protein, low-calorie diet program is equivalent in prediabetic, diabetic and normoglycemic obese patients. Nutr Diabetes 2014; 4:e105.
53. **Mishra S, Xu J, Agarwal U, Gonzales J, Levin S, Barnard ND.** A multicenter randomized controlled trial of a plant-based nutrition program to reduce body weight and cardiovascular risk in the corporate setting: the GEICO study. Eur J Clin Nutr 2013; 67:718–724.
54. **Parker B, Noakes M, Luscombe N, Clifton P.** Effect of a high-protein, high-monounsaturated fat weight loss diet on glycemic control and lipid levels in type 2 diabetes. Diabetes Care 2002; 25:425–430.
55. **Ajala O, English P, Pinkney J.** Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes. Am J Clin Nutr 2013; 97:505–516.
56. **Gannon MC, Nuttall FQ.** Effect of a high-protein, low-carbohydrate diet on blood glucose control in people with type 2 diabetes. Diabetes 2004; 53:2375–2382.

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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.

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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 effects 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 approach[6] 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

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% ± 0.41 vs 0.31% ± 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 ± 0.4 vs 0.94 mU/L ± 0.21, $P = .031$), and systolic blood pressure (−6.9 mm Hg ± 5.19 vs 1.22 mm Hg ± 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 al[21] 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 al[24] 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 al[25] demonstrated that combined aerobic and resistance training markedly improved HbA1c (from 8.31% ± 1.73 to 7.1% ± 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 Hopkins[26] 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 colleagues[27] 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.

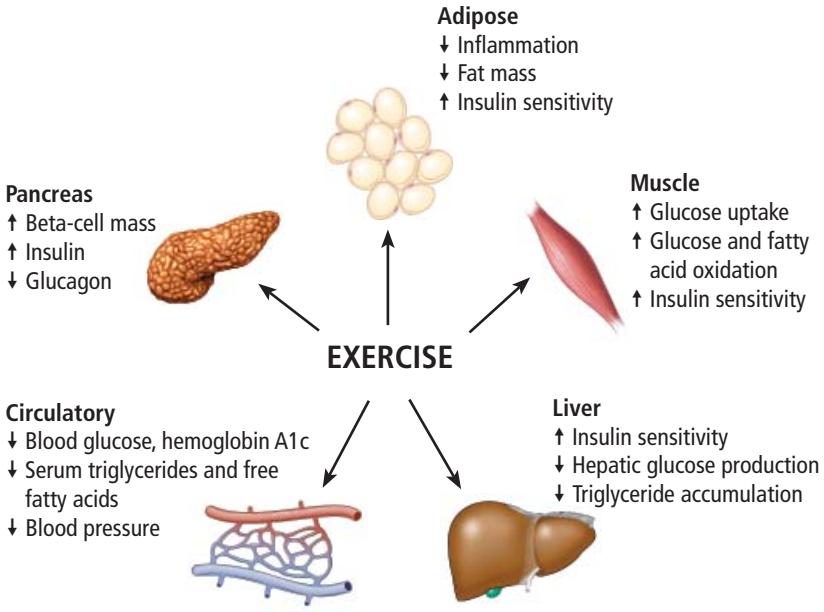

FIGURE 1. Tissue-specific metabolic effects of exercise in patients with type 2 diabetes.

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 mechanisms 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 oxidation[10] 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 al[43] 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 colleagues[51] 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 frequency[56] 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.

REFERENCES

1. **Centers for Disease Control and Prevention.** National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014. US Department of Health and Human Services; 2014.
2. **Whiting DR, Guariguata L, Weil C, Shaw J.** IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 2011; 94:311–321.
3. **Korner J, Bessler M, Cirilo LJ, et al.** Effects of Roux-en-Y gastric bypass surgery on fasting and postprandial concentrations of plasma ghrelin, peptide YY, and insulin. J Clin Endocrinol Metab 2005; 90:359–365.
4. **Schauer PR, Bhatt DL, Kirwan JP, et al; for the STAMPEDE Investigators.** Bariatric surgery versus intensive medical therapy for diabetes—3-year outcomes. N Engl J Med 2014; 370:2002–2013.
5. **Schauer PR, Kashyap SR, Wolski K, et al.** Bariatric surgery versus intensive medical therapy in obese patients with diabetes. N Engl J Med 2012; 366:1567–1576.
6. **Wing RR, Bolin P, Brancati FL, et al; for the Look AHEAD Research Group.** Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013; 369:145–154.
7. **Tipton CM.** The history of "Exercise Is Medicine" in ancient civilizations. Adv Physiol Educ 2014; 38:109–117.
8. **Zanuso S, Jimenez A, Pugliese G, Corigliano G, Balducci S.** Exercise for the management of type 2 diabetes: a review of the evidence. Acta Diabetol 2010; 47:15–22.
9. **Sigal RJ, Kenny GP, Wasserman DH, Castaneda-Sceppa C, White RD.** Physical activity/exercise and type 2 diabetes: a consensus statement from the American Diabetes Association. Diabetes Care 2006; 29:1433–1438.
10. **Garber CE, Blissmer B, Deschenes MR, et al; for the American College of Sports Medicine.** Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc 2011; 43:1334–1359.
11. **Boulé NG, Kenny GP, Haddad E, Wells GA, Sigal RJ.** Meta-analysis of the effect of structured exercise training on cardiorespiratory fitness in type 2 diabetes mellitus. Diabetologia 2003; 46:1071–1081.
12. **Wei M, Gibbons LW, Kampert JB, Nichaman MZ, Blair SN.** Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with type 2 diabetes. Ann Intern Med 2000; 132:605–611.
13. **Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M.** Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998; 339:229–234.
14. **Kadoglou NPE, Iliadis F, Angelopoulou N, et al.** The anti-inflammatory effects of exercise training in patients with type 2 diabetes mellitus. Eur J Cardiovasc Prev Rehabil 2007; 14:837–843.
15. **Kirwan JP, Solomon TPJ, Wojta DM, Staten MA, Holloszy JO.** Effects of 7 days of exercise training on insulin sensitivity and responsiveness in type 2 diabetes mellitus. Am J Physiol Endocrinol Metab 2009; 297:E151–E156.
16. **Winnick JJ, Sherman WM, Habash DL, et al.** Short-term aerobic exercise training in obese humans with type 2 diabetes mellitus improves whole-body insulin sensitivity through gains in peripheral, not hepatic insulin sensitivity. J Clin Endocrinol Metab 2008; 93:771–778.
17. **King DS, Baldus PJ, Sharp RL, Kesl LD, Feltmeyer TL, Riddle MS.** Time course for exercise-induced alterations in insulin action and glucose tolerance in middle-aged people. J Appl Physiol (1985) 1995; 78:17–22.
18. **Colberg SR, Sigal RJ, Yardley JE, et al.** Physical activity/exercise and diabetes: a position statement of the American Diabetes Association. Diabetes Care 2016; 39:2065–2079.
19. **Sluik D, Buijsse B, Muckelbauer R, et al.** Physical activity and mortality in individuals with diabetes mellitus: a prospective study and meta-analysis. Arch Intern Med 2012; 172:1285–1295.
20. **Gordon BA, Benson AC, Bird SR, Fraser SF.** Resistance training improves metabolic health in type 2 diabetes: a systematic review. Diabetes Res Clin Pract 2009; 83:157–175.
21. **Dunstan DW, Daly RM, Owen N, et al.** High-intensity resistance training improves glycemic control in older patients with type 2 diabetes. Diabetes Care 2002; 25:1729–1736.
22. **Dunstan DW, Puddey IB, Beilin LJ, Burke V, Morton AR, Stanton KG.** Effects of a short-term circuit weight training program on glycaemic control in NIDDM. Diabetes Res Clin Pract 1998; 40:53–61.
23. **Castaneda C, Layne JE, Munoz-Orians L, et al.** A randomized controlled trial of resistance exercise training to improve glycemic control in older adults with type 2 diabetes. Diabetes Care 2002; 25:2335–2341.
24. **Cuff DJ, Meneilly GS, Martin A, Ignaszewski A, Tildesley HD, Frohlich JJ.** Effective exercise modality to reduce insulin resistance

in women with type 2 diabetes. Diabetes Care 2003; 26:2977–2982.
25. **Balducci S, Leonetti F, Di Mario U, Fallucca F.** Is a long-term aerobic plus resistance training program feasible for and effective on metabolic profiles in type 2 diabetic patients [letter]? Diabetes Care 2004; 27:841–842.
26. **Snowling NJ, Hopkins WG.** Effects of different modes of exercise training on glucose control and risk factors for complications in type 2 diabetic patients: a meta-analysis. Diabetes Care 2006; 29:2518–2527.
27. **Schwingshackl L, Missbach B, Dias S, König J, Hoffmann G.** Impact of different training modalities on glycaemic control and blood lipids in patients with type 2 diabetes: a systematic review and network meta-analysis. Diabetologia 2014; 57:1789–1797.
28. **Jelleyman C, Yates T, O'Donovan G, et al.** The effects of high-intensity interval training on glucose regulation and insulin resistance: a meta-analysis. Obes Rev 2015; 16:942–961.
29. **Gibala MJ, Little JP, Macdonald MJ, Hawley JA.** Physiological adaptations to low-volume, high-intensity interval training in health and disease. J Physiol 2012; 590:1077–1084.
30. **Nieuwoudt S, Fealy CE, Foucher JA, et al.** Functional high intensity training improves pancreatic beta-cell function in adults with type 2 diabetes. Am J Physiol Endocrinol Metab 2017. doi 10.1152/ajpendo.00407.2016 [Epub ahead of print]
31. **Lawrence RD.** The effect of exercise on insulin action in diabetes. Br Med J 1926; 1:648–650.
32. **Hawley JA, Lessard SJ.** Exercise training-induced improvements in insulin action. Acta Physiol (Oxf) 2008; 192:127–135.
33. **Magkos F, Tsekouras Y, Kavouras SA, Mittendorfer B, Sidossis LS.** Improved insulin sensitivity after a single bout of exercise is curvilinearly related to exercise energy expenditure. Clin Sci (Lond) 2008; 114:59–64.
34. **Holloszy JO.** Exercise-induced increase in muscle insulin sensitivity. J Appl Physiol (1985) 2005; 99:338–343.
35. **Hawley JA, Hargreaves M, Zierath JR.** Signalling mechanisms in skeletal muscle: role in substrate selection and muscle adaptation. Essays Biochem 2006; 42:1–12.
36. **Ruderman NB, Carling D, Prentki M, Cacicedo JM.** AMPK, insulin resistance, and the metabolic syndrome. J Clin Invest 2013; 123:2764–2772.
37. **Mulya A, Haus JM, Solomon TPJ, et al.** Exercise training-induced improvement in skeletal muscle PGC-1alpha-mediated fat metabolism is independent of dietary glycemic index. Obesity (Silver Spring) 2017; 25:721–729.
38. **Dandona P, Aljada A, Chaudhuri A, Bandyopadhyay A.** The potential influence of inflammation and insulin resistance on the pathogenesis and treatment of atherosclerosis-related complications in type 2 diabetes. J Clin Endocrinol Metab 2003; 88:2422–2429.
39. **Kritchevsky SB, Cesari M, Pahor M.** Inflammatory markers and cardiovascular health in older adults. Cardiovasc Res 2005; 66:265–275.
40. **Cusi K.** The role of adipose tissue and lipotoxicity in the pathogenesis of type 2 diabetes. Curr Diab Rep 2010; 10:306–315.
41. **Balducci S, Zanuso S, Nicolucci A, et al.** Anti-inflammatory effect of exercise training in subjects with type 2 diabetes and the metabolic syndrome is dependent on exercise modalities and independent of weight loss. Nutr Metab Cardiovasc Dis 2010; 20:608–617.
42. **Jorge MLMP, de Oliveira VN, Resende NM, et al.** The effects of aerobic, resistance, and combined exercise on metabolic control, inflammatory markers, adipocytokines, and muscle insulin signaling in patients with type 2 diabetes mellitus. Metabolism 2011; 60:1244–1252.
43. **Ibañez J, Izquierdo M, Argüelles I, et al.** Twice-weekly progressive resistance training decreases abdominal fat and improves insulin sensitivity in older men with type 2 diabetes. Diabetes Care 2005; 28:662–667.
44. **Basu R, Chandramouli V, Dicke B, Landau B, Rizza R.** Obesity and type 2 diabetes impair insulin-induced suppression of glycogenolysis as well as gluconeogenesis. Diabetes 2005; 54:1942–1948.
45. **Wallace TM, Levy JC, Matthews DR.** Use and abuse of HOMA modeling. Diabetes Care 2004; 27:1487–1495.
46. **Petersen KF, Dufour S, Befroy D, Lehrke M, Hendler RE, Shulman GI.** Reversal of nonalcoholic hepatic steatosis, hepatic insulin resistance, and hyperglycemia by moderate weight reduction in patients with type 2 diabetes. Diabetes 2005; 54:603–608.
47. **Carlson CL, Winder WW.** Liver AMP-activated protein kinase and acetyl-CoA carboxylase during and after exercise. J Appl Physiol (1985) 1999; 86:669–674.
48. **Haus JM, Solomon TPJ, Marchetti CM, et al.** Decreased visfatin after exercise training correlates with improved glucose tolerance. Med Sci Sports Exerc 2009; 41:1255–1260.
49. **DeFronzo RA.** Pathogenesis of type 2 (non-insulin dependent) diabetes mellitus: a balanced overview. Diabetologia 1992; 35:389–397.
50. **Cersosimo E, Solis-Herrera C, Trautmann ME, Malloy J, Triplitt CL.** Assessment of pancreatic beta-cell function: review of methods and clinical applications. Curr Diabetes Rev 2014; 10:2–42.
51. **Dela F, von Linstow ME, Mikines KJ, Galbo H.** Physical training may enhance beta-cell function in type 2 diabetes. Am J Physiol Endocrinol Metab 2004; 287:E1024–E1031.
52. **Solomon TPJ, Haus JM, Kelly KR, Rocco M, Kashyap SR, Kirwan JP.** Improved pancreatic beta-cell function in type 2 diabetic patients after lifestyle-induced weight loss is related to glucose-dependent insulinotropic polypeptide. Diabetes Care 2010; 33:1561–1566.
53. **Kirwan JP, Kohrt WM, Wojta DM, Bourey RE, Holloszy JO.** Endurance exercise training reduces glucose-stimulated insulin levels in 60- to 70-year-old men and women. J Gerontol 1993; 48:M84–M90.
54. **Solomon TPJ, Malin SK, Karstoft K, Kashyap SR, Haus JM, Kirwan JP.** Pancreatic beta-cell function is a stronger predictor of changes in glycemic control after an aerobic exercise intervention than insulin sensitivity. J Clin Endocrinol Metab 2013; 98:4176–4186.
55. **Madsen SM, Thorup AC, Overgaard K, Jeppesen PB.** High intensity interval training improves glycaemic control and pancreatic beta cell function of type 2 diabetes patients. PloS One 2015; 10:e0133286.
56. **Umpierre D, Ribeiro PAB, Schaan BD, Ribeiro JP.** Volume of supervised exercise training impacts glycaemic control in patients with type 2 diabetes: a systematic review with meta-regression analysis. Diabetologia 2013; 56:242–251.

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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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Diabesity was a term coined by Sims et al[1] 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]

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 Iepsen et al.[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 µg (−1.6 ± 0.4 kg) and exenatide 10 µg (−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 µg 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 µg 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/m^2), 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 10 µg BID	0.5 to 0.7 0.7 to –1.7	–1.1 to –2.7 –1.5 to –2.9
Liraglutide (Victoza)[10]	Once daily at any time of day	0.6 mg QD 1.2 mg QD 1.8 mg QD	 0.8 to 1.1 0.5 to 1.5	 +0.3 to –2.6 –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 50 mg QW	0.7 to 0.8 0.6 to 0.9	–0.4 to –1.2
Dulaglutide (Trulicity)[13]	Once weekly at any time of day	0.75 mg QW 1.5 mg QW	0.7 to 1.6 0.8 to 1.6	+0.2 to –2.8 –0.9 to –3.1
Lixisenatide (Adlyxin)[14]	Within 60 minutes before main meal	10 µg QD 20 µg QD	0.6 to 0.9	+0.31 to –2.7

[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 al[21] 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 al[35] 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 intolerance[58] occurring early in therapy have been noted to account for weight loss in short-term studies of nondiabetic 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 B_{12} 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 diabesity.

REFERENCES

1. **Sims EAH, Danforth E Jr, Horton ES, Bray GA, Glennon JA, Salans LB.** Endocrine and metabolic effects of experimental obesity in man. Recent Prog Horm Res 1973; 29:457–496.
2. **Scheen AJ, Van Gaal LF.** Combating the dual burden: therapeutic targeting of common pathways in obesity and type 2 diabetes. Lancet Diabetes Endocrinol 2014; 2:911–922.
3. **Kahn SE, Hull RL, Utzschneider KM.** Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature 2006; 444:840–846.
4. **Iepsen EW, Torekov SS, Holst JJ.** Therapies for inter-relating diabetes and obesity—GLP-1 and obesity. Expert Opin Pharmacother 2014; 15:2487–2500.
5. **Meier JJ, Nauck MA.** Glucagon-like peptide 1(GLP-1) in biology and pathology. Diabetes Metab Res Rev 2005; 21:91–117.
6. **Turton MD, O'Shea D, Gunn I, et al.** A role for glucagon-like peptide-1 in the central regulation of feeding. Nature 1996; 379:69–72.
7. **Drucker DJ.** Glucagon-like peptides: regulators of cell proliferation, differentiation, and apoptosis. Mol Endocrinol 2003; 17:161–171.
8. **Shyangdan DS, Royle P, Clar C, Sharma P, Waugh N, Snaith A.** Glucagon-like peptide analogues for type 2 diabetes mellitus. Cochrane Database Syst Rev 2011; 10:CD006423. doi:10.1002/14651858.CD006423.pub2.
9. Byetta [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2015. Available at http://www.azpicentral.com/byetta/pi_byetta.pdf. Accessed June 22, 2017.
10. Victoza [package insert]. Bagsvaerd, Denmark: Novo Nordisk A/S; 2016. Available at http://www.novo-pi.com/victoza.pdf. Accessed June 22, 2017.
11. Bydureon [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2015. Available at http://www.azpicentral.com/bydureon/pi_bydureon.pdf. Accessed June 22, 2017.
12. Tanzeum [package insert]. Wilmington, DE: GlaxoSmithKline; 2016. Available at https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Tanzeum/pdf/TANZEUM-PI-MG-IFU-COMBINED.PDF. Accessed June 22, 2017.

13. Trulicity [package insert]. Indianapolis, IN: Eli Lilly and Company 2014. Available at http://pi.lilly.com/us/trulicity-uspi.pdf. Accessed June 22, 2017.
14. Adlyxin [package insert]. Bridgewater, NJ: Sanofi-Aventis U.S. LLC; 2016. Available at http://products.sanofi.us/adlyxin/adlyxin.pdf. Accessed June 22, 2017.
15. **DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD.** Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. Diabetes Care 2005; 28:1092–1100.
16. **Nikfar S, Abdollahi M, Salari P.** The efficacy and tolerability of exenatide in comparison to placebo; a systematic review and meta-analysis of randomized clinical trials. J Pharm Pharm Sci 2012; 15:1–30.
17. **Blonde L, Russell-Jones D.** The safety and efficacy of liraglutide with or without oral antidiabetic drug therapy in type 2 diabetes: an overview of the LEAD 1-5 studies. Diabetes Obes Metab 2009; 11(suppl 3):26–34.
18. **Garber A, Henry R, Ratner R, et al; LEAD-3 (Mono) Study Group.** Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. Lancet 2009; 373:473–481.
19. **Zinman B, Gerich J, Buse JB, et al; LEAD-4 Study Investigators.** Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). Diabetes Care 2009; 32:1224–1230.
20. **Davies MJ, Bergenstal R, Bode B, et al.** Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE Diabetes Randomized Clinical Trial. JAMA 2015; 314:687–699.
21. **Pi-Sunyer X, Astrup A, Fujioka K, et al; SCALE Obesity and Prediabetes NN8022-1839 Study Group.** A randomized, controlled trial of 3.0 mg of liraglutide in weight management. N Engl J Med 2015; 373:11–22.
22. **Vilsboll T, Christensen M, Junker AE, Knop FK, Gluud LL.** Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. BMJ 2012; 344:d7771.
23. **Valsamakis G, Konstantakou P, Mastorakos G.** New targets for drug treatment of obesity. Annu Rev Pharmacol Toxicol 2017; 57:585–605.
24. **Sivertsen J, Rosenmeier J, Holst JJ, Vilsboll T.** The effect of glucagon-like peptide 1 on cardiovascular risk. Nat Rev Cardiol 2012; 9:209–222.
25. **Marso SP, Daniels GH, Brown-Frandsen K, et al; LEADER Steering Committee; LEADER Trial Investigators.** Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016; 375:311–322.
26. **Lean ME, Carraro R, Finer N, et al; NN8022-1807 Investigators.** Tolerability of nausea and vomiting and associations with weight loss in a randomized trial of liraglutide in obese, non-diabetic adults. Int J Obes (Lond) 2014; 38:689–697.
27. **Aroda VR, Rosenstock J, Wysham C, et al; LixiLan-L Trial Investigators.** Efficacy and safety of lixilan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide in type 2 diabetes inadequately controlled on basal insulin and metformin: the LixiLan-L Randomized Trial. Diabetes Care 2016; 39:1972–1980.
28. **Rosenstock J, Diamant M, Aroda VR, et al; LixiLan PoC Study Group.** Efficacy and safety of LixiLan, a titratable fixed-ratio combination of lixisenatide and insulin glargine, versus insulin glargine in type 2 diabetes inadequately controlled on metformin monotherapy: the LixiLan Proof-of-Concept Randomized Trial. Diabetes Care 2016; 39:1579–1586.
29. **Monica Reddy RP, Inzucchi SE.** SGLT2 inhibitors in the management of type 2 diabetes. Endocrine 2016; 53:364–372.
30. **DeFronzo RA, Davidson JA, Del Prato S.** The role of the kidneys in glucose homeostasis: a new path towards normalizing glycaemia. Diabetes Obes Metab 2012; 14:5–14.
31. **Liu JJ, Lee T, DeFronzo RA.** Why do SGLT2 inhibitors inhibit only 30-50% of renal glucose reabsorption in humans? Diabetes 2012; 61:2199–2204.
32. **Vasilakou D, Karagiannis T, Athanasiadou E, et al.** Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2013; 159:262–274.
33. **Stenlof K, Cefalu WT, Kim KA, et al.** Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes Obes Metab 2013; 15:372–382.
34. **Kadowaki T, Haneda M, Inagaki N, et al.** Empagliflozin monotherapy in Japanese patients with type 2 diabetes mellitus: a randomized, 12-week, double-blind, placebo-controlled, phase II trial. Adv Ther 2014; 31:621–638.
35. **Bolinder J, Ljunggren O, Kullberg J, et al.** Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. J Clin Endocrinol Metab 2012; 97:1020–1031.
36. **Bolinder J, Ljunggren O, Johansson L, et al.** Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabetes mellitus inadequately controlled on metformin. Diabetes Obes Metab 2014; 16:159–169.
37. **Zinman B, Wanner C, Lachin JM, et al; EMPA-REG OUTCOME Investigators.** Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015; 373:2117–2128.
38. **Lutz TA.** Effects of amylin on eating and adiposity. Handb Exp Pharmacol 2012; (209):231–250.
39. **Hieronymus L, Griffin S.** Role of amylin in type 1 and type 2 diabetes. Diabetes Educ 2015; 41(suppl 1):47S–56S.
40. **Aronoff SL.** Rationale for treatment options for mealtime glucose control in patients with type 2 diabetes. Postgrad Med 2017; 129:231–241.
41. **Ratner RE, Dickey R, Fineman M, et al.** Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in type 1 diabetes mellitus: a 1-year, randomized controlled trial. Diabet Med 2004; 21:1204–1212.
42. **Edelman S, Garg S, Frias J, et al.** A double-blind, placebo-controlled trial assessing pramlintide treatment in the setting of intensive insulin therapy in type 1 diabetes. Diabetes Care 2006; 29:2189–2195.
43. **Riddle M, Frias J, Zhang B, et al.** Pramlintide improved glycemic control and reduced weight in patients with type 2 diabetes using basal insulin. Diabetes Care 2007; 30:2794–2799.
44. **Hollander PA, Levy P, Fineman MS, et al.** Pramlintide as an adjunct to insulin therapy improves long-term glycemic and weight control in patients with type 2 diabetes: a 1-year randomized controlled trial. Diabetes Care 2003; 26:784–790.
45. **Singh-Franco D, Perez A, Harrington C.** The effect of pramlintide acetate on glycemic control and weight in patients with type 2 diabetes mellitus and in obese patients without diabetes: a systematic review and meta-analysis. Diabetes Obes Metab 2011; 13:169–180.
46. **Wysham C, Lush C, Zhang B, Maier H, Wilhelm K.** Effect of pramlintide as an adjunct to basal insulin on markers of cardiovascular risk in patients with type 2 diabetes. Curr Med Res Opin 2008; 24:79–85.
47. **Bischoff H.** Pharmacology of alpha-glucosidase inhibition. Eur J Clin Invest 1994; 24(suppl 3):3–10.
48. **Lee A, Patrick P, Wishart J, Horowitz M, Morley JE.** The effects of miglitol on glucagon-like peptide-1 secretion and appetite sensations in obese type 2 diabetics. Diabetes Obes Metab 2002; 4:329–335.
49. **van de Laar FA, Lucassen PL, Akkermans RP, van de Lisdonk EH, Rutten GE, van Weel C.** Alpha-glucosidase inhibitors for patients with type 2 diabetes: results from a Cochrane systematic review and meta-analysis. Diabetes Care 2005; 28:154–163.
50. **Gross JL, Kramer CK, Leitao CB, et al; Diabetes and Endocrinology Meta-analysis Group (DEMA).** Effect of antihyperglycemic agents added to metformin and a sulfonylurea on glycemic control and weight gain in type 2 diabetes: a network meta-analysis. Ann Intern Med 2011; 154:672–679.
51. **Schnell O, Weng J, Sheu WH, et al.** Acarbose reduces body weight irrespective of glycemic control in patients with diabetes: results of

a worldwide, non-interventional, observational study data pool. J Diabetes Complications 2016; 30:628–637.
52. **Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M; STOP-NIDDM Trial Research Group.** Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. JAMA 2003; 290:486–494.
53. **Inzucchi SE, Bergenstal RM, Buse JB, et al.** Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015; 38:140–149.
54. **American Diabetes Association.** Pharmacologic approaches to glycemic treatment. Diabetes Care 2017; 40:S64–S74.
55. **Tan MH, Alquraini H, Mizokami-Stout K, MacEachern M.** Metformin: From research to clinical practice. Endocrinol Metab Clin North Am 2016; 45:819–843.
56. **Paolisso G, Amato L, Eccellente R, et al.** Effect of metformin on food intake in obese subjects. Eur J Clin Invest 1998; 28: 441–446.
57. **Lee A, Morley JE.** Metformin decreases food consumption and induces weight loss in subjects with obesity with type II noninsulin-dependent diabetes. Obes Res 1998; 6: 47–53.
58. **Scarpello JH.** Optimal dosing strategies for maximising the clinical response to metformin in type 2 diabetes. Br J Diabetes Vasc Dis 2001; 1: 28–36.
59. **Golay A.** Metformin and body weight. Int J Obes (Lond) 2008; 32:61–72.
60. **UK Prospective Diabetes Study (UKPDS) Group.** Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998; 352:854–865.
61. **Knowler WC, Barrett-Connor E, Fowler SE, et al; Diabetes Prevention Program Research Group.** Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002; 346:393–403.
62. **Fujita Y, Inagaki N.** Metformin: new preparations and nonglycemic benefits. Curr Diab Rep 2017; 17:5.

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For your adult patients with T2DM uncontrolled on basal insulin (<60 Units daily) or lixisenatide as an adjunct to diet and exercise

HELP MORE PATIENTS PUT HIGH HbA1c PERCENTAGES BEHIND THEM

SOLIQUA 100/33 combines the powerful control of Lantus® and lixisenatide, a GLP-1 Receptor Agonist

Indications and Usage for SOLIQUA® 100/33

SOLIQUA 100/33 is a combination of insulin glargine and lixisenatide and is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on basal insulin (less than 60 units daily) or lixisenatide.

Limitations of Use:

- Has not been studied in patients with a history of unexplained pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.
- Is not recommended for use in combination with lixisenatide or another GLP-1 RA.
- Is not indicated for use in patients with type 1 diabetes mellitus or diabetic ketoacidosis.
- Has not been studied in patients with gastroparesis and is not recommended for use in patients with gastroparesis.
- Has not been studied in combination with prandial insulin.

Important Safety Information for SOLIQUA® 100/33

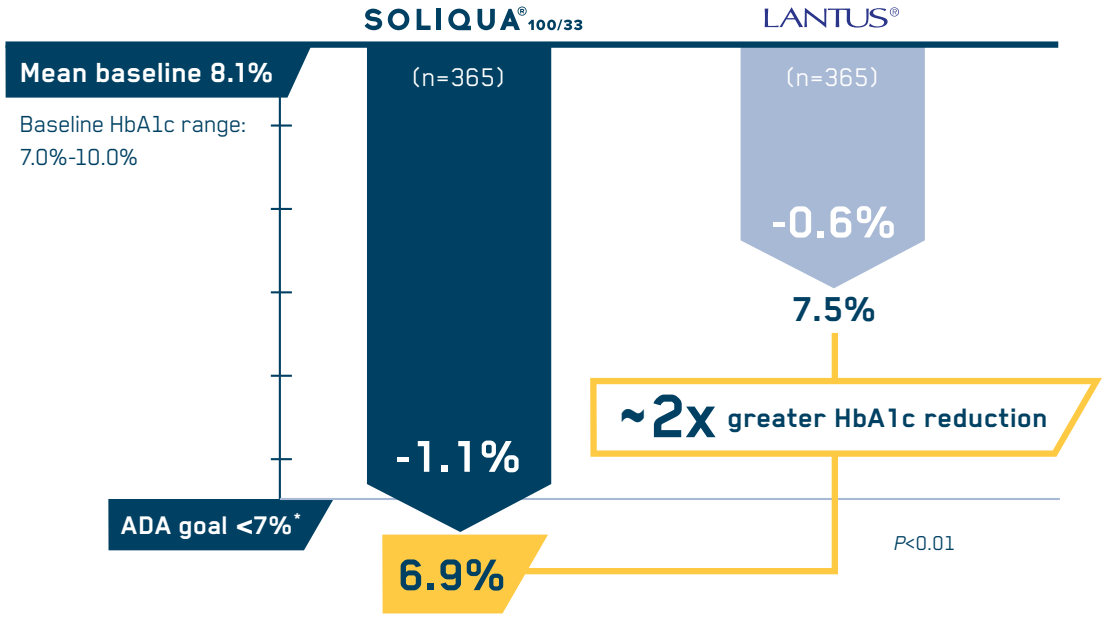
Contraindications

- During episodes of hypoglycemia.
- In patients with known hypersensitivity to the active substance(s) or to any of the product components.

Please see additional Important Safety Information for SOLIQUA 100/33 on the following pages.
Please see Brief Summary of Full Prescribing Information on the following pages.

SOLIQUA® 100/33
insulin glargine & lixisenatide injection
100 Units/mL & 33 mcg/mL

~2x greater reduction in mean HbA1c, statistically significant vs Lantus®



* American Diabetes Association. Standards of medical care in diabetes–2017. *Diabetes Care.* 2017.

The mean final dose of SOLIQUA 100/33 and insulin glargine 100 Units/mL at Week 30 was equivalent–46.7 Units (for SOLIQUA 100/33: 46.7 Units insulin glargine/15.6 mcg lixisenatide).

The difference in effect observed in the trial may not necessarily reflect the effect that will be observed in the care setting where alternative insulin glargine dosage can be used.

CLINICAL STUDY DESIGN

A total of 736 patients with T2DM participated in a randomized, 30-week, open-label, multicenter study to evaluate the efficacy and safety of SOLIQUA 100/33 compared to Lantus®.

- Adult patients with T2DM, mean age 60 years, uncontrolled on a stable daily basal insulin dose ± 1 or 2 oral antidiabetic drugs (OADs) for ≥6 months (HbA1c of 7.5%-10%; fasting plasma glucose [FPG] ≤180 mg/dL) were screened
- Eligible patients (n=1018) were enrolled in a 6-week run-in period during which they remained on or were switched to Lantus® if on another basal insulin, and had their dose titrated/stabilized while continuing on metformin (if previously taken). Any other OADs were discontinued
- Patients inadequately controlled at the end of the run-in period (n=736; HbA1c between 7% and 10%; FPG ≤140 mg/dL) and on an insulin glargine dose of 20-50 Units (mean dose of 35 Units) were randomized to SOLIQUA 100/33 (n=367) or Lantus® (n=369)
- The primary endpoint was change in mean HbA1c at Week 30
- The maximum allowable insulin glargine dose was 60 Units for both treatment groups
- The trial was designed to show the contribution of the GLP-1 component to glycemic lowering and the insulin glargine dose and the dosing algorithm was selected to isolate the effect of the GLP-1 component

SOLIQUA® 100/33
insulin glargine & lixisenatide injection
100 Units/mL & 33 mcg/mL

Safety shown in clinical trials

INCIDENCE OF HYPOGLYCEMIA IN ADULT PATIENTS WITH T2DM TREATED WITH SOLIQUA 100/33 IN CLINICAL TRIALS

	Study A (N=469)	Study B (N=365)
Severe symptomatic hypoglycemia*	0.0%	1.1%
Documented symptomatic hypoglycemia†	25.6%	40.0%

*__Severe symptomatic hypoglycemia__ defined as an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

†__Documented symptomatic hypoglycemia__ defined as an event with typical symptoms of hypoglycemia accompanied by a self-monitored plasma glucose value equal to or less than 70 mg/dL.

TREATMENT-EMERGENT ADVERSE EVENTS (WITH FREQUENCY ≥5%) IN 2 POOLED CLINICAL TRIALS

Adverse Event	SOLIQUA 100/33 (N=834)
Nausea‡	10.0%
Diarrhea‡	7.0%
Nasopharyngitis	7.0%
Upper respiratory tract infection	5.5%
Headache	5.4%

‡__Gastrointestinal adverse reactions__ occur more frequently at the beginning of therapy.

Important Safety Information for SOLIQUA® 100/33

Warnings and Precautions

- **Anaphylaxis and Serious Hypersensitivity Reactions:** In clinical trials of lixisenatide, there have been cases of anaphylaxis and other serious hypersensitivity reactions including angioedema. Severe, life-threatening, generalized allergy, including anaphylaxis and angioedema, can occur with insulins, including insulin glargine. If hypersensitivity reactions occur, discontinue SOLIQUA 100/33. Use caution in patients with a history of anaphylaxis or angioedema with another GLP-1 RA because it is unknown whether such patients will be predisposed to anaphylaxis.
- **Pancreatitis:** Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with GLP-1 RAs. Cases of pancreatitis were reported in clinical trials of lixisenatide. After initiation of SOLIQUA 100/33, observe patients for signs and symptoms of pancreatitis (e.g., persistent severe abdominal pain, sometimes radiating to the back and which may be accompanied

Please see additional Important Safety Information for SOLIQUA 100/33 on the following page.
Please see Brief Summary of Full Prescribing Information on the following pages.

Reference: SOLIQUA 100/33 Prescribing Information.

SANOFI

Visit gosoliqua100-33.com

SOLIQUA® 100/33
insulin glargine & lixisenatide injection
100 Units/mL & 33 mcg/mL

Important Safety Information for SOLIQUA® 100/33

Warnings and Precautions

by vomiting). If pancreatitis is suspected, SOLIQUA 100/33 should promptly be discontinued. If pancreatitis is confirmed, restarting SOLIQUA 100/33 is not recommended and other antidiabetic therapies should be considered.

- **Never Share a SOLIQUA 100/33 SoloStar® Pen between Patients:** Pen-sharing poses a risk for transmission of blood-borne pathogens, even if the needle is changed. Do not withdraw SOLIQUA 100/33 from the pen with a syringe.
- **Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen:** Changes in SOLIQUA 100/33 regimen may affect glycemic control and predispose to hypoglycemia or hyperglycemia. Changes should be made cautiously and the frequency of blood glucose monitoring should be increased. Adjustments in concomitant oral antidiabetic treatment may be needed.
- **Medication Errors:** SOLIQUA 100/33 contains two drugs. Do not administer more than 60 units of SOLIQUA 100/33, which may result in overdose of the lixisenatide component. Do not use other GLP-1 RAs. Accidental mix-ups between insulin products have been reported. Instruct patients to always check the label before administration.
- **Hypoglycemia:** Hypoglycemia is the most common adverse reaction associated with insulin-containing therapy, which may be life-threatening. Increase frequency of glucose monitoring with changes to: insulin dosage, coadministered glucose lowering medications, meal pattern, physical activity, and in patients with renal or hepatic impairment and hypoglycemia unawareness.
- **Acute Kidney Injury:** There have been reports of acute renal failure and worsening of chronic failure, which may sometimes require hemodialysis in patients treated with GLP-1 RAs, such as lixisenatide. Some of these events were reported in patients without known underlying renal disease. Most reports occurred in patients who experienced nausea, vomiting, diarrhea, or dehydration; advise patients to take precautions to avoid fluid depletion. Monitor blood glucose and renal function in patients with renal impairment. SOLIQUA 100/33 is not recommended in patients with end-stage renal disease.
- **Immunogenicity:** Patients may develop antibodies to insulin and lixisenatide. If there is worsening glycemic control or failure to achieve targeted glycemic control, significant injection site reactions or allergic reactions, then other antidiabetic therapy should be considered.
- **Hypokalemia:** All insulin containing products can cause hypokalemia, which may be life-threatening. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk of hypokalemia and treat if indicated.
- **Fluid Retention and Heart Failure with Concomitant Use of PPAR-gamma Agonists:** Fluid retention, which may lead to or exacerbate heart failure, can occur with concomitant use of thiazolidinediones (TZDs) and insulin. These patients should be observed for signs and symptoms of heart failure. If heart failure occurs, dosage reduction or discontinuation of TZD must be considered.
- **Macrovascular Outcomes:** Clinical studies have not shown macrovascular risk reduction with SOLIQUA 100/33.

Most Common Adverse Reactions

The most common adverse reactions associated with SOLIQUA 100/33 include hypoglycemia, nausea, nasopharyngitis, diarrhea, upper respiratory tract infection, and headache.

Drug Interactions

- Certain drugs may affect glucose metabolism, requiring dose adjustment of SOLIQUA 100/33 and close monitoring of blood glucose.
- The signs of hypoglycemia may be reduced or absent in patients taking anti-adrenergic drugs (eg, beta-blockers, clonidine, guanethidine, and reserpine).
- SOLIQUA 100/33 delays gastric emptying, which may reduce the rate of absorption of orally administered medication with a narrow therapeutic ratio or that require careful clinical monitoring. If such medications are to be administered with food, do not co-administer with SOLIQUA 100/33.
- Antibiotics, acetaminophen, or other medications that are dependent on threshold concentrations for efficacy, or where a delay in effect is undesirable, should be administered at least 1 hour before SOLIQUA 100/33 injection.
- Oral contraceptives should be taken at least 1 hour before SOLIQUA 100/33 administration or 11 hours after.

Please see Brief Summary of Full Prescribing Information on the following pages.

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SANOFI

SOLIQUA™ **Rx Only**
(insulin glargine and lixisenatide injection), for subcutaneous use

Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE

SOLIQUA 100/33 is a combination of insulin glargine and lixisenatide and is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on basal insulin (less than 60 units daily) or lixisenatide.

Limitations of Use:

- SOLIQUA 100/33 has not been studied in patients with a history of pancreatitis *[see Warnings and Precautions (5.2)]*. Consider other antidiabetic therapies in patients with a history of pancreatitis.
- SOLIQUA 100/33 is not recommended for use in combination with any other product containing lixisenatide or another GLP-1 receptor agonist *[see Warnings and Precautions (5.5)]*.
- SOLIQUA 100/33 is not indicated for use in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.
- SOLIQUA 100/33 has not been studied in patients with gastroparesis and is not recommended in patients with gastroparesis.
- SOLIQUA 100/33 has not been studied in combination with prandial insulin.

4 CONTRAINDICATIONS

SOLIQUA 100/33 is contraindicated:

- During episodes of hypoglycemia *[see Warnings and Precautions (5.6)]*.
- In patients with hypersensitivity to SOLIQUA 100/33, either of the active drug substances (insulin glargine or lixisenatide), or any of its excipients. Hypersensitivity reactions including anaphylaxis have occurred with both lixisenatide and insulin glargine *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis and Serious Hypersensitivity Reactions

In clinical trials of lixisenatide, a component of SOLIQUA 100/33, there have been cases of anaphylaxis (frequency of 0.1% or 10 cases per 10,000 patient-years) and other serious hypersensitivity reactions including angioedema. Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock can occur with insulins, including insulin glargine, a component of SOLIQUA 100/33 *[see Adverse Reactions (6.1)]*. Inform and closely monitor patients with a history of anaphylaxis or angioedema with another GLP-1 receptor agonist for allergic reactions, because it is unknown whether such patients will be predisposed to anaphylaxis with lixisenatide. SOLIQUA 100/33 is contraindicated in patients with known hypersensitivity to lixisenatide or insulin glargine *[see Contraindications (4)]*. If a hypersensitivity reaction occurs, the patient should discontinue SOLIQUA 100/33 and promptly seek medical attention.

5.2 Pancreatitis

Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been reported postmarketing in patients treated with GLP-1 receptor agonists. In clinical trials of lixisenatide, a component of SOLIQUA 100/33, there were 21 cases of pancreatitis among lixisenatide-treated patients and 14 cases in comparator-treated patients (incidence rate of 21 vs 17 per 10,000 patient-years). Lixisenatide cases were reported as acute pancreatitis (n=3), pancreatitis (n=12), chronic pancreatitis (n=5), and edematous pancreatitis (n=1). Some patients had risk factors for pancreatitis, such as a history of cholelithiasis or alcohol abuse.

After initiation of SOLIQUA 100/33, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, promptly discontinue SOLIQUA 100/33 and initiate appropriate management. If pancreatitis is confirmed, restarting SOLIQUA 100/33 is not recommended. Consider antidiabetic therapies other than SOLIQUA 100/33 in patients with a history of pancreatitis.

5.3 Never Share a SOLIQUA 100/33 Prefilled Pen Between Patients

SOLIQUA 100/33 prefilled pens must never be shared between patients, even if the needle is changed. Sharing of the pen poses a risk for transmission of blood-borne pathogens.

5.4 Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen

Changes in SOLIQUA 100/33 regimen may affect glycemic control and predispose to hypoglycemia or hyperglycemia. These changes should be made cautiously and only under close medical supervision, and the frequency of blood glucose monitoring should be increased. Adjustments in concomitant oral antidiabetic treatment may be needed. When converting from basal insulin therapy or lixisenatide to SOLIQUA 100/33 follow dosing recommendations *[see Dosage and Administration (2.1, 2.2)]*.

5.5 Overdose Due to Medication Errors

SOLIQUA 100/33 contains two drugs: insulin glargine and lixisenatide. Administration of more than 60 units of SOLIQUA 100/33 daily can result in overdose of the lixisenatide component. Do not exceed the 20 mcg maximum recommended dose of lixisenatide or use with other glucagon-like peptide-1 receptor agonists.

Accidental mix-ups between insulin products have been reported. To avoid medication errors between SOLIQUA 100/33 (an insulin containing product) and other insulins, instruct patients to always check the insulin label before each injection.

5.6 Hypoglycemia

Hypoglycemia is the most common adverse reaction associated with insulin containing products, including SOLIQUA 100/33 *[see Adverse Reactions (6.1)]*. Severe hypoglycemia can cause seizures, may be life-threatening or cause death. Hypoglycemia can impair concentration ability and reaction time; this may place an individual and others at risk in situations where these abilities are important (e.g., driving or operating other machinery). SOLIQUA 100/33 (an insulin-containing product), or any insulin, should not be used during episodes of hypoglycemia *[see Contraindications (4)]*.

Hypoglycemia can happen suddenly and symptoms may differ in each individual and change over time in the same individual. Symptomatic awareness of hypoglycemia may be less pronounced in patients with longstanding diabetes, in patients with diabetic nerve disease, in patients using medications that block the sympathetic nervous system (e.g., beta-blockers) *[see Drug Interactions (7.1)]*, or in patients who experience recurrent hypoglycemia.

Risk Factors for Hypoglycemia

The risk of hypoglycemia generally increases with intensity of glycemic control. The risk of hypoglycemia after an injection is related to the duration of action of the insulin and, in general, is highest when the glucose lowering effect of the insulin is maximal. As with all insulin containing preparations, the glucose lowering effect time course of SOLIQUA 100/33 may vary in different individuals or at different times in the same individual and depends on many conditions, including the area of injection as well as the injection-site blood supply and temperature *[see Clinical Pharmacology (12.2) in the full prescribing information]*.

Other factors which may increase the risk of hypoglycemia include changes in meal pattern (e.g., macronutrient content or timing of meals), changes in level of physical activity, or changes to coadministered medication *[see Drug Interactions (7.1)]*. Patients with renal or hepatic impairment may be at higher risk of hypoglycemia *[see Use in Specific Populations (8.6, 8.7)]*.

Risk Mitigation Strategies for Hypoglycemia

Patients and caregivers must be educated to recognize and manage hypoglycemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia. In patients at higher risk for hypoglycemia and patients who have reduced symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring is recommended.

The long-acting effect of the insulin glargine component of SOLIQUA 100/33 may delay recovery from hypoglycemia.

5.7 Acute Kidney Injury

Acute kidney injury and worsening of chronic renal failure, which may sometimes require hemodialysis, has been reported postmarketing in patients treated with GLP-1 receptor agonists, such as lixisenatide, a component of SOLIQUA 100/33. Some of these events were reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration.

Monitor renal function when initiating or escalating doses of SOLIQUA 100/33 in patients with renal impairment and in patients reporting severe gastrointestinal reactions. Advise patients of the potential risk of dehydration due to gastrointestinal adverse reactions and take precautions to avoid fluid depletion. SOLIQUA 100/33 is not recommended in patients with end-stage renal disease *[see Use in Specific Populations (8.6)]*.

5.8 Immunogenicity

Patients may develop antibodies to insulin and lixisenatide, components of SOLIQUA 100/33, following treatment. A pooled analysis of studies of lixisenatide-treated patients showed that 70% were antibody positive at Week 24. In the subset of patients (2.4%) with the highest antibody concentrations (>100 nmol/L), an attenuated glycemic response was observed. A higher incidence of allergic reactions and injection-site reactions occurred in antibody positive patients. *[see Warnings and Precautions (5.1), Adverse Reactions (6.2)]*.

If there is worsening glycemic control or failure to achieve targeted glycemic control, significant injection-site reactions or allergic reactions, alternative antidiabetic therapy should be considered.

5.9 Hypokalemia

All insulin-containing products, including SOLIQUA 100/33, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk for hypokalemia if indicated (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).

5.10 Fluid Retention and Heart Failure with Concomitant Use of PPAR-gamma Agonists

Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin containing products, including SOLIQUA 100/33. Fluid retention may lead to or exacerbate heart failure. Patients treated with insulin containing products, including SOLIQUA 100/33, and a PPAR-gamma agonist should be observed for signs and symptoms of heart failure. If heart failure develops, it should be managed according to current standards of care, and discontinuation or dose reduction of the PPAR-gamma agonist must be considered.

5.11 Macrovascular Outcomes

There have been no clinical studies establishing macrovascular risk reduction with SOLIQUA 100/33 or any other antidiabetic drug.

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere:

- Anaphylaxis and Serious Hypersensitivity Reactions *[see Warnings and Precautions (5.1)]*
- Pancreatitis *[see Warnings and Precautions (5.2)]*
- Hypoglycemia *[see Warnings and Precautions (5.6)]*

- Acute Kidney Injury *[see Warnings and Precautions (5.7)]*
- Hypokalemia *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trial of another drug and may not reflect the rates observed in practice.

The safety of SOLIQUA 100/33 (n=834, with a mean treatment duration of 203 days) has been evaluated in two clinical studies (30 weeks duration) in type 2 diabetes patients. The studies had the following characteristics: mean age was approximately 59 years; approximately 50% were male, 90% were Caucasian, 6% were Black or African American and 18 % were Hispanic. The mean duration of diabetes was 10.3 years, mean HbA1c at screening for Study A was 8.2 and Study B 8.5. The mean BMI at baseline was 32 kg/m^2. Baseline eGFR was ≥60 mL/min in 87.2% of the pooled study population and mean baseline eGFR was 83.0 ml/min/1.73m^2.

Table 3: Adverse Reactions Occurring in ≥5% of SOLIQUA 100/33-Treated Patients with Type 2 Diabetes Mellitus from Two Pooled Clinical Trials

	SOLIQUA 100/33, % (n=834)
Nausea	10.0
Nasopharyngitis	7.0
Diarrhea	7.0
Upper respiratory tract infection	5.5
Headache	5.4

Hypoglycemia

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, and insulin containing products including SOLIQUA 100/33 *[see Warnings and Precautions (5.6)]*. The rates of reported hypoglycemia depend on the definition of hypoglycemia used, diabetes type, insulin dose, intensity of glucose control, background therapies, and other intrinsic and extrinsic patient factors. For these reasons, comparing rates of hypoglycemia in clinical trials for SOLIQUA 100/33 with the incidence of hypoglycemia for other products may be misleading and also, may not be representative of hypoglycemia rates that will occur in clinical practice.

In the SOLIQUA 100/33 program, severe hypoglycemia was defined as an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions and documented symptomatic hypoglycemia was defined as an event with typical symptoms of hypoglycemia accompanied by a self-monitored plasma glucose value equal to or less than 70 mg/dL (see Table 4).

Table 4: Severe or Documented Symptomatic Hypoglycemic Episodes in SOLIQUA-Treated Patients with T2DM

	SOLIQUA 100/33 Study A N=469	SOLIQUA 100/33 Study B N=365
Severe symptomatic hypoglycemia* (%)	0	1.1
Documented symptomatic hypoglycemia† (%)	25.6	40

*Defined as an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions

†Defined as an event with typical symptoms of hypoglycemia accompanied by a self-monitored plasma glucose value equal to or less than 70 mg/dL

Gastrointestinal Adverse Reactions

Gastrointestinal adverse reactions occur more frequently at the beginning of SOLIQUA 100/33 therapy. Gastrointestinal adverse reactions including nausea, diarrhea, vomiting, constipation, dyspepsia, gastritis, abdominal pain, flatulence, gastroesophageal reflux disease, abdominal distension and decreased appetite have been reported in patients treated with SOLIQUA 100/33.

Lipodystrophy

Administration of insulin subcutaneously, including SOLIQUA 100/33, has resulted in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue) in some patients *[see Dosage and Administration (2.4)]*.

Anaphylaxis and Hypersensitivity

Lixisenatide

In the lixisenatide development program anaphylaxis cases were adjudicated. Anaphylaxis was defined as a skin or mucosal lesion of acute onset associated with at least 1 other organ system involvement. Symptoms such as hypotension, laryngeal edema or severe bronchospasm could be present but were not required for the case definition. More cases adjudicated as meeting the definition for anaphylaxis occurred in lixisenatide-treated patients (incidence rate of 0.2% or 16 cases per 10,000 patient years) than placebo-treated patient (incidence rate of 0.1% or 7 cases per 10,000 patient years).

Allergic reactions (such as anaphylactic reaction, angioedema and urticaria) adjudicated as possibly related to the study medication were observed more frequently in lixisenatide-treated patients (0.4%) than placebo-treated patients (0.2%) *[see Warnings and Precautions (5.1)]*.

Insulin glargine

Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including SOLIQUA 100/33 and may be life threatening.

Injection-Site Reactions

As with any insulin or GLP-1 receptor agonist–containing product, patients taking SOLIQUA 100/33 may experience injection-site reactions, including injection-site hematoma, pain, hemorrhage, erythema, nodules, swelling, discoloration, pruritus, warmth, and injection-site mass. In the clinical program the proportion of injection-site reactions occurring in patients treated with SOLIQUA 100/33 was 1.7%.

Insulin Initiation and Intensification of Glucose Control

Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.

Peripheral Edema

Some patients taking insulin glargine, a component of SOLIQUA 100/30 have experienced sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Weight Gain

Weight gain can occur with insulin containing products, including SOLIQUA 100/33, and has been attributed to the anabolic effects of insulin.

6.2 Immunogenicity

SOLIQUA 100/33

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to SOLIQUA 100/33 in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

After 30 weeks of treatment with SOLIQUA 100/33 in two phase 3 trials, the incidence of formation of anti-insulin glargine antibodies was 21.0% and 26.2%. In approximately 93% of the patients, anti-insulin glargine antibodies showed cross-reactivity to human insulin. The incidence of formation of anti-lixisenatide antibodies was approximately 43%.

Lixisenatide

In the pool of 9 placebo-controlled studies, 70% of patients exposed to lixisenatide tested positive for anti-lixisenatide antibodies during the trials. In the subset of patients (2.4%) with the highest antibody concentrations (>100 nmol/L), an attenuated glycemic response was observed. A higher incidence of allergic reactions and injection-site reactions occurred in antibody positive patients *[see Warnings and Precautions (5.8)]*.

Anti-lixisenatide antibody characterization studies have demonstrated the potential for development of antibodies cross-reactive with endogenous GLP-1 and glucagon, but their incidence has not been fully determined and the clinical significance of these antibodies is not currently known.

No information regarding the presence of neutralizing antibodies is currently available.

7 DRUG INTERACTIONS

7.1 Medications that Can Affect Glucose Metabolism

A number of medications affect glucose metabolism and may require dose adjustment of SOLIQUA 100/33 and particularly close monitoring.

Drugs That May Increase the Risk of Hypoglycemia	
Drugs:	Antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analogs (e.g., octreotide), and sulfonamide antibiotics.
Intervention:	Dose reductions and increased frequency of glucose monitoring may be required when SOLIQUA 100/33 is coadministered with these drugs.
Drugs That May Decrease the Blood Glucose Lowering Effect of SOLIQUA 100/33	
Drugs:	Atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones
Intervention:	Dose increases and increased frequency of glucose monitoring may be required when SOLIQUA 100/33 is coadministered with these drugs.

Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of SOLIQUA 100/33	
Drugs:	Alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.
Intervention:	Dose adjustment and increased frequency of glucose monitoring may be required when SOLIQUA 100/33 is coadministered with these drugs.
Drugs That May Blunt Signs and Symptoms of Hypoglycemia	
Drugs:	Beta-blockers, clonidine, guanethidine, and reserpine
Intervention:	Increased frequency of glucose monitoring may be required when SOLIQUA 100/33 is coadministered with these drugs.

7.2 Effects of Delayed Gastric Emptying on Oral Medications

Lixisenatide delays gastric emptying which may reduce the rate of absorption of orally administered medications. Use caution when coadministering oral medications that have a narrow therapeutic ratio or that require careful clinical monitoring. These medications should be adequately monitored when concomitantly administered with lixisenatide. If such medications are to be administered with food, patients should be advised to take them with a meal or snack when lixisenatide is not administered.

- Antibiotics, acetaminophen, or other medications that are particularly dependent on threshold concentrations for efficacy or for which a delay in effect is undesirable, should be administered at least 1 hour before SOLIQUA 100/33 injection *[see Clinical Pharmacology (12.3) in the full prescribing information]*.
- Oral contraceptives should be taken at least 1 hour before SOLIQUA 100/33 administration or 11 hours after *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal reproduction studies, there may be risks to the fetus from exposure to lixisenatide, a component of SOLIQUA 100/33, during pregnancy. SOLIQUA 100/33 should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The limited available data with SOLIQUA 100/33 and lixisenatide in pregnant women are not sufficient to inform a drug-associated risk of major birth defects and miscarriage. Published studies with insulin glargine use during pregnancy have not reported a clear association with insulin glargine and major birth defect or miscarriage risk *[see Data]*. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *[see Clinical Considerations]*.

Lixisenatide administered to pregnant rats and rabbits during organogenesis was associated with visceral closure and skeletal defects at systemic exposures that decreased maternal food intake and weight gain during gestation, and that are 1-time and 6-times higher than the 20 mcg/day highest clinical dose, respectively, based on plasma AUC *[see Data]*.

The estimated background risk of major birth defects is 6%–10% in women with pre-gestational diabetes with an HbA1c >7 and has been reported to be as high as 20%–25% in women with a HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%–4% and 15%–20%, respectively.

Clinical considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, still birth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia related morbidity.

Data

Human data

Insulin glargine

Published data do not report a clear association with insulin glargine and major birth defects, miscarriage, or adverse maternal or fetal outcomes when insulin glargine is used during pregnancy. However, these studies cannot definitely establish the absence of any risk because of methodological limitations including small sample size and some lacking comparator groups.

Animal data

Animal reproduction studies were not conducted with the combined products in SOLIQUA 100/33. The following data are based on studies conducted with the individual components of SOLIQUA 100/33.

Lixisenatide

In pregnant rats receiving twice daily subcutaneous doses of 2.5, 35, or 500 mcg/kg during organogenesis (gestation day 6 to 17), fetuses were present with visceral closure defects (e.g., microphthalmia, bilateral anophthalmia, diaphragmatic hernia) and stunted growth. Impaired ossification associated with skeletal malformations (e.g., bent limbs, scapula, clavicle, and pelvis) were observed at ≥2.5 mcg/kg/dose, resulting in systemic exposure that is 1-time the 20 mcg/day clinical dose, based on plasma AUC. Decreases in maternal body weight, food consumption, and motor activity were observed concurrent with the adverse fetal findings, which confounds the interpretation of relevance of these malformations to the human risk assessment. Placental transfer of lixisenatide to developing rat fetuses is low with a concentration ratio in fetal/maternal plasma of 0.1%.

In pregnant rabbits receiving twice daily subcutaneous doses of 2.5, 25, 250 mcg/kg during organogenesis (gestation day 6 to 18), fetuses were present with multiple visceral and skeletal malformations, including closure defects, at ≥5 mcg/kg/day or systemic exposures that are 6-times the 20 mcg/day highest clinical dose, based on plasma AUC. Decreases in maternal body weight, food consumption, and motor activity were observed concurrent with the fetal findings, which confounds the interpretation of relevance of these malformations to the human risk assessment. Placental transfer of lixisenatide to developing rabbit fetuses is low with a concentration ratio in fetal/maternal plasma of ≤0.3%. In a second study in pregnant rabbits, no drug-related malformations were observed from twice daily subcutaneous doses of 0.15, 1.0, and 2.5 mcg/kg administered during organogenesis, resulting in systemic exposures up to 9-times the clinical exposure at 20 mcg/day, based on plasma AUC.

In pregnant rats given twice daily subcutaneous doses of 2, 20, or 200 mcg/kg from gestation day 6 through lactation, decreases in maternal body weight, food consumption, and motor activity were observed at all doses. Skeletal malformations and increased pup mortality were observed at 400 mcg/kg/day, which is approximately 200-times the 20 mcg/day clinical dose based on mcg/m^2.

Insulin glargine

Subcutaneous reproduction and teratology studies have been performed with insulin glargine and regular human insulin in rats and Himalayan rabbits. Insulin glargine was given to female rats before mating, during mating, and throughout pregnancy at doses up to 0.36 mg/kg/day, which is approximately 2-times the recommended human subcutaneous high dose of 60 units/day (0.0364 mg/kg/day), based on mg/m^2. In rabbits, doses up to 0.072 mg/kg/day, which is approximately 1-times the maximum recommended human subcutaneous dose of 60 units/day (0.0364 mg/kg/day), based on mg/m^2, were administered during organogenesis. The effects of insulin glargine did not generally differ from those observed with regular human insulin in rats or rabbits. However, in rabbits, five fetuses from two litters of the high-dose group exhibited dilation of the cerebral ventricles. Fertility and early embryonic development appeared normal.

8.2 Lactation

Risk Summary

There is no information regarding the presence of lixisenatide and insulin glargine in human milk, the effects on the breastfed infant, or the effects on milk production. Endogenous insulin is present in human milk. Lixisenatide is present in rat milk *[see Data]*.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SOLIQUA 100/33 and any potential adverse effects on the breastfed child from SOLIQUA 100/33 or from the underlying maternal condition.

Data

Lixisenatide

A study in lactating rats showed low (9.4%) transfer of lixisenatide and its metabolites into milk and negligible (0.01%) levels of unchanged lixisenatide peptide in the gastric contents of weaning offspring.

8.4 Pediatric Use

Safety and effectiveness of SOLIQUA 100/33 have not been established in pediatric patients below 18 years of age.

8.5 Geriatric Use

Of the total number of subjects (n=834) in controlled clinical studies of patients with type 2 diabetes, who were treated with SOLIQUA 100/33, 25.2% (n=210) were ≥65 years of age and 4% (n=33) were ≥75 years of age. No overall differences in effectiveness and safety were observed in the subgroup analyses across the age groups.

Nevertheless, caution should be exercised when SOLIQUA 100/33 is administered to geriatric patients. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly.

8.6 Renal Impairment

Frequent glucose monitoring and dose adjustment may be necessary for SOLIQUA 100/33 in patients with renal impairment *[see Warnings and Precautions (5.7)]*.

Insulin Glargine

Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure.

Lixisenatide

In patients with mild and moderate renal impairment no dose adjustment is required but close monitoring for lixisenatide related adverse reactions and for changes in renal function is recommended because of higher incidences of hypoglycemia, nausea and vomiting that were observed in these patients. Increased gastrointestinal adverse reactions may lead to dehydration and acute renal failure and worsening of chronic failure in these patients.

Clinical experience in patients with severe renal impairment is limited as there were only 5 patients with severe renal impairment (eGFR 15 to less than 30 mL/min/1.73 m^2) exposed to lixisenatide in all controlled studies. Lixisenatide exposure was higher in these patients *[see Clinical Pharmacology (12.3) in the full prescribing information]*. Patients with severe renal impairment exposed to lixisenatide should be closely monitored for occurrence of gastrointestinal adverse reactions and for changes in renal function.

There is no therapeutic experience in patients with end-stage renal disease (eGFR <15 mL/min/1.73 m^2), and it is not recommended to use SOLIQUA 100/33 in this population.

8.7 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of SOLIQUA 100/33 has not been studied. Frequent glucose monitoring and dose adjustment may be necessary for SOLIQUA 100/33 in patients with hepatic impairment *[see Warnings and Precautions (5.6)]*.

8.8 Patients with Gastroparesis

Lixisenatide, one of the components of SOLIQUA 100/33, slows gastric emptying. Patients with preexisting gastroparesis were excluded from clinical trials of SOLIQUA 100/33. SOLIQUA 100/33 is not recommended in patients with severe gastroparesis.

10 OVERDOSAGE

Insulin Glargine

Excess insulin administration may cause hypoglycemia and hypokalemia *[see Warnings and Precautions (5.6, 5.9)]*. Mild episodes of hypoglycemia can usually be treated with oral carbohydrates. Adjustments in drug dosage, meal patterns, or exercise may be needed.

More severe episodes of hypoglycemia with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid recurrence of hypoglycemia. Hypokalemia must be corrected appropriately.

Lixisenatide

During clinical studies, doses up to 30 mcg of lixisenatide twice daily (3 times the daily recommended dose) were administered to type 2 diabetic patients in a 13-week study. An increased incidence of gastrointestinal disorders was observed.

In case of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms and the SOLIQUA 100/33 dose should be reduced to the prescribed dose.

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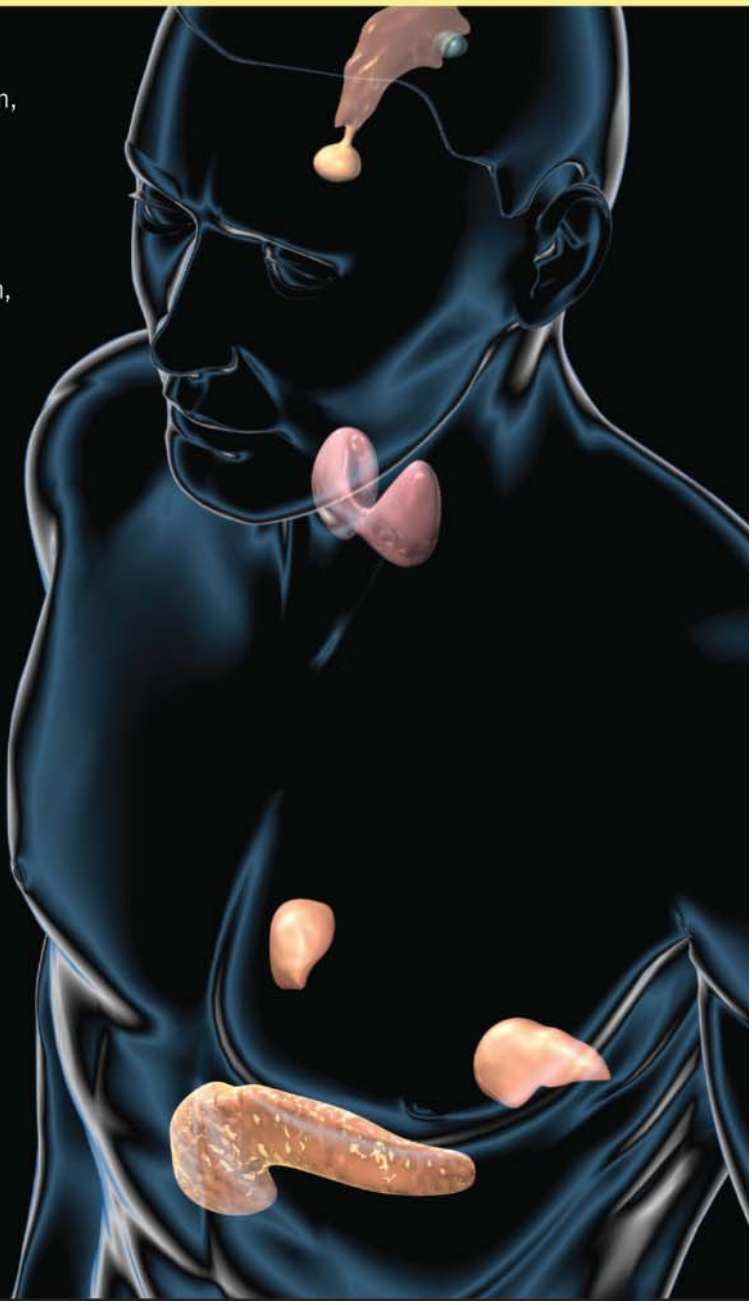

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Antiobesity drugs in the management of type 2 diabetes: A shift in thinking?

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.

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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/m^2 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

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 frustration, 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 (intial); 2 tablets (bupropion 180 mg/naltrexone 16 mg) twice daily (usual); maximum daily dose: bupropion 360 mg/naltrexone 32 mg
Diethylpropion (Tenuate, Tenuate Dospan)	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 serotoninergic 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 trial[25] 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-

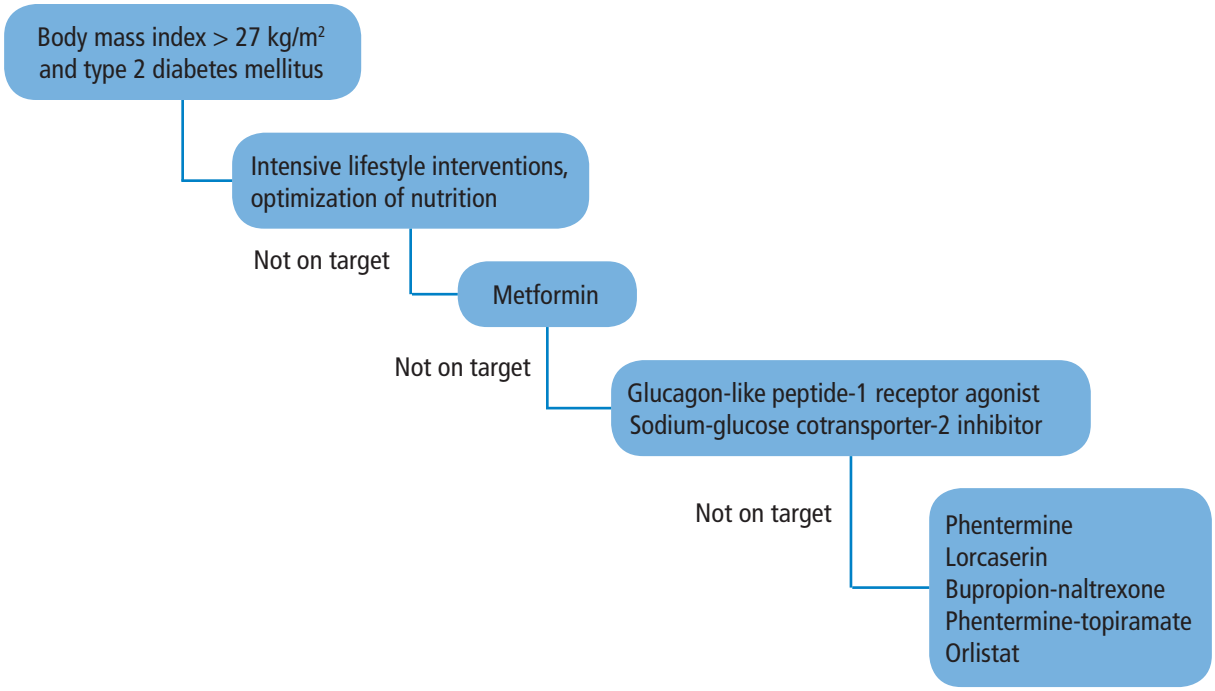

FIGURE 1. Therapeutic algorithm for patients with obesity and type 2 diabetes mellitus.

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.

REFERENCES

1. **Ogden CL, Carroll MD, Fryar CD, Flegal KM.** Prevalence of obesity among adults and youth: United States, 2011–2014. NCHS Data Brief 2015; (219):1–8.
2. **Lyznicki JM, Young DC, Riggs JA, Davis RM; for the Council on Scientific Affairs, American Medical Association.** Obesity: assessment and management in primary care. Am Fam Physician 2001; 63:2185–2196.
3. **World Health Organization (WHO).** Obesity and overweight fact sheet. www.who.int/mediacentre/factsheets/fs311/en. Updated June 2016. Accessed June 22, 2017.
4. **Daniels J.** Obesity: America's epidemic. Am J Nurs 2006; 106:40–49.
5. **Colditz GA, Willett WC, Rotnitzky A, Manson JE.** Weight gain as a risk factor for clinical diabetes mellitus in women. Ann Intern Med 1995; 122:481–486.
6. **Schauer PR, Bhatt DL, Kirwan JP, et al; STAMPEDE Investigators.** Bariatric surgery versus intensive medical therapy for diabetes-5-year outcomes. N Engl J Med 2017; 376:641–651.
7. **Oldridge NB, Stump TE, Nothwehr FK, Clark DO.** Prevalence and outcomes of comorbid metabolic and cardiovascular conditions in middle- and older-age adults. J Clin Epidemiol 2001; 54:928–934.
8. **Garber AJ, Abrahamson MJ, Barzilay JI, et al.** Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm—2016 executive summary. Endocr Pract 2016; 22:84–113.
9. **McFarlane SI.** Antidiabetic medications and weight gain: implications for the practicing physician. Curr Diab Rep 2009; 9:249–254.
10. **UK Prospective Diabetes Study (UKPDS) Group.** Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998; 352:854–865.
11. **Beal E.** The pros and cons of designating obesity a disease: the new AMA designation stirs debate. Am J Nurs 2013; 113:18–19.
12. **Kraschnewski JL, Sciamanna CN, Stuckey HL, et al.** A silent response to the obesity epidemic: decline in US physician weight counseling. Med Care 2013; 51:186–192.
13. **Potter MB, Vu JD, Croughan-Minihane M.** Weight management: what patients want from their primary care physicians. J Fam Pract 2001; 50:513–518.
14. **Pappachan JM, Viswanath AK.** Medical management of diabesity: do we have realistic targets? Curr Diab Rep 2017; 17:4.
15. Lexicomp Online, Lexi-Drugs, Hudson, OH: Wolters Kluwer Clinical Drug Information, Inc., 2017.
16. **Torgerson JS, Hauptman J, Boldrin MN, Sjöström L.** XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. Diabetes Care 2004; 27:155–161.
17. **Buysschaert B, Aydin S, Morelle J, Hermans MP, Jadoul M, Demoulin N.** Weight loss at a high cost: orlistat-induced late-onset severe kidney disease. Diabetes Metab 2016; 42:62–64.
18. **Colman E.** Anorectics on trial: a half century of federal regulation of prescription appetite suppressants. Ann Intern Med 2005; 143:380–385.
19. **Aronne LJ, Wadden TA, Peterson C, Winslow D, Odeh S, Gadde KM.** Evaluation of phentermine and topiramate versus phentermine/topiramate extended-release in obese adults. Obesity (Silver Spring) 2013; 21:2163–2171.
20. **Solas M, Milagro FI, Martínez-Urbistondo D, Ramirez MJ, Martínez JA.** Precision obesity treatments including pharmacogenetic and nutrigenetic approaches. Trends Pharmacol Sci 2016; 37:575–593.
21. **Gadde KM, Allison DB, Ryan DH, et al.** Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. Lancet 2011; 377:1341–1352.
22. **Hollander P, Gupta AK, Plodkowski R, et al; for the COR-Diabetes Study Group.** Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes. Diabetes Care 2013; 36:4022–4029.
23. **Cercato C, Roizenblatt VA, Leança CC, et al.** A randomized double-blind placebo-controlled study of the long-term efficacy and safety of diethylpropion in the treatment of obese subjects. Int J Obes (Lond) 2009; 33:857–865.
24. **Gardin JM, Schumacher D, Constantine G, Davis KD, Leung C, Reid CL.** Valvular abnormalities and cardiovascular status fol-

lowing exposure to dexfenfluramine or phentermine/fenfluramine. JAMA 2000; 283:1703–1709.
25. **O'Neil PM, Smith SR, Weissman NJ, et al.** Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. Obesity (Silver Spring) 2012; 20:1426–1436.
26. **Amori RE, Lau J, Pittas AG.** Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. JAMA 2007; 298:194–206.
27. **Blonde L, Russell-Jones D.** The safety and efficacy of liraglutide with or without oral antidiabetic drug therapy in type 2 diabetes: an overview of the LEAD 1–5 studies. Diabetes Obes Metab 2009; 11(suppl 3):26–34.
28. **Buse JB, Rosenstock J, Sesti G, et al; for the LEAD-6 Study Group.** Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet 2009; 374:39–47.
29. **Davies MJ, Bergenstal R, Bode B, et al; for the NN8022-1922 Study Group.** Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE diabetes randomized clinical trial. JAMA 2015; 314:687–699.
30. **Marso SP, Daniels GH, Brown-Frandsen K, et al; for the LEADER Steering Committee on behalf of the LEADER Trial Investigators.** Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016; 375:311–322.
31. **Salpeter SR, Buckley NS, Kahn JA, Salpeter EE.** Meta-analysis: metformin treatment in persons at risk for diabetes mellitus. Am J Med 2008; 121:149–157.
32. **Vasilakou D, Karagiannis T, Athanasiadou E, et al.** Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2013; 159:262–274.
33. **Burguera B, Jesus Tur J; Escudero AJ, et al.** An intensive lifestyle intervention is an effective treatment of morbid obesity: the TRAMOMTANA study—a two-year randomized controlled clinical trial. Int J Endocrinol 2015; 2015:194696.
34. **Hargraves I, LeBlanc A, Shah ND, Montori VM.** Shared decision making: the need for patient-clinician conversation, not just information. Health Aff (Millwood) 2016; 35:627–629.
35. **Lin P-J, Kent DM, Winn AN, Cohen JT, Neumann PJ.** Multiple chronic conditions in type 2 diabetes mellitus: prevalence and consequences. Am J Manag Care 2015; 21:e23–e34.
36. **Russell LB, Suh D-C, Safford MA.** Time requirements for diabetes self-management: too much for many? J Fam Pract 2005; 54:52–56.
37. **Serrano V, Rodriguez-Gutierrez R, Hargraves I, Gionfriddo MR, Tamhane S, Montori VM.** Shared decision-making in the care of individuals with diabetes. Diabet Med 2016; 33:742–751.
38. **Wyatt KD, Stuart LM, Brito JP, et al.** Out of context: clinical practice guidelines and patients with multiple chronic conditions: a systematic review. Med Care 2014; 52(suppl 3):S92–S100.

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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/m^2.

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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/m^2) or obese (BMI > 30.0 kg/m^2) (**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,

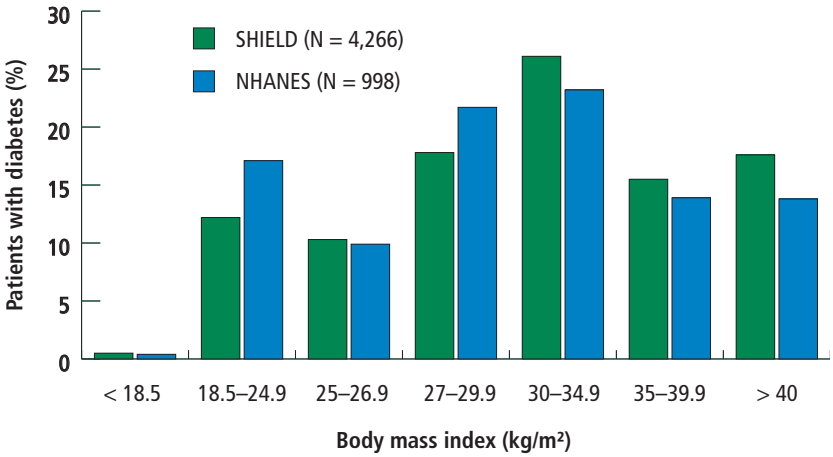


FIGURE 1. Relative distribution of body mass index of patients with diabetes.
SHIELD = Study to Help Improve Early Evaluation and Management of Risk Factors Leading to Diabetes (2004); 4,266 of 127,420 survey respondents with diabetes (type 1 = 368; type 2 = 3,898).
NHANES = National Health and Nutrition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

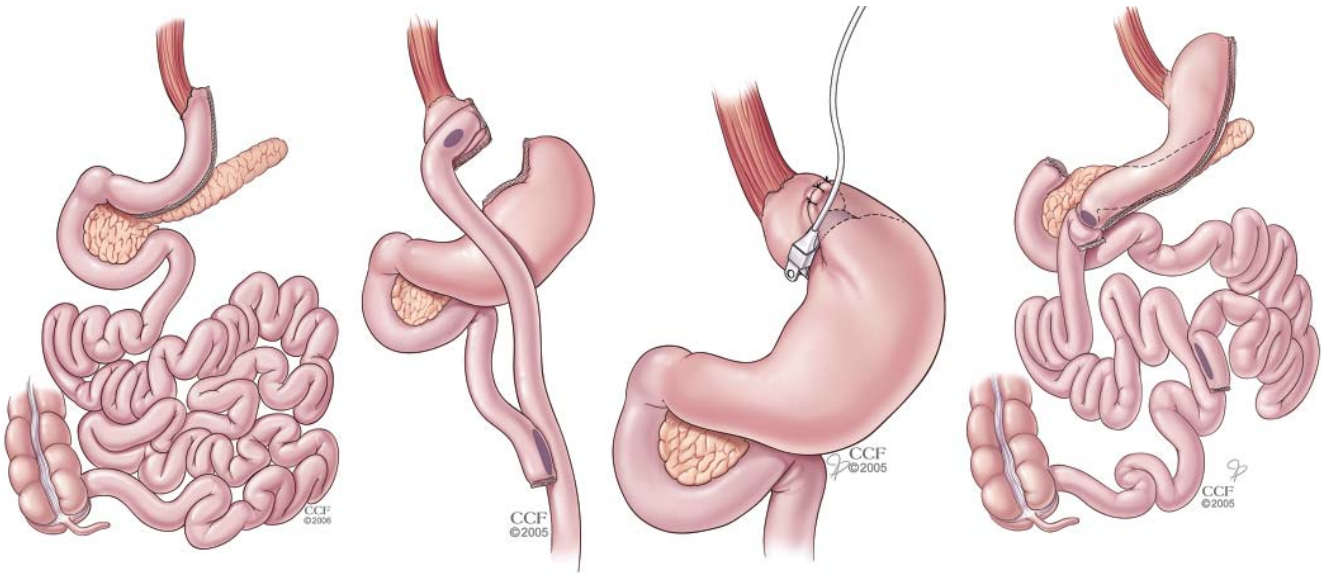
Between 150,000 and 200,000 bariatric procedures are performed annually in the United States, and nearly 500,000 worldwide.[8] The most common procedures are sleeve gastrectomy (SG, 49%), Roux-en-Y gastric bypass (RYGB, 43%), laparoscopic adjustable gastric banding (LAGB, 6%), and biliopancreatic diversion 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/m^2 or greater or a BMI of 35 kg/m^2 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/m^2 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-



Sleeve gastrectomy
Frequency 49%

Roux-en-Y gastric bypass
Frequency 43%

Laparoscopic adjustable gastric banding
Frequency 6%

Biliopancreatic diversion with duodenal switch
Frequency 2%

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/m²	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.

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/m^2, with 11 of 12 studies including patients with BMI less than 35 kg/m^2. 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.

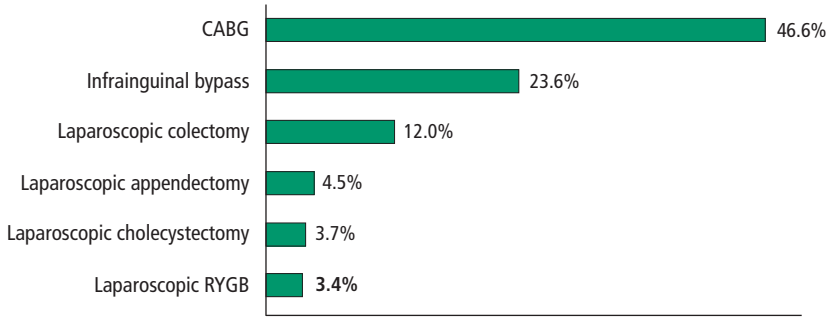


FIGURE 3. Postoperative complication rates of surgical procedures in patients with type 2 diabetes mellitus: US data.

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

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 al[43] 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/m^2), nearly all RCTs showed that the surgical procedures, especially RYGB and SG, were equally effective in patients with BMI 30 to 35 kg/m^2. This is particularly important given that most patients with type 2 DM have a BMI less than 35 kg/m^2. 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) trial[43] 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

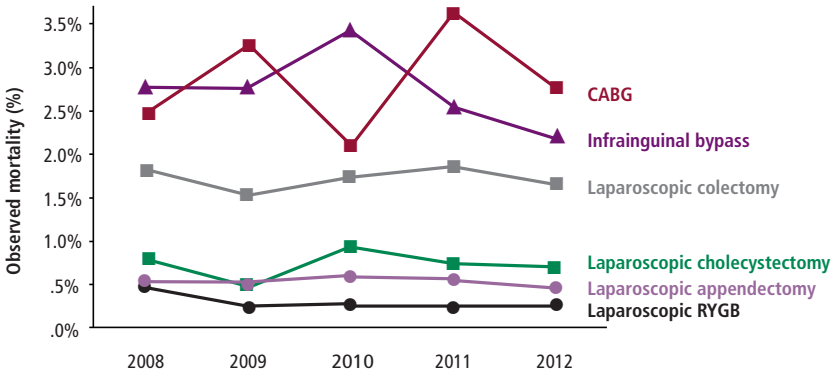


FIGURE 4. Mortality rates of 8 procedures in patients with diabetes (2008–2012).
CABG = coronary artery bypass grafting; RYGB = Roux-en-Y gastric bypass

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 B_{12} (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 B_{12}, as well from pre-existing iron deficiency anemia in premenopausal patients.[52] Deficiencies in trace minerals (selenium, zinc, and copper) and vitamins (B_{12}, B_1, 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.

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-soluable 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.

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 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/m^2) regardless of glycemic control and in those with class II obesity (BMI 35.0–39.9 kg/m^2) 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/m^2 if hyperglycemia is inadequately controlled despite optimal treatment with either oral or injectable medications. These BMI thresholds should be reduced by 2.5 kg/m^2 for Asian patients.

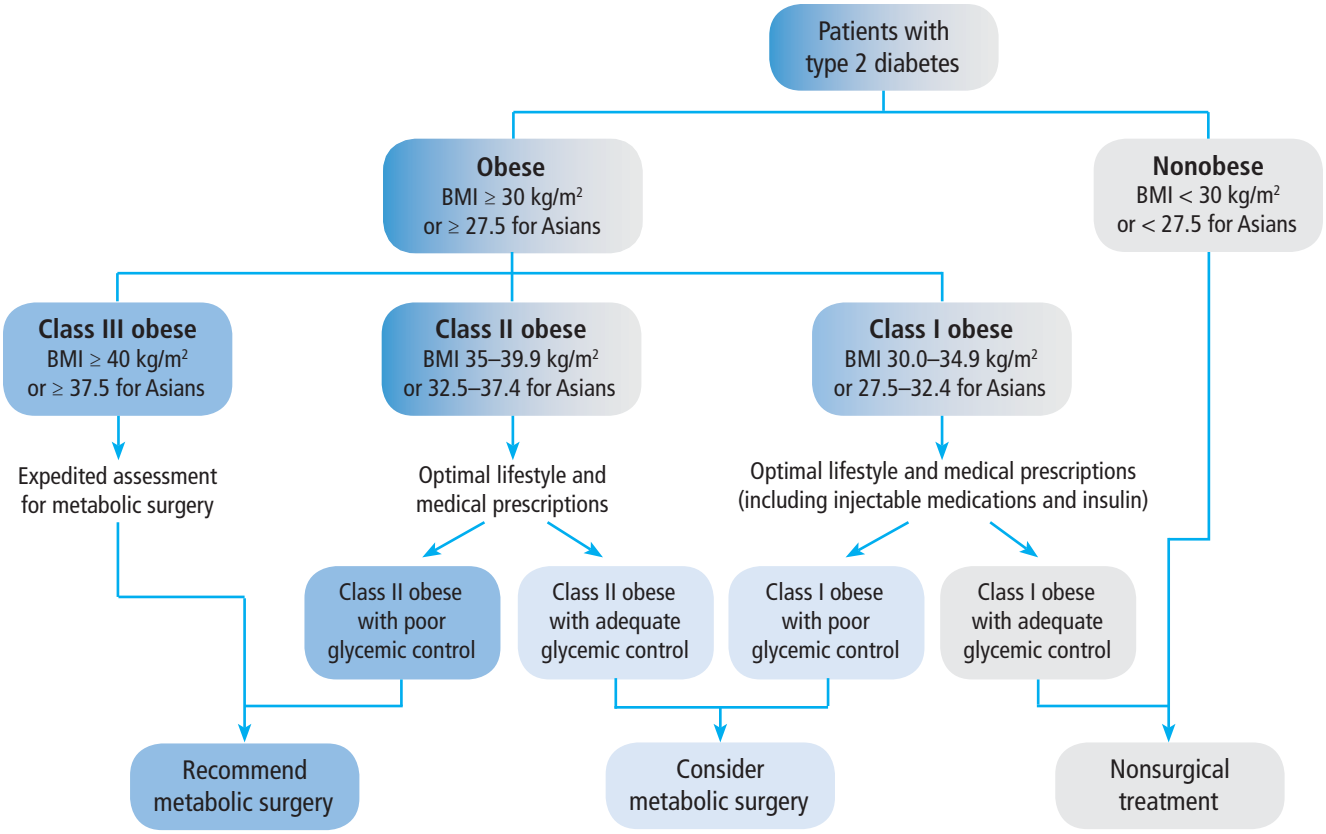


FIGURE 5. Algorithm for the treatment of type 2 diabetes, as recommended by the 2nd Diabetes Surgery Summit's voting delegates.

From Rubino F, et al. Metabolic surgery in the treatment algorithm for type 2 diabetes: a joint statement by international diabetes organizations. Diabetes Care 2016; 39:861–877.

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

	Body mass index category (kg/m²)				
Treatment	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.

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.

REFERENCES

1. **Bays HE, Chapman RH, Grandy S; for the SHIELD Investigators Group.** The relationship of body mass index to diabetes mellitus, hypertension and dyslipidaemia: comparison of data from two national surveys. Int J Clin Pract May 2007; 61:737–747.
2. **Marathe PH, Gao HX, Close KL.** American Diabetes Association standards of medical care in diabetes—2017. Diabetes Care 2017; 40(suppl 1):S1–S135.
3. **Fox CS, Golden SH, Anderson C, et al; American Heart Association; American Diabetes Association.** Update on prevention of cardiovascular disease in adults with type 2 diabetes mellitus in light of recent evidence: a scientific statement from the American Heart Association and the American Diabetes Association. Circulation 2015; 132:691–718.
4. **Jensen MD, Ryan DH, Apovian CM, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines; Obesity Society.** 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. J Am Coll Cardiol 2014; 63:2985–3023.
5. **Rubino F, Nathan DM, Eckel RH, et al; Delegates of the 2nd Diabetes Surgery Summit.** Metabolic surgery in the treatment algorithm for type 2 diabetes: a joint statement by international diabetes organizations. Diabetes Care 2016; 39:861–877.
6. **Stark Casagrande S, Fradkin JE, Saydah SH, Rust KF, Cowie CC.** The prevalence of meeting A1C, blood pressure, and LDL goals among people with diabetes, 1988–2010. Diabetes Care 2013; 36:2271–2279.
7. **Kolandaivelu K, Leiden BB, O'Gara PT, Bhatt DL.** Non-adherence to cardiovascular medications. Eur Heart J 2014; 35:3267–3276.
8. **Angrisani L, Santonicola A, Iovino P, Formisano G, Buchwald H, Scopinaro N.** Bariatric surgery worldwide 2013. Obes Surg 2015; 25:1822–1832.
9. **Schauer PR, Mingrone G, Ikramuddin S, Wolfe B.** Clinical outcomes of metabolic surgery: efficacy of glycemic control, weight loss, and remission of diabetes. Diabetes Care 2016; 39:902–911.
10. **Khorgami Z, Andalib A, Corcelles R, Aminian A, Brethauer S, Schauer P.** Recent national trends in the surgical treatment of obesity: sleeve gastrectomy dominates. Surg Obes Relat Dis 2015; 11(suppl):S1–S34 [Abstract A111].
11. **Consensus Development Conference Panel.** NIH conference. Gastrointestinal surgery for severe obesity. Ann Intern Med 1991; 115:956–961.
12. **Pories WJ, MacDonald KG Jr, Flickinger EG, et al.** Is type II diabetes mellitus (NIDDM) a surgical disease? Ann Surg 1992; 215:633–642.
13. **Schauer PR, Burguera B, Ikramuddin S, et al.** Effect of laparoscopic Roux-en Y gastric bypass on type 2 diabetes mellitus. Ann Surg 2003; 238:467–484.
14. **Rubino F, Marescaux J.** Effect of duodenal-jejunal exclusion in a non-obese animal model of type 2 diabetes : a new perspective for an old disease. Ann Surg 2004; 239:1–11.
15. **Batterham RL, Cummings DE.** Mechanisms of diabetes improvement following bariatric/metabolic surgery. Diabetes Care 2016; 39:893–901.
16. **Buchwald H, Avidor Y, Braunwald E, et al.** Bariatric surgery: a systematic review and meta-analysis. JAMA 2004; 292:1724–1737.
17. **Brethauer SA, Hammel JP, Schauer PR.** Systematic review of sleeve gastrectomy as staging and primary bariatric procedure. Surg Obes Relat Dis 2009; 5:469–475.
18. **Eid GM, Brethauer S, Mattar SG, Titchner RL, Gourash W, Schauer PR.** Laparoscopic sleeve gastrectomy for super obese patients: forty-eight percent excess weight loss after 6 to 8 years with 93% follow-up. Ann Surg 2012; 256:262–265.
19. **Sjöström L, Peltonen M, Jacobson P, et al.** Bariatric surgery and long-term cardiovascular events. JAMA 2012; 307:56–65.
20. **Maciejewski ML, Arterburn DE, Van Scoyoc L, et al.** Bariatric surgery and long-term durability of weight loss. JAMA Surg 2016; 151:1046–1055.
21. **Wing RR, Bolin P, Brancati FL, et al; for the Look AHEAD Research Group.** Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013; 369:145–154.
22. **Buchwald H, Estok R, Fahrbach K, et al.** Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. Am J Med 2009; 122:248–256.
23. **Sjöström L, Lindroos AK, Peltonen M, et al; Swedish Obese Subjects Study Scientific Group.** Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. N Engl J Med 2004; 351:2683–2693.
24. **Vest AR, Heneghan HM, Agarwal S, Schauer PR, Young JB.** Bariatric surgery and cardiovascular outcomes: a systematic review. Heart 2012; 98:1763–1777.
25. **Vest AR, Heneghan HM, Schauer PR, Young JB.** Surgical management of obesity and the relationship to cardiovascular disease. Circulation 2013; 127:945–959.
26. **Arterburn DE, Olsen MK, Smith VA, et al.** Association between bariatric surgery and long-term survival. JAMA 2015; 313:62–70.
27. **Sjöström L, Peltonen M, Jacobson P, et al.** Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. JAMA 2014; 311:2297–2304.
28. **Dixon JB, O'Brien PE, Playfair J, et al.** Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. JAMA 2008; 299:316–323.
29. **Schauer PR, Kashyap SR, Wolski K, et al.** Bariatric surgery versus intensive medical therapy in obese patients with diabetes. N Engl J Med 2012; 366:1567–1576.
30. **Schauer PR, Bhatt DL, Kirwan JP, et al; STAMPEDE Investigators.** Bariatric surgery versus intensive medical therapy for diabetes—3-year outcomes. N Engl J Med 2014; 370:2002–2013.
31. **Mingrone G, Panunzi S, De Gaetano A, et al.** Bariatric surgery versus conventional medical therapy for type 2 diabetes. N Engl J Med 2012; 366:1577–1585.
32. **Mingrone G, Panunzi S, De Gaetano A, et al.** Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomized controlled trial. Lancet 2015; 386:964–973.
33. **Ikramuddin S, Korner J, Lee WJ, et al.** Roux-en-Y gastric bypass vs intensive medical management for the control of type 2 diabetes, hypertension, and hyperlipidemia: the Diabetes Surgery Study randomized clinical trial. JAMA 2013; 309:2240–2249.
34. **Ikramuddin S, Billington CJ, Lee WJ, et al.** Roux-en-Y gastric bypass for diabetes (the Diabetes Surgery Study): 2-year outcomes of a 5-year, randomized, controlled trial. Lancet Diabetes Endocrinol 2015; 3:413–422.

35. **Liang Z, Wu Q, Chen B, Yu P, Zhao H, Ouyang X.** Effect of laparoscopic Roux-en-Y gastric bypass surgery on type 2 diabetes mellitus with hypertension: a randomized controlled trial. Diabetes Res Clin Pract 2013; 101:50–56.
36. **Halperin F, Ding SA, Simonson DC, et al.** Roux-en-Y gastric bypass surgery or lifestyle with intensive medical management in patients with type 2 diabetes: feasibility and 1-year results of a randomized clinical trial. JAMA Surg 2014; 149:716–726.
37. **Courcoulas AP, Goodpaster BH, Eagleton JK, et al.** Surgical vs medical treatments for type 2 diabetes mellitus: a randomized clinical trial. JAMA Surg 2014; 149:707–715.
38. **Courcoulas AP, Belle SH, Neiberg RH, et al.** Three-year outcomes of bariatric surgery vs. lifestyle intervention for type 2 diabetes mellitus treatment: a randomized clinical trial. JAMA Surg 2015; 150:931–940.
39. **Wentworth JM, Playfair J, Laurie C, et al.** Multidisciplinary diabetes care with and without bariatric surgery in overweight people: a randomised controlled trial. Lancet Diabetes Endocrinol 2014; 2:545–552.
40. **Parikh M, Chung M, Sheth S, et al.** Randomized pilot trial of bariatric surgery versus intensive medical weight management on diabetes remission in type 2 diabetic patients who do not meet NIH criteria for surgery and the role of soluble RAGE as a novel biomarker of success. Ann Surg 2014; 260:617–622.
41. **Ding SA, Simonson DC, Wewalka M, et al.** Adjustable gastric band surgery or medical management in patients with type 2 diabetes: a randomized clinical trial. J Clin Endocrinol Metab 2015; 100:2546–2556.
42. **Cummings DE, Arterburn DE, Westbrook EO, et al.** Gastric bypass surgery vs. intensive lifestyle and medical intervention for type 2 diabetes: the CROSSROADS randomized controlled trial. Diabetologia 2016; 59:945–953.
43. **Schauer PR, Bhatt DL, Kirwan JP, et al; STAMPEDE Investigators.** Metabolic surgery vs. intensive medical therapy for diabetes: 5-year outcomes. N Engl J Med 2017; 376:641–651.
44. **Shah SS, Todkar J, Phadake U, et al.** Gastric bypass vs. medical/lifestyle care for type 2 diabetes in South Asians with BMI 25-40 kg/m^2: the COSMID randomized trial [261-OR]. Presented at the American Diabetes Association's 76th Scientific Session; June 10–14, 2016; New Orleans, LA.
45. **Flum DR, Belle SH, King WC, et al; Longitudinal Assessment of Bariatric Surgery (LABS) Consortium.** Perioperative safety in the longitudinal assessment of bariatric surgery. N Engl J Med 2009; 361:445–454.
46. **Aminian A, Brethauer SA, Kirwan JP, Kashyap SR, Burguera B, Schauer PR.** How safe is metabolic/diabetes surgery? Diabetes Obes Metab 2015; 17:198–201.
47. **Thodiyil PA, Yenumula P, Rogula T, et al.** Selective non operative management of leaks after gastric bypass: lessons learned from 2675 consecutive patients. Ann Surg 2008; 248:782–792.
48. **Rogula T, Yenumula PR, Schauer PR.** A complication of Roux-en-Y gastric bypass: intestinal obstruction. Surg Endosc 2007; 21:1914–1918.
49. **Thornton CM, Rozen WM, So D, Kaplan ED, Wilkinson S.** Reducing band slippage in laparoscopic adjustable gastric banding: the mesh plication pars flaccida technique. Obes Surg 2009; 19:1702–1706.
50. **Himpens J, Cadière G-B, Bazi M, Vouche M, Cadière B, Dapri G.** Long-term outcomes of laparoscopic adjustable gastric banding. Arch Surg 2011; 146:802–807.
51. **Madan AK, Orth WS, Tichansky DS, Ternovits CA.** Vitamin and trace mineral levels after laparoscopic gastric bypass. Obes Surg 2006; 16:603–606.
52. **Love AL, Billett HH.** Obesity, bariatric surgery, and iron deficiency: true, true, true and related. Am J Hematol 2008; 83:403–409.
53. **Shankar P, Boylan M, Sriram K.** Micronutrient deficiencies after bariatric surgery. Nutrition 2010; 26:1031–1037.
54. **Gong K, Gagner M, Pomp A, Almahmeed T, Bardaro SJ.** Micronutrient deficiencies after laparoscopic gastric bypass: recommendations. Obes Surg 2008; 18:1062–1066.
55. **Scibora LM.** Skeletal effects of bariatric surgery: examining bone loss, potential mechanisms and clinical relevance. Diabetes Obes Metab 2014; 16:1204–1213.
56. **Baptista V, Wassef W.** Bariatric procedures: an update on techniques, outcomes and complications. Curr Opin Gastroenterol 2013; 29:684–693.
57. **Matlaga BR, Shore AD, Magnuson T, Clark JM, Johns R, Makary MA.** Effect of gastric bypass surgery on kidney stone disease. J Urol 2009; 181:2573–2577.
58. **Sakhaee K, Poindexter J, Aguirre C.** The effects of bariatric surgery on bone and nephrolithiasis. Bone 2016; 84:1–8.
59. **Li L, Wu LT.** Substance use after bariatric surgery: a review. J Psychiatr Res 2016; 76:16–29.
60. **Ayloo S, Thompson K, Choudhury N, Sheriffdeen R.** Correlation between the Beck Depression Inventory and bariatric surgical procedures. Surg Obes Relat Dis 2015; 11:637–342.
61. **Adams TD, Gress RE, Smith SC, et al.** Long-term mortality after gastric bypass surgery. N Engl J Med 2007; 357:753–761.
62. **Sjöström L, Narbro K, Sjöström CD, et al; Swedish Obese Subjects Study.** Effects of bariatric surgery on mortality in Swedish obese subjects. N Engl J Med 2007; 357:741–752.
63. **Mitchell JE, Crosby R, de Zwaan M, et al.** Possible risk factors for increased suicide following bariatric surgery. Obesity (Silver Spring) 2013; 21:665–672.
64. **Fouse T, Schauer P.** The socioeconomic impact of morbid obesity and factors affecting access to obesity surgery. Surg Clin North Am 2016; 96:669–679.
65. **Rubin JK, Hinrichs-Krapels S, Hesketh R, Martin A, Herman WH, Rubino F.** Identifying barriers to appropriate use of metabolic/bariatric surgery for type 2 diabetes treatment: policy lab results. Diabetes Care 2016; 39:954–963.

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— Bonus Article —

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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: metfomin (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)
- Glulisine 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 Association[8] 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 PROactive 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 diabetes 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.

References

1. **Mitka M.** Report quantifies diabetes complications. JAMA 2007; 297:2337–2338.
2. **Welschen LM, Bloemendal E, Nijpels G, et al.** Self-monitoring of blood glucose in patients with type 2 diabetes who are not using insulin: a systematic review. Diabetes Care 2005; 28:1510–1517.
3. **UK Prospective Diabetes Study (UKPDS) Group.** Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34) [published erratum appears in Lancet 1998; 352:1558]. Lancet 1998; 352:854–865.
4. **Chase HP, Jackson WE, Hoops SL, Cockerham RS, Archer PG, O'Brien D.** Glucose control and the renal and retinal complications of insulin-dependent diabetes. JAMA 1989; 261:1155–1160.
5. **The Diabetes Control and Complications Trial Research Group.** The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329:977–986.
6. **Evans JM, Newton RW, Ruta DA, MacDonald TM, Stevenson RJ, Morris AD.** Frequency of blood glucose monitoring in relation to glycaemic control: observational study with diabetes database. BMJ 1999; 319:83–86.
7. **Bergenstal, RM, James GR III; Global Consensus Conference on Glucose Monitoring Panel.** The role of self-monitoring of blood glucose in the care of people with diabetes: report of a global consensus conference. Am J Med 2005; 118(suppl 9A):1S–6S.
8. **American Diabetes Association.** Standards of medical care in diabetes—2017: summary of revisions. Diabetes Care 2017; 40(suppl 1):S1–S135.
9. **Schwedes U, Siebolds M, Mertes G; for the SMBG Study Group.** Meal-related structured self-monitoring of blood glucose: effect on diabetes control in non-insulin-treated type 2 diabetic patients. Diabetes Care 2002; 25:1928–1932.
10. **Saudek CD, Derr RL, Kalyani RR.** Assessing glycemia in diabetes using self-monitoring blood glucose and hemoglobin A1c. JAMA 2006; 295:1688–1697.
11. **Delamater A.** Clinical use of hemoglobin A1c to improve diabetes management. Clinical Diabetes 2006; 24:6–8.
12. **Inzucchi SE, Bergenstal RM, Buse JB, et al.** Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015; 38:140–149.
13. **Nathan DM, Buse JB, Davidson MB, et al; American Diabetes Association; European Association for Study of Diabetes.** Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009; 32:193–203.
14. **Bailey CJ, Turner RC.** Metformin. N Engl J Med 1996; 334:574–579.
15. **Bailey CJ.** Biguanides and NIDDM. Diabetes Care 1992; 15:755–772.
16. **Dormandy JA, Charbonnel C, Eckland DJ, et al; PROactive investigators.** Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005; 366:1279–1289.
17. **Fonseca VA, Kulkarni KD.** Management of type 2 diabetes: oral agents, insulin, and injectables. J Am Diet Assoc 2008; 108(4 suppl 1):S29–S33.
18. **Nathan DM, Buse JB, Davidson MB, et al.** Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy—update regarding thiazolidinediones: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2008; 31:173–175.
19. **UK Prospective Diabetes Study (UKPDS) Group.** Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33) [erratum published in Lancet 1999; 354:602]. Lancet 1998; 352:837–853.
20. **Chiasson J-L, Josse RG, Gomis R, Hanefeld M, Karsik A, Laakso M; for the STOP-NIDDM Trial Research Group.** Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: The STOP-NIDDM Trial. JAMA 2003; 290:486–494.
21. Victoza [package insert]. Bagsvaerd, Denmark: Novo Nordisk; 2010. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022341lbl.pdf. Accessed June 26, 2017.
22. **Nauck MA, Vilsbøll T, Gallwitz B, Garber A, Madsbad S.** Incretin-based therapies viewpoints on the way to consensus. Diabetes Care 2009; 32(suppl 2):S223–S231.
23. **ZinmanB, Wanner C, Larchin JM; EMPA-REG OUTCOME Investigators.** Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015; 373:2117–2128.
24. **Abdul-Ghani MA, Norton L, DeFronzo RA.** Role of sodium-glucose cotransporter 2 (SGLT 2) inhibitors in the treatment of type 2 diabetes. Endocr Rev 2011; 32:515–531.
25. Symlin (Pramlintide acetate) [package insert]. Wilmington DE: AstraZeneca; 2015. Pharmaceuticals LP. http://www.azpicentral.com/symlin/pi_symlin.pdf#page=1. Accessed June 26, 2017.
26. **Gaziano JM, Cincotta AH, O'Connor CM, et al.** Randomized clinical trial of quick-release bromocriptine among patients with type 2 diabetes on overall safety and cardiovascular outcomes. Diabetes Care 2010; 33:1503–1508.
27. Cycloset [package insert]. Tiverton, RI: VeroScience LLC; 2016. http://www.veroscience.com/documents/CyclosetPackageInsertFeb062017.pdf. Accessed June 26, 2017.
28. **Hirsch IB, Bergenstal RM, Parkin CG, Wright Jr, E, Buse JB.** A real-world approach to insulin therapy in primary care practice. Clinical Diabetes 2005; 23:78–86.
29. **Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group; Tamborlane WV, Beck RW, Bode BW, et al.** Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med 2008; 359:1464–1476.

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Geriatric Use: Two thousand thirty-four (2034) patients 65 years and older, and 345 patients 75 years and older were exposed to INVOKANA in nine clinical studies of INVOKANA *[see Clinical Studies (14.3) in full Prescribing Information]*.

Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300 mg daily dose, compared to younger patients; a more prominent increase in the incidence was seen in patients who were 75 years and older *[see Dosage and Administration (2.1) in full Prescribing Information and Adverse Reactions]*. Smaller reductions in HbA1C with INVOKANA relative to placebo were seen in older (65 years and older; -0.61% with INVOKANA 100 mg and -0.74% with INVOKANA 300 mg relative to placebo) compared to younger patients (-0.72% with INVOKANA 100 mg and -0.87% with INVOKANA 300 mg relative to placebo).

Renal Impairment: The efficacy and safety of INVOKANA were evaluated in a study that included patients with moderate renal impairment (eGFR 30 to less than 50 mL/min/1.73 m^2) *[see Clinical Studies (14.3) in full Prescribing Information]*. These patients had less overall glycemic efficacy and had a higher occurrence of adverse reactions related to reduced intravascular volume, renal-related adverse reactions, and decreases in eGFR compared to patients with mild renal impairment or normal renal function (eGFR greater than or equal to 60 mL/min/1.73 m^2). Dose-related, transient mean increases in serum potassium were observed early after initiation of INVOKANA (i.e., within 3 weeks) in this trial. Increases in serum potassium of greater than 5.4 mEq/L and 15% above baseline occurred in 16.1%, 12.4%, and 27.0% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Severe elevations (greater than or equal to 6.5 mEq/L) occurred in 1.1%, 2.2%, and 2.2% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively *[see Dosage and Administration (2.2) in full Prescribing Information, Warnings and Precautions, and Adverse Reactions]*.

The efficacy and safety of INVOKANA have not been established in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), with ESRD, or receiving dialysis. INVOKANA is not expected to be effective in these patient populations *[see Contraindications and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Hepatic Impairment: No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The use of INVOKANA has not been studied in patients with severe hepatic impairment and is therefore not recommended *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

OVERDOSAGE

There were no reports of overdose during the clinical development program of INVOKANA (canagliflozin).

In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Instructions: Instruct patients to read the Medication Guide before starting INVOKANA (canagliflozin) therapy and to reread it each time the prescription is renewed.

Inform patients of the potential risks and benefits of INVOKANA and of alternative modes of therapy. Also inform patients about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and HbA1C testing, recognition and management of hypoglycemia and hyperglycemia, and assessment for diabetes complications. Advise patients to seek medical advice promptly during periods of stress such as fever, trauma, infection, or surgery, as medication requirements may change.

Instruct patients to take INVOKANA only as prescribed. If a dose is missed, advise patients to take it as soon as it is remembered unless it is almost time for the next dose, in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time. Advise patients not to take two doses of INVOKANA at the same time.

Inform patients that the most common adverse reactions associated with INVOKANA are genital mycotic infection, urinary tract infection, and increased urination.

INVOKANA® (canagliflozin) tablets

Inform female patients of child bearing age that the use of INVOKANA during pregnancy has not been studied in humans, and that INVOKANA should only be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Instruct patients to report pregnancies to their physicians as soon as possible.

Inform nursing mothers to discontinue INVOKANA or nursing, taking into account the importance of drug to the mother.

Laboratory Tests: Due to its mechanism of action, patients taking INVOKANA will test positive for glucose in their urine.

Hypotension: Inform patients that symptomatic hypotension may occur with INVOKANA and advise them to contact their doctor if they experience such symptoms *[see Warnings and Precautions]*. Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

Ketoacidosis: Inform patients that ketoacidosis is a serious life-threatening condition. Cases of ketoacidosis have been reported during use of INVOKANA. Instruct patients to check ketones (when possible) if symptoms consistent with ketoacidosis occur even if blood glucose is not elevated. If symptoms of ketoacidosis (including nausea, vomiting, abdominal pain, tiredness, and labored breathing) occur, instruct patients to discontinue INVOKANA and seek medical advice immediately *[see Warnings and Precautions]*.

Acute Kidney Injury: Inform patients that acute kidney injury has been reported during use of INVOKANA. Advise patients to seek medical advice immediately if they have reduced oral intake (such as due to acute illness or fasting) or increased fluid losses (such as due to vomiting, diarrhea, or excessive heat exposure), as it may be appropriate to temporarily discontinue INVOKANA use in those settings *[see Warnings and Precautions]*.

Serious Urinary Tract Infections: Inform patients of the potential for urinary tract infections, which may be serious. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur *[see Warnings and Precautions]*.

Genital Mycotic Infections in Females (e.g., Vulvovaginitis): Inform female patients that vaginal yeast infection may occur and provide them with information on the signs and symptoms of vaginal yeast infection. Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions]*.

Genital Mycotic Infections in Males (e.g., Balanitis or Balanoposthitis): Inform male patients that yeast infection of penis (e.g., balanitis or balanoposthitis) may occur, especially in uncircumcised males and patients with prior history. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions]*.

Hypersensitivity Reactions: Inform patients that serious hypersensitivity reactions, such as urticaria, rash, anaphylaxis, and angioedema, have been reported with INVOKANA. Advise patients to report immediately any signs or symptoms suggesting allergic reaction, and to discontinue drug until they have consulted prescribing physicians.

Bone Fracture: Inform patients that bone fractures have been reported in patients taking INVOKANA. Provide them with information on factors that may contribute to fracture risk.

Pregnancy: Advise pregnant women, and females of reproductive potential of the potential risk to a fetus with treatment with INVOKANA *[see Use in Specific Populations]*. Instruct females of reproductive potential to report pregnancies to their physicians as soon as possible.

Lactation: Advise women that breastfeeding is not recommended during treatment with INVOKANA *[see Use in Specific Populations]*.

Active ingredient made in Belgium

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

Finished product manufactured by:
Janssen Ortho, LLC
Gurabo, PR 00778

or

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Increases in Serum Magnesium: Dose-related increases in serum magnesium were observed early after initiation of INVOKANA (within 6 weeks) and remained elevated throughout treatment. In the pool of four placebo-controlled trials, the mean percent change in serum magnesium levels was 8.1% and 9.3% with INVOKANA 100 mg and INVOKANA 300 mg, respectively, compared to -0.6% with placebo. In a trial of patients with moderate renal impairment *[see Clinical Studies (14.3) in full Prescribing Information]*, serum magnesium levels increased by 0.2%, 9.2%, and 14.8% with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Increases in Serum Phosphate: Dose-related increases in serum phosphate levels were observed with INVOKANA. In the pool of four placebo controlled trials, the mean percent change in serum phosphate levels were 3.6% and 5.1% with INVOKANA 100 mg and INVOKANA 300 mg, respectively, compared to 1.5% with placebo. In a trial of patients with moderate renal impairment *[see Clinical Studies (14.3) in full Prescribing Information]*, the mean serum phosphate levels increased by 1.2%, 5.0%, and 9.3% with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Increases in Low-Density Lipoprotein Cholesterol (LDL-C) and non-High-Density Lipoprotein Cholesterol (non-HDL-C): In the pool of four placebo-controlled trials, dose-related increases in LDL-C with INVOKANA were observed. Mean changes (percent changes) from baseline in LDL-C relative to placebo were 4.4 mg/dL (4.5%) and 8.2 mg/dL (8.0%) with INVOKANA 100 mg and INVOKANA 300 mg, respectively. The mean baseline LDL-C levels were 104 to 110 mg/dL across treatment groups *[see Warnings and Precautions]*.

Dose-related increases in non-HDL-C with INVOKANA were observed. Mean changes (percent changes) from baseline in non-HDL-C relative to placebo were 2.1 mg/dL (1.5%) and 5.1 mg/dL (3.6%) with INVOKANA 100 mg and 300 mg, respectively. The mean baseline non-HDL-C levels were 140 to 147 mg/dL across treatment groups.

Increases in Hemoglobin: In the pool of four placebo-controlled trials, mean changes (percent changes) from baseline in hemoglobin were -0.18 g/dL (-1.1%) with placebo, 0.47 g/dL (3.5%) with INVOKANA 100 mg, and 0.51 g/dL (3.8%) with INVOKANA 300 mg. The mean baseline hemoglobin value was approximately 14.1 g/dL across treatment groups. At the end of treatment, 0.8%, 4.0%, and 2.7% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively, had hemoglobin above the upper limit of normal.

Decreases in Bone Mineral Density: Bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry in a clinical trial of 714 older adults (mean age 64 years) *[see Clinical Studies (14.3) in full Prescribing Information]*. At 2 years, patients randomized to INVOKANA 100 mg and INVOKANA 300 mg had placebo-corrected declines in BMD at the total hip of 0.9% and 1.2%, respectively, and at the lumbar spine of 0.3% and 0.7%, respectively. Additionally, placebo-adjusted BMD declines were 0.1% at the femoral neck for both INVOKANA doses and 0.4% at the distal forearm for patients randomized to INVOKANA 300 mg. The placebo-adjusted change at the distal forearm for patients randomized to INVOKANA 100 mg was 0%.

Postmarketing Experience: Additional adverse reactions have been identified during postapproval use of INVOKANA. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Ketoacidosis *[see Warnings and Precautions]*

Acute Kidney Injury and Impairment in Renal Function *[see Warnings and Precautions]*

Anaphylaxis, Angioedema *[see Warnings and Precautions]*

Urosepsis and Pyelonephritis *[see Warnings and Precautions]*

DRUG INTERACTIONS

UGT Enzyme Inducers: Rifampin: Co-administration of canagliflozin with rifampin, a nonselective inducer of several UGT enzymes, including UGT1A9, UGT2B4, decreased canagliflozin area under the curve (AUC) by 51%. This decrease in exposure to canagliflozin may decrease efficacy. If an inducer of these UGTs (e.g., rifampin, phenytoin, phenobarbital, ritonavir) must be co-administered with INVOKANA (canagliflozin), consider increasing the dose to 300 mg once daily if patients are currently tolerating INVOKANA 100 mg once daily, have an eGFR greater than 60 mL/min/1.73 m^2, and require additional glycemic control. Consider other antihyperglycemic therapy in patients with an eGFR of 45 to less than 60 mL/min/1.73 m^2 receiving concurrent therapy with a UGT inducer and require additional glycemic control *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

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Digoxin: There was an increase in the AUC and mean peak drug concentration (C_{max}) of digoxin (20% and 36%, respectively) when co-administered with INVOKANA 300 mg *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Patients taking INVOKANA with concomitant digoxin should be monitored appropriately.

Positive Urine Glucose Test: Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

Interference with 1,5-anhydroglucitol (1,5-AG) Assay: Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

USE IN SPECIFIC POPULATIONS

Pregnancy: Risk Summary: Based on animal data showing adverse renal effects, INVOKANA is not recommended during the second and third trimesters of pregnancy.

Limited data with INVOKANA in pregnant women are not sufficient to determine a drug-associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *[see Clinical Considerations]*.

In animal studies, adverse renal pelvic and tubule dilatations that were not reversible were observed in rats when canagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy, at an exposure 0.5-times the 300 mg clinical dose, based on AUC.

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20-25% in women with a HbA1c >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations: *Disease-associated maternal and/or embryo/fetal risk:* Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Animal Data: Canagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 4, 20, 65, or 100 mg/kg increased kidney weights and dose dependently increased the incidence and severity of renal pelvic and tubular dilatation at all doses tested. Exposure at the lowest dose was greater than or equal to 0.5-times the 300 mg clinical dose, based on AUC. These outcomes occurred with drug exposure during periods of renal development in rats that correspond to the late second and third trimester of human renal development. The renal pelvic dilatations observed in juvenile animals did not fully reverse within a 1 month recovery period.

In embryo-fetal development studies in rats and rabbits, canagliflozin was administered for intervals coinciding with the first trimester period of organogenesis in humans. No developmental toxicities independent of maternal toxicity were observed when canagliflozin was administered at doses up to 100 mg/kg in pregnant rats and 160 mg/kg in pregnant rabbits during embryonic organogenesis or during a study in which maternal rats were dosed from gestation day (GD) 6 through PND 21, yielding exposures up to approximately 19-times the 300 mg clinical dose, based on AUC.

Lactation: Risk Summary: There is no information regarding the presence of INVOKANA in human milk, the effects on the breastfed infant, or the effects on milk production. Canagliflozin is present in the milk of lactating rats *[see Data]*. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney.

Because of the potential for serious adverse reactions in a breastfed infant, advise women that use of INVOKANA is not recommended while breastfeeding.

Data: *Animal Data:* Radiolabeled canagliflozin administered to lactating rats on day 13 post-partum was present at a milk/plasma ratio of 1.40, indicating that canagliflozin and its metabolites are transferred into milk at a concentration comparable to that in plasma. Juvenile rats directly exposed to canagliflozin showed a risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

Pediatric Use: Safety and effectiveness of INVOKANA in pediatric patients under 18 years of age have not been established.

In the pool of four placebo-controlled trials where patients had normal or mildly impaired baseline renal function, the proportion of patients who experienced at least one event of significant renal function decline, defined as an eGFR below 80 mL/min/1.73 m^2 and 30% lower than baseline, was 2.1% with placebo, 2.0% with INVOKANA 100 mg, and 4.1% with INVOKANA 300 mg. At the end of treatment, 0.5% with placebo, 0.7% with INVOKANA 100 mg, and 1.4% with INVOKANA 300 mg had a significant renal function decline.

In a trial carried out in patients with moderate renal impairment with a baseline eGFR of 30 to less than 50 mL/min/1.73 m^2 (mean baseline eGFR 39 mL/min/1.73 m^2) *[see Clinical Studies (14.3) in full Prescribing Information]*, the proportion of patients who experienced at least one event of significant renal function decline, defined as an eGFR 30% lower than baseline, was 6.9% with placebo, 18% with INVOKANA 100 mg, and 22.5% with INVOKANA 300 mg. At the end of treatment, 4.6% with placebo, 3.4% with INVOKANA 100 mg, and 2.2% with INVOKANA 300 mg had a significant renal function decline.

In a pooled population of patients with moderate renal impairment (N=1085) with baseline eGFR of 30 to less than 60 mL/min/1.73 m^2 (mean baseline eGFR 48 mL/min/1.73 m^2), the overall incidence of these events was lower than in the dedicated trial but a dose-dependent increase in incident episodes of significant renal function decline compared to placebo was still observed.

Use of INVOKANA has been associated with an increased incidence of renal-related adverse reactions (e.g., increased blood creatinine, decreased glomerular filtration rate, renal impairment, and acute renal failure), particularly in patients with moderate renal impairment.

In the pooled analysis of patients with moderate renal impairment, the incidence of renal-related adverse reactions was 3.7% with placebo, 8.9% with INVOKANA 100 mg, and 9.3% with INVOKANA 300 mg. Discontinuations due to renal-related adverse events occurred in 1.0% with placebo, 1.2% with INVOKANA 100 mg, and 1.6% with INVOKANA 300 mg *[see Warnings and Precautions]*.

Genital Mycotic Infections: In the pool of four placebo-controlled clinical trials, female genital mycotic infections (e.g., vulvovaginal mycotic infection, vulvovaginal candidiasis, and vulvovaginitis) occurred in 2.8%, 10.6%, and 11.6% of females treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections on INVOKANA. Female patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrence and require treatment with oral or topical antifungal agents and anti-microbial agents. In females, discontinuation due to genital mycotic infections occurred in 0% and 0.7% of patients treated with placebo and INVOKANA, respectively *[see Warnings and Precautions]*.

In the pool of four placebo-controlled clinical trials, male genital mycotic infections (e.g., candidal balanitis, balanoposthitis) occurred in 0.7%, 4.2%, and 3.8% of males treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Male genital mycotic infections occurred more commonly in uncircumcised males and in males with a prior history of balanitis or balanoposthitis. Male patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrent infections (22% on INVOKANA versus none on placebo), and require treatment with oral or topical antifungal agents and anti-microbial agents than patients on comparators. In males, discontinuations due to genital mycotic infections occurred in 0% and 0.5% of patients treated with placebo and INVOKANA, respectively. In the pooled analysis of 8 controlled trials, phimosis was reported in 0.3% of uncircumcised male patients treated with INVOKANA and 0.2% required circumcision to treat the phimosis *[see Warnings and Precautions]*.

Hypoglycemia: In all clinical trials, hypoglycemia was defined as any event regardless of symptoms, where biochemical hypoglycemia was documented (any glucose value below or equal to 70 mg/dL). Severe hypoglycemia was defined as an event consistent with hypoglycemia where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained). In individual clinical trials *[see Clinical Studies (14) in full Prescribing Information]*, episodes of hypoglycemia occurred at a higher rate when INVOKANA was co-administered with insulin or sulfonylureas (Table 4) *[see Warnings and Precautions]*.

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Table 4: Incidence of Hypoglycemia* in Controlled Clinical Studies

Monotherapy (26 weeks)	**Placebo (N=192)**	**INVOKANA 100 mg (N=195)**	**INVOKANA 300 mg (N=197)**
Overall [N (%)]	5 (2.6)	7 (3.6)	6 (3.0)
In Combination with Metformin (26 weeks)	**Placebo + Metformin (N=183)**	**INVOKANA 100 mg + Metformin (N=368)**	**INVOKANA 300 mg + Metformin (N=367)**
Overall [N (%)]	3 (1.6)	16 (4.3)	17 (4.6)
Severe [N (%)]†	0 (0)	1 (0.3)	1 (0.3)
In Combination with Metformin (52 weeks)	**Glimepiride + Metformin (N=482)**	**INVOKANA 100 mg + Metformin (N=483)**	**INVOKANA 300 mg + Metformin (N=485)**
Overall [N (%)]	165 (34.2)	27 (5.6)	24 (4.9)
Severe [N (%)]†	15 (3.1)	2 (0.4)	3 (0.6)
In Combination with Sulfonylurea (18 weeks)	**Placebo + Sulfonylurea (N=69)**	**INVOKANA 100 mg + Sulfonylurea (N=74)**	**INVOKANA 300 mg + Sulfonylurea (N=72)**
Overall [N (%)]	4 (5.8)	3 (4.1)	9 (12.5)
In Combination with Metformin + Sulfonylurea (26 weeks)	**Placebo + Metformin + Sulfonylurea (N=156)**	**INVOKANA 100 mg + Metformin + Sulfonylurea (N=157)**	**INVOKANA 300 mg + Metformin + Sulfonylurea (N=156)**
Overall [N (%)]	24 (15.4)	43 (27.4)	47 (30.1)
Severe [N (%)]†	1 (0.6)	1 (0.6)	0
In Combination with Metformin + Sulfonylurea (52 weeks)	**Sitagliptin + Metformin + Sulfonylurea (N=378)**		**INVOKANA 300 mg + Metformin + Sulfonylurea (N=377)**
Overall [N (%)]	154 (40.7)		163 (43.2)
Severe [N (%)]†	13 (3.4)		15 (4.0)
In Combination with Metformin + Pioglitazone (26 weeks)	**Placebo + Metformin + Pioglitazone (N=115)**	**INVOKANA 100 mg + Metformin + Pioglitazone (N=113)**	**INVOKANA 300 mg + Metformin + Pioglitazone (N=114)**
Overall [N (%)]	3 (2.6)	3 (2.7)	6 (5.3)
In Combination with Insulin (18 weeks)	**Placebo (N=565)**	**INVOKANA 100 mg (N=566)**	**INVOKANA 300 mg (N=587)**
Overall [N (%)]	208 (36.8)	279 (49.3)	285 (48.6)
Severe [N (%)]†	14 (2.5)	10 (1.8)	16 (2.7)

* Number of patients experiencing at least one event of hypoglycemia based on either biochemically documented episodes or severe hypoglycemic events in the intent-to-treat population

† Severe episodes of hypoglycemia were defined as those where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained)

Bone Fracture: The occurrence of bone fractures was evaluated in a pool of nine clinical trials with a mean duration of exposure to INVOKANA of 85 weeks. The incidence rates of adjudicated bone fractures were 1.1, 1.4, and 1.5 per 100 patient-years of exposure in the comparator, INVOKANA 100 mg, and INVOKANA 300 mg groups, respectively. Fractures were observed as early as 12 weeks after treatment initiation and were more likely to be low trauma (e.g., fall from no more than standing height), and affect the upper extremities *[see Warnings and Precautions]*.

Laboratory and Imaging Tests: *Increases in Serum Potassium* In a pooled population of patients (N=723) with moderate renal impairment (eGFR 45 to less than 60 mL/min/1.73 m^2), increases in serum potassium to greater than 5.4 mEq/L and 15% above baseline occurred in 5.3%, 5.0%, and 8.8% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Severe elevations (greater than or equal to 6.5 mEq/L) occurred in 0.4% of patients treated with placebo, no patients treated with INVOKANA 100 mg, and 1.3% of patients treated with INVOKANA 300 mg.

In these patients, increases in potassium were more commonly seen in those with elevated potassium at baseline. Among patients with moderate renal impairment, approximately 84% were taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, angiotensin-converting-enzyme inhibitors, and angiotensin-receptor blockers *[see Warnings and Precautions and Use in Specific Populations]*.

INVOKANA of 24 weeks. Patients received INVOKANA 100 mg (N=833), INVOKANA 300 mg (N=834) or placebo (N=646) once daily. The mean age of the population was 56 years and 2% were older than 75 years of age. Fifty percent (50%) of the population was male and 72% were Caucasian, 12% were Asian, and 5% were Black or African American. At baseline the population had diabetes for an average of 7.3 years, had a mean HbA1C of 8.0% and 20% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 88 mL/min/1.73 m^2).

Table 1 shows common adverse reactions associated with the use of INVOKANA. These adverse reactions were not present at baseline, occurred more commonly on INVOKANA than on placebo, and occurred in at least 2% of patients treated with either INVOKANA 100 mg or INVOKANA 300 mg.

Table 1: Adverse Reactions From Pool of Four 26–Week Placebo-Controlled Studies Reported in ≥ 2% of INVOKANA-Treated Patients*

Adverse Reaction	Placebo N=646	INVOKANA 100 mg N=833	INVOKANA 300 mg N=834
Urinary tract infections‡	3.8%	5.9%	4.4%
Increased urination§	0.7%	5.1%	4.6%
Thirst#	0.1%	2.8%	2.4%
Constipation	0.9%	1.8%	2.4%
Nausea	1.6%	2.1%	2.3%
	N=312	**N=425**	**N=430**
Female genital mycotic infections†	2.8%	10.6%	11.6%
Vulvovaginal pruritus	0.0%	1.6%	3.2%
	N=334	**N=408**	**N=404**
Male genital mycotic infections¶	0.7%	4.2%	3.8%

* The four placebo-controlled trials included one monotherapy trial and three add-on combination trials with metformin, metformin and sulfonylurea, or metformin and pioglitazone.

† Female genital mycotic infections include the following adverse reactions: Vulvovaginal candidiasis, Vulvovaginal mycotic infection, Vulvovaginitis, Vaginal infection, Vulvitis, and Genital infection fungal.

‡ Urinary tract infections include the following adverse reactions: Urinary tract infection, Cystitis, Kidney infection, and Urosepsis.

§ Increased urination includes the following adverse reactions: Polyuria, Pollakiuria, Urine output increased, Micturition urgency, and Nocturia.

¶ Male genital mycotic infections include the following adverse reactions: Balanitis or Balanoposthitis, Balanitis candida, and Genital infection fungal.

Thirst includes the following adverse reactions: Thirst, Dry mouth, and Polydipsia.

Note: Percentages were weighted by studies. Study weights were proportional to the harmonic mean of the three treatment sample sizes.

Abdominal pain was also more commonly reported in patients taking INVOKANA 100 mg (1.8%), 300 mg (1.7%) than in patients taking placebo (0.8%).

Pool of Placebo- and Active-Controlled Trials: The occurrence of adverse reactions for canagliflozin was evaluated in a larger pool of patients participating in placebo- and active-controlled trials.

The data combined eight clinical trials *[see Clinical Studies (14) in full Prescribing Information]* and reflect exposure of 6177 patients to INVOKANA. The mean duration of exposure to INVOKANA was 38 weeks with 1832 individuals exposed to INVOKANA for greater than 50 weeks. Patients received INVOKANA 100 mg (N=3092), INVOKANA 300 mg (N=3085) or comparator (N=3262) once daily. The mean age of the population was 60 years and 5% were older than 75 years of age. Fifty-eight percent (58%) of the population was male and 73% were Caucasian, 16% were Asian, and 4% were Black or African American. At baseline, the population had diabetes for an average of 11 years, had a mean HbA1C of 8.0% and 33% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 81 mL/min/1.73 m^2).

The types and frequency of common adverse reactions observed in the pool of eight clinical trials were consistent with those listed in Table 1. Percentages were weighted by studies. Study weights were proportional to the harmonic mean of the three treatment sample sizes. In this pool, INVOKANA was also associated with the adverse reactions of fatigue (1.8% with comparator, 2.2% with INVOKANA 100 mg, and 2.0% with INVOKANA 300 mg) and loss of strength or energy (i.e., asthenia) (0.6% with comparator, 0.7% with INVOKANA 100 mg, and 1.1% with INVOKANA 300 mg).

In the pool of eight clinical trials, the incidence rate of pancreatitis (acute or chronic) was 0.1%, 0.2%, and 0.1% receiving comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

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In the pool of eight clinical trials, hypersensitivity-related adverse reactions (including erythema, rash, pruritus, urticaria, and angioedema) occurred in 3.0%, 3.8%, and 4.2% of patients receiving comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Five patients experienced serious adverse reactions of hypersensitivity with INVOKANA, which included 4 patients with urticaria and 1 patient with a diffuse rash and urticaria occurring within hours of exposure to INVOKANA. Among these patients, 2 patients discontinued INVOKANA. One patient with urticaria had recurrence when INVOKANA was re-initiated.

Photosensitivity-related adverse reactions (including photosensitivity reaction, polymorphic light eruption, and sunburn) occurred in 0.1%, 0.2%, and 0.2% of patients receiving comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Other adverse reactions occurring more frequently on INVOKANA than on comparator were:

Volume Depletion-Related Adverse Reactions: INVOKANA results in an osmotic diuresis, which may lead to reductions in intravascular volume. In clinical studies, treatment with INVOKANA was associated with a dose-dependent increase in the incidence of volume depletion-related adverse reactions (e.g., hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration). An increased incidence was observed in patients on the 300 mg dose. The three factors associated with the largest increase in volume depletion-related adverse reactions were the use of loop diuretics, moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m^2), and age 75 years and older (Table 2) *[see Dosage and Administration (2.2) in full Prescribing Information, Warnings and Precautions, and Use in Specific Populations]*.

Table 2: Proportion of Patients With at Least One Volume Depletion-Related Adverse Reaction (Pooled Results from 8 Clinical Trials)

Baseline Characteristic	Comparator Group* %	INVOKANA 100 mg %	INVOKANA 300 mg %
Overall population	1.5%	2.3%	3.4%
75 years of age and older†	2.6%	4.9%	8.7%
eGFR less than 60 mL/min/1.73 m^{2}†	2.5%	4.7%	8.1%
Use of loop diuretic†	4.7%	3.2%	8.8%

***** Includes placebo and active-comparator groups

† Patients could have more than 1 of the listed risk factors

Falls: In a pool of nine clinical trials with mean duration of exposure to INVOKANA of 85 weeks, the proportion of patients who experienced falls was 1.3%, 1.5%, and 2.1% with comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. The higher risk of falls for patients treated with INVOKANA was observed within the first few weeks of treatment.

Impairment in Renal Function: INVOKANA is associated with a dose-dependent increase in serum creatinine and a concomitant fall in estimated GFR (Table 3). Patients with moderate renal impairment at baseline had larger mean changes.

Table 3: Changes in Serum Creatinine and eGFR Associated with INVOKANA in the Pool of Four Placebo-Controlled Trials and Moderate Renal Impairment Trial

			Placebo N=646	INVOKANA 100 mg N=833	INVOKANA 300 mg N=834
Pool of Four Placebo-Controlled Trials	Baseline	Creatinine (mg/dL)	0.84	0.82	0.82
		eGFR (mL/min/1.73 m^2)	87.0	88.3	88.8
	Week 6 Change	Creatinine (mg/dL)	0.01	0.03	0.05
		eGFR (mL/min/1.73 m^2)	-1.6	-3.8	-5.0
	End of Treatment Change*	Creatinine (mg/dL)	0.01	0.02	0.03
		eGFR (mL/min/1.73 m^2)	-1.6	-2.3	-3.4
			Placebo N=90	**INVOKANA 100 mg N=90**	**INVOKANA 300 mg N=89**
Moderate Renal Impairment Trial	Baseline	Creatinine (mg/dL)	1.61	1.62	1.63
		eGFR (mL/min/1.73 m^2)	40.1	39.7	38.5
	Week 3 Change	Creatinine (mg/dL)	0.03	0.18	0.28
		eGFR (mL/min/1.73 m^2)	-0.7	-4.6	-6.2
	End of Treatment Change*	Creatinine (mg/dL)	0.07	0.16	0.18
		eGFR (mL/min/1.73 m^2)	-1.5	-3.6	-4.0

***** Week 26 in mITT LOCF population

INVOKANA®

(canagliflozin) tablets, for oral use
Brief Summary of Prescribing Information.

INDICATIONS AND USAGE

INVOKANA® (canagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus *[see Clinical Studies (14) in full Prescribing Information]*.

Limitation of Use: INVOKANA is not recommended in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to INVOKANA, such as anaphylaxis or angioedema *[see Warnings and Precautions and Adverse Reactions]*.
- Severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), end stage renal disease (ESRD), or patients on dialysis *[see Warnings and Precautions and Use in Specific Populations]*.

WARNINGS AND PRECAUTIONS

Hypotension: INVOKANA causes intravascular volume contraction. Symptomatic hypotension can occur after initiating INVOKANA *[see Adverse Reactions]* particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (e.g., angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with low systolic blood pressure. Before initiating INVOKANA in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating therapy.

Ketoacidosis: Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including INVOKANA. Fatal cases of ketoacidosis have been reported in patients taking INVOKANA. INVOKANA is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage]*.

Patients treated with INVOKANA who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels, as ketoacidosis associated with INVOKANA may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, INVOKANA should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement.

In many of the postmarketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized and institution of treatment was delayed because presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis such as insulin dose reduction, acute febrile illness, reduced caloric intake due to illness or surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating INVOKANA, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse. In patients treated with INVOKANA consider monitoring for ketoacidosis and temporarily discontinuing INVOKANA in clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or surgery).

Acute Kidney Injury and Impairment in Renal Function: INVOKANA causes intravascular volume contraction *[see Warnings and Precautions]* and can cause renal impairment *[see Adverse Reactions]*. There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving INVOKANA; some reports involved patients younger than 65 years of age.

Before initiating INVOKANA, consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heart failure and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs). Consider temporarily discontinuing INVOKANA in any setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue INVOKANA promptly and institute treatment.

INVOKANA increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating INVOKANA *[see Adverse Reactions]*.

Renal function should be evaluated prior to initiation of INVOKANA and monitored periodically thereafter. Dosage adjustment and more frequent renal function monitoring are recommended in patients with an eGFR below 60 mL/min/1.73 m^2. Use of INVOKANA is not recommended when eGFR is persistently less than 45 mL/min/1.73 m^2 and is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2 *[see Dosage and Administration (2.2) in full Prescribing Information, Contraindications and Use in Specific Populations]*.

Hyperkalemia: INVOKANA can lead to hyperkalemia. Patients with moderate renal impairment who are taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system are at an increased risk of developing hyperkalemia *[see Dosage and Administration (2.2) in full Prescribing Information and Adverse Reactions]*.

Monitor serum potassium levels periodically after initiating INVOKANA in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions.

Urosepsis and Pyelonephritis: There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including INVOKANA. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated *[see Adverse Reactions]*.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues: Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue *[see Adverse Reactions]*. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA.

Genital Mycotic Infections: INVOKANA increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections *[see Adverse Reactions]*. Monitor and treat appropriately.

Hypersensitivity Reactions: Hypersensitivity reactions, including angioedema and anaphylaxis, have been reported with INVOKANA. These reactions generally occurred within hours to days after initiating INVOKANA. If hypersensitivity reactions occur, discontinue use of INVOKANA; treat and monitor until signs and symptoms resolve *[see Contraindications and Adverse Reactions]*.

Bone Fracture: An increased risk of bone fracture, occurring as early as 12 weeks after treatment initiation, was observed in patients using INVOKANA. Consider factors that contribute to fracture risk prior to initiating INVOKANA *[see Adverse Reactions]*.

Increases in Low-Density Lipoprotein (LDL-C): Dose-related increases in LDL-C occur with INVOKANA *[see Adverse Reactions]*. Monitor LDL-C and treat if appropriate after initiating INVOKANA.

Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with INVOKANA *[see Adverse Reactions]*.

ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Hypotension *[see Warnings and Precautions]*
- Ketoacidosis *[see Warnings and Precautions]*
- Acute Kidney Injury and Impairment in Renal Function *[see Warnings and Precautions]*
- Hyperkalemia *[see Warnings and Precautions]*
- Urosepsis and Pyelonephritis *[see Warnings and Precautions]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions]*
- Genital Mycotic Infections *[see Warnings and Precautions]*
- Hypersensitivity Reactions *[see Warnings and Precautions]*
- Bone Fracture *[see Warnings and Precautions]*
- Increases in Low-Density Lipoprotein (LDL-C) *[see Warnings and Precautions]*

Clinical Studies Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Pool of Placebo-Controlled Trials: The data in Table 1 is derived from four 26-week placebo-controlled trials. In one trial INVOKANA was used as monotherapy and in three trials INVOKANA was used as add-on therapy *[see Clinical Studies (14) in full Prescribing Information]*. These data reflect exposure of 1667 patients to INVOKANA and a mean duration of exposure to

IMPORTANT SAFETY INFORMATION (cont'd)

- **Urosepsis and Pyelonephritis:** There have been reports of serious urinary tract infections, including urosepsis and pyelonephritis, requiring hospitalization in patients receiving SGLT2 inhibitors, including INVOKANA®. Treatment with SGLT2 inhibitors increases this risk. Evaluate patients for signs and symptoms and treat promptly.
- **Hypoglycemia With Concomitant Use With Insulin and Insulin Secretagogues:** INVOKANA® can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. A lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA®.
- **Genital Mycotic Infections:** INVOKANA® increases risk of genital mycotic infections. Patients with history of these infections and uncircumcised males were more likely to develop these infections. Monitor and treat appropriately.
- **Hypersensitivity Reactions:** Hypersensitivity reactions, including angioedema and anaphylaxis, were reported with INVOKANA®; these reactions generally occurred within hours to days after initiation. If reactions occur, discontinue INVOKANA®, treat per standard of care, and monitor until signs and symptoms resolve.
- **Bone Fracture:** Increased risk of bone fracture, occurring as early as 12 weeks after treatment initiation, was observed in patients using INVOKANA®. Consider factors that contribute to fracture risk prior to initiating INVOKANA®.
- **Increases in Low-Density Lipoprotein (LDL-C):** Dose-related increases in LDL-C can occur with INVOKANA®. Monitor LDL-C and treat per standard of care after initiating.
- **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with INVOKANA®.

DRUG INTERACTIONS

- **UGT Enzyme Inducers:** Rifampin: Co-administration of INVOKANA® with rifampin decreased INVOKANA® area under the curve (AUC) by 51% and therefore may decrease efficacy. If an inducer of UGT enzymes must be co-administered with INVOKANA®, consider increasing the dose to 300 mg once daily if patients are currently tolerating INVOKANA® 100 mg once daily, have an eGFR ≥60 mL/min/1.73 m^2, and require additional glycemic control. Consider other antihyperglycemic therapy in patients with an eGFR <60 mL/min/1.73 m^2 who require additional glycemic control.
- **Digoxin:** There was an increase in the AUC and mean peak drug concentration of digoxin (20% and 36%, respectively) when co-administered with INVOKANA® 300 mg. Monitor appropriately.
- **Positive Urine Glucose Test:** Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose test results. Use alternative methods to monitor glycemic control.
- **Interference With 1,5-Anhydroglucitol (1,5-AG) Assay:** Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** Based on animal data showing adverse renal effects, INVOKANA® is not recommended during the second and third trimesters of pregnancy. Limited data with INVOKANA® in pregnant women are not sufficient to determine a drug-associated risk for major birth defects or miscarriage. There are risks to mother and fetus associated with poorly controlled diabetes in pregnancy.
- **Nursing Mothers:** There is no information regarding the presence of INVOKANA® in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed infant, advise women that use of INVOKANA® is not recommended while breastfeeding.
- **Pediatric Use:** Safety and effectiveness in patients <18 years of age have not been established.
- **Geriatric Use:** 2034 patients ≥65 years and 345 patients ≥75 years were exposed to INVOKANA® in 9 clinical studies. Patients ≥65 years had a higher incidence of adverse reactions related to reduced intravascular volume (eg, hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300-mg dose, compared to younger patients; more prominent increase in the incidence was seen in patients who were ≥75 years. Smaller reductions in HbA1c relative to placebo were seen in patients ≥65 years (−0.61% with INVOKANA® 100 mg and −0.74% with INVOKANA® 300 mg) compared to younger patients (−0.72% with INVOKANA® 100 mg and −0.87% with INVOKANA® 300 mg).
- **Renal Impairment:** Efficacy and safety were evaluated in a study that included patients with moderate renal impairment (eGFR 30 to <50 mL/min/1.73 m^2). These patients had less overall glycemic efficacy and a higher occurrence of adverse reactions related to reduced intravascular volume, renal-related adverse reactions, and decreases in eGFR compared to patients with mild renal impairment or normal renal function (eGFR ≥60 mL/min/1.73 m^2); patients treated with 300 mg were more likely to experience increases in potassium. INVOKANA® is not recommended in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2), with end-stage renal disease, or receiving dialysis.
- **Hepatic Impairment:** INVOKANA® has not been studied in patients with severe hepatic impairment and is not recommended in this population.

OVERDOSAGE

- In the event of an overdose, contact the Poison Control Center and employ the usual supportive measures, eg, remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as needed.

ADVERSE REACTIONS

- The most common adverse reactions associated with INVOKANA® (5% or greater incidence) were female genital mycotic infections, urinary tract infections, and increased urination.

Please see Brief Summary of full Prescribing Information at left and on the previous pages.

References: 1. Data on file. Janssen Pharmaceuticals, Inc. Based on IMS Health, NPA Weekly, Total Prescriptions, April 2013-December 23, 2016. **2.** INVOKANA® [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc. **3.** Schernthaner G, Gross JL, Rosenstock J, et al. Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea: a 52-week randomized trial [published correction appears in *Diabetes Care*. 2013;36(12):4172]. *Diabetes Care*. 2013;36(9):2508-2515. **4.** Lavalle-González FJ, Januszewicz A, Davidson J, et al. Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. *Diabetologia*. 2013;56:2582-2592. Supplemental tables available at: http://link.springer.com/article/10.1007%2Fs00125-013-3039-1. Accessed February 5, 2017. **5.** MMRx data on file. Janssen Pharmaceuticals, Inc. Data as of 1/10/2017.

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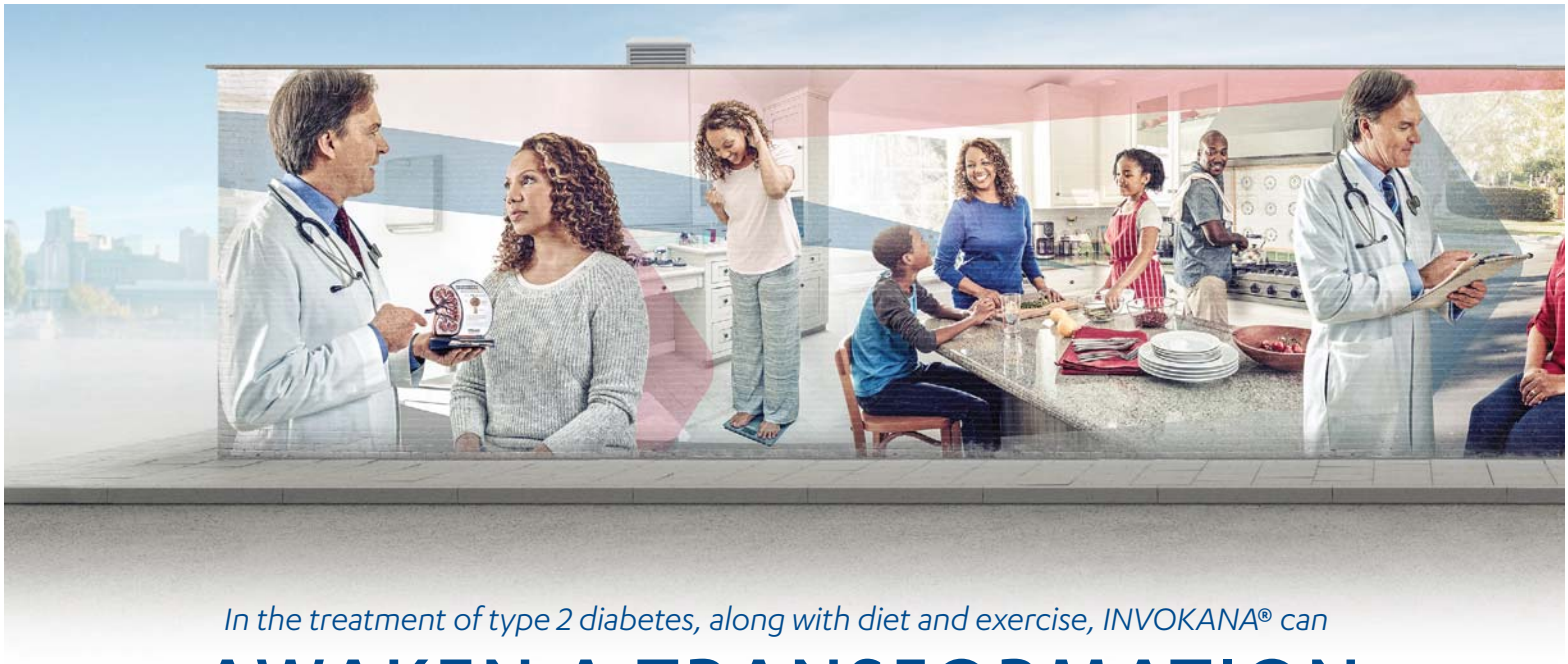


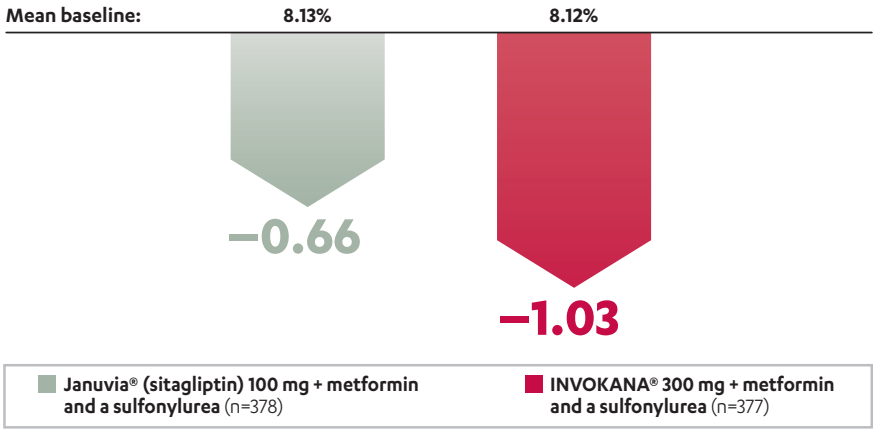
In the treatment of type 2 diabetes, along with diet and exercise, INVOKANA® can

AWAKEN A TRANSFORMATION

INVOKANA® 300 mg demonstrated superior reductions in A1C, body weight,* and systolic blood pressure (BP)* vs Januvia® 100 mg[2-4]

» In a prespecified analysis, superiority was determined once noninferiority was confirmed[3†]

Adjusted Mean Change in A1C From Baseline at 52 Weeks (%)[2]



» INVOKANA® 300 mg difference from Januvia® 100 mg: −0.37% (95% CI: −0.50, −0.25; *P*<0.05)

Prespecified secondary endpoints:

Adjusted mean change in body weight from baseline at 52 weeks[2]

» **Difference from Januvia®: −2.8%** (−5.3 lb) (95% CI: −3.3, −2.2; *P*<0.001)

Adjusted mean change in systolic BP from baseline at 52 weeks[3]

» **Difference from Januvia®: −5.9 mm Hg** (95% CI: −7.6, −4.2; *P*<0.001)

INVOKANA® starting dose: 100 mg once daily. In patients tolerating the starting dose who have an eGFR ≥60 mL/min/1.73 m^2 and require additional glycemic control, the dose can be increased to 300 mg once daily.[2]

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS and PRECAUTIONS

» **Hypotension:** INVOKANA® causes intravascular volume contraction. Symptomatic hypotension can occur after initiating INVOKANA®, particularly in patients with impaired renal function (eGFR <60 mL/min/1.73 m^2), elderly patients, patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system, or patients with low systolic blood pressure. Before initiating in patients with ≥1 of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating.

Similar overall incidence of AEs vs Januvia®[3]

Incidence of any AE, Januvia® 100 mg: 77.5%; INVOKANA® 300 mg: 76.7%

Incidences of specific AEs were similar between groups, except for:

Male/female genital mycotic infection, Januvia® 100 mg: 0.5%/4.3%; INVOKANA® 300 mg: 9.2%/15.3%

Superior Reductions vs Januvia®[2,3‡]
- A1C†
- Body weight*
- Systolic BP*

Similar Rate of Hypoglycemia and Overall Tolerability Profile to Januvia®[2-4§]

Preferred[‖] coverage for most commercial and Medicare Part D patients[5]

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INVOKANAhcp.com

*Prespecified secondary endpoint. **INVOKANA® is not indicated for weight loss or as an antihypertensive treatment.**

† Noninferiority of INVOKANA® + metformin and a sulfonylurea to Januvia® + metformin and a sulfonylurea was assessed based on a prespecified margin of 0.3% for the upper limit of the 2-sided 95% CI for the comparison in the primary last observation carried forward analysis. If noninferiority was demonstrated, then superiority was assessed, as determined by an upper bound of the 95% CI around the between-group difference (INVOKANA® minus Januvia®) of <0.0%.[3]

‡ **INVOKANA® 300 mg vs Januvia® 100 mg.**

§ Similar overall incidence of adverse events vs Januvia® 100 mg across multiple studies.[3,4]

‖ For most plans, brand-name drugs that are generally covered at lower co-payments than higher tier brand-name drugs. (The lowest tiers are generally reserved for generic drugs.)

A randomized, double-blind, active-controlled, 52-week study of 755 patients with type 2 diabetes inadequately controlled on maximally or near-maximally effective doses of metformin (≥2000 mg/day, or ≥1500 mg/day if higher dose not tolerated) and a sulfonylurea. The primary endpoint was the change in A1C from baseline to 52 weeks.[2,3]

- **Ketoacidosis:** Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization, have been identified in patients with type 1 and 2 diabetes mellitus receiving SGLT2 inhibitors, including INVOKANA®. Fatal cases of ketoacidosis have been reported in patients taking INVOKANA®. Before initiating INVOKANA®, consider factors in patient history that may predispose to ketoacidosis, including pancreatic insulin deficiency, caloric restriction disorders, and alcohol abuse. In patients treated with INVOKANA®, consider monitoring for ketoacidosis and temporarily discontinuing in clinical situations known to predispose to ketoacidosis (eg, prolonged fasting due to acute illness or surgery).
- **Acute Kidney Injury and Impairment in Renal Function:** INVOKANA® causes intravascular volume contraction and can cause renal impairment. Postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, were reported; some reports involved patients younger than 65 years of age. Before initiation, consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heart failure and concomitant medications. Consider temporarily discontinuing INVOKANA® in any setting of reduced oral intake or fluid losses; monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue promptly and institute treatment.

  INVOKANA® increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiation. Renal function should be evaluated prior to initiation and periodically thereafter. Dose adjustment and more frequent renal function monitoring are recommended in patients with an eGFR <60 mL/min/1.73 m^2.
- **Hyperkalemia:** INVOKANA® can lead to hyperkalemia. Patients with moderate renal impairment who are taking medications that interfere with potassium excretion or medications that interfere with the renin-angiotensin-aldosterone system are more likely to develop hyperkalemia. Monitor serum potassium levels periodically in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the previous pages and the following page.

MORE THAN **11 MILLION PRESCRIPTIONS** TO DATE[1]

In the treatment of type 2 diabetes, along with diet and exercise, INVOKANA® can

AWAKEN A TRANSFORMATION

INVOKANA® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

INVOKANA® is not recommended in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to INVOKANA®, such as anaphylaxis or angioedema
- Severe renal impairment (eGFR <30 mL/min/1.73 m^2), end-stage renal disease, or patients on dialysis

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the previous pages.

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