

article also reviews the weight and glycemic control effects of approved drugs for the treatment of obesity.

Insulin

Abnormalities in insulin production, release, and effectiveness underlie the major pathophysiology of both type 1 and type 2 diabetes. Insulin therapy was first introduced in 1921 and completely changed the course of diabetes treatment. The ability to optimize insulin therapy, however, arose in the 1980s, with the introduction of blood glucose self-monitoring technology and the A1C assay. Before then, glucose control was often suboptimal and excess weight gain was generally not a major problem. In fact, many type 1 diabetic patients were basically malnourished and had difficulties gaining weight. The results of the DCCT and the Kumamoto trial not only validated the glycemic hypothesis, but also helped the diabetes community better use insulin in a more physiological manner to achieve better glucose control. Weight gain was associated with improved glycemic control in both studies. Weight gain was also seen in the insulin-therapy group of the UKPDS, which gained 8.8 lb more than the conventional diet-treated group during a 10-year period.³ Average weight gain in the DCCT during the first year of therapy was 11.2 lb in the intensified group, versus 5.7 lb in the conventional group.^{1,10}

A major factor in weight accrual

stems from the decrease in glycosuria when insulin therapy is started or intensified. In a small study on intensification in type 2 diabetes, metabolic factors were measured closely.¹¹ A1C decreased from 12.9 to 9.6%, with a weight gain of 5.7 lb. Fat mass increased by 5.2 lb, and 70% of the gain was attributed to correction of glycosuria. Weight gain may be minimized in most patients by reduction in calorie intake. Unfortunately, patients often do not get the adequate nutrition therapy and education needed to complement their change in medical therapy.

Another factor that has been shown to fuel weight gain with insulin therapy is hypoglycemia. Frequent hypoglycemia and treatment, often overtreatment, can cause weight gain.¹² Frequency of hypoglycemia and increase in weight were linked in the intensified group in the DCCT.¹⁰ There is also evidence that insulin may play a direct role in fat creation and deposition.¹³ Moreover, it has long been debated whether insulin, especially supraphysiological levels of insulin, may have a direct effect on receptors in the central nervous system that govern appetite.¹⁴

The early landmark studies that tested the glycemic hypothesis were done using human DNA insulins, including regular, NPH, and ultralente insulins. During the past 15 years, new injectable analog insulins have been introduced, and more recently inhaled insulin has become available. The

nature of the analog action profiles, including basal insulins glargine and detemir and bolus insulins lispro, aspart, and glulisine, allow for a more physiological approach to therapy than the older insulin formulations. Provision of lower basal insulin levels and more direct and limited capture of prandial glucose excursions by rapid-acting insulins could decrease hypoglycemia and better utilize calories, thereby decreasing weight changes. Results of such studies have been variable depending on the comparison regimens and whether both groups were intensified to the same degree.¹⁵⁻¹⁹ De Leeuw et al.¹⁵ compared NPH versus detemir as basal insulin in an intensified regimen for patients with type 1 diabetes, patients on the detemir regimen had a mean weight loss of 0.22 lb, whereas the NPH group gained 2.6 lb. Rosenstock et al.¹⁶ performed a 28-week study of glargine versus NPH regimens in a treat-to-target trial of basal insulins in type 2 diabetes. A1C declined 0.7% in both groups from an average of 8.5%, but the glargine-treated group gained 0.88 lb versus 3.0 lb in the group treated with NPH. A 28-week study by Anderson et al.¹⁷ compared lispro and regular insulin at mealtimes and found no difference in weight gain between the two groups of patients with type 2 diabetes. Reduction in A1C also did not differ between the two groups.

The insulin delivery method may also play a role in weight gain. In a 6-month study by Hollander et al.²⁰ involving patients with type 2 diabetes, patients on a multiple daily injection insulin regimen were randomized either to continue their current therapy or to switch to a regimen of inhaled insulin and ultralente insulin. A1C decreased by 0.7% in both groups. No weight gain was seen in the patients using inhaled insulin, whereas a gain of 2.8 lb was seen in the patients on subcutaneous insulin. Data from 2-year safety studies on patients with type 1 or type 2 diabetes also found less weight gain in the inhaled insulin treatment groups versus patients treated with subcutaneous insulin.^{21,22}

Sulfonylureas

Sulfonylureas are a class of oral hypoglycemic agent that has been used for the treatment of type 2 diabetes for more than 50 years. They are described as insulin secretagogues and

Table 1. Anti-Diabetes Medications With Their Reductions in A1C and Effects on Weight

Drug Class	Reductions in A1C (%)	Weight Effects (lb)
Insulin	> 2.5	+8.8–11.0
Inhaled insulin	1–2	+2.2–4.4
Sulfonylureas	1.6	+3.5–5.7
Repaglinide and nateglinide	0.8–1.5	+1.54–3.9
Metformin	1.5	–10.1–+0.88
Thiazolidinediones	0.8–1.0	+9.2–10.6
α-Glucosidase inhibitors	0.5–0.8	+0.0–0.44
DPP-IV inhibitors	0.5–1.0	+0.0–0.88
GLP-1 mimetic	0.6–0.8	–2.8–6.6
Amylin analogs	0.6	–3.1

act on a set of receptors on the β -cell, thereby increasing insulin secretion. Currently, three agents are available in the United States: glyburide, glipizide, and glimepiride. The three drugs are fairly similar in action, and in a drug-naïve patient may lower glucose by up to 1.5%. There is some evidence that glipizide and glimepiride may be associated with less hypoglycemia than glyburide. Unlike the action of other classes of available insulin secretagogues, which are glucose dependent, sulfonylureas are not. The sustained effect on the β -cell contributes both to the degree of efficacy and also to the rate of hypoglycemia seen with this class.

All three drugs have been associated with weight gain, whether given as monotherapy or in combination with other classes of oral agents or insulin.^{3,23-26} In the UKPDS, patients on glibenclamide gained 5.7 lb more than patients on nutrition therapy over a 10-year period.³ Hermann et al.²⁴ found in a 6-month study that glyburide treatment in drug-naïve patients resulted in a 5.7-lb weight gain, along with a 1.3% decrease in A1C. Recently, the study known as A Diabetes Outcome Progression Study (ADOPT) followed patients for a mean of 4 years in a sequential three-arm study to evaluate glycemic durability.²⁵ Mean A1C at the start of the study was 7.3%. Weight gain of 3.5 lb in the sulfonylurea arm of the study at the end of 1 year was correlated with a decrease in A1C of 0.9%. No further increase in weight was seen during the remainder of the treatment period. Increased and sustained insulin secretion, along with decreased glycosuria and increased hypoglycemia, are thought to fuel the weight gain seen with this drug class. Sulfonylureas are not believed to have independent effects on adipose deposition or appetite.

Repaglinide and Nateglinide

Often described as being in the same class of drugs, repaglinide and nateglinide actually have very different chemical backgrounds but have similar mechanisms of action. Repaglinide is a meglitinide, and nateglinide is a D-phenylalanine derivative. Both drugs fall into the category of insulin secretagogues and have their effect by stimulating the β -cell. The action of both drugs is glucose dependent, and, in contrast to the sulfonylureas, they

stimulate insulin secretion only in the face of abnormal glucose levels. These drugs are given before meals and decrease postprandial glucose levels.

Weight gain is seen with both drugs. These drugs cause a decrease in urinary glucose excretion that may play the major role in weight gain. Although the action of both classes of drug is glucose dependent, hypoglycemia can occur. With insulin secretagogues, efficacy and weight gain often have a linear relationship. Rosenstock et al.²⁷ reported a 6-month study that compared nateglinide to repaglinide therapy. A1C fell by 1.57% for the repaglinide group versus 1.0% for the nateglinide group. Respective weight gain was 3.9 versus 1.54 lb.

Metformin

Metformin is an interesting drug and difficult to categorize. It was introduced in 1957 in Europe but was not approved in the United States until 1995, after two major registration trials. Initially thought to act on both the peripheral insulin resistance and abnormal hepatic glucose output that characterize type 2 diabetes, it is now thought to have its main effect on normalizing hepatic glucose output. Treatment with metformin may actually result in weight loss or at least weight neutrality. In clinical trials in which the comparator of treatment is an insulin secretagogue, less weight gain has been seen in the metformin group. This result was found in the UKPDS, with the metformin group gaining only 1.1–2.2 lb over a 10-year period.⁴ This finding was echoed by a 6-month study by Hermann et al.²⁴ in which drug-naïve patients treated with metformin lost 1.4–3.3 lb and A1C dropped by 1.6%. When metformin was added to patients treated with diet in registration studies on metformin, the 29-week monotherapy study saw an 8.4-lb decrease in weight and a 1.6% decline in A1C.²⁸ When metformin was added to patients treated with glyburide, an additional 1.7% decrease in A1C was observed, with only a 0.88-lb weight gain. In the ADOPT study, patients treated with metformin lost 2.9 kg during the first year and were stable over the remaining time of the study;²⁵ A1C declined by 0.6%.

The weight effect of metformin may result from a number of mechanisms. It does not stimulate insulin production, hypoglycemia is rare to

nonexistent, and normalizing glucose production in the liver may have some effect in terms of adipose creation. Some patients do have adverse gastrointestinal symptoms with metformin, such as cramping, diarrhea, and nausea. Whether those symptoms may have an effect on food intake is unclear, but it has been suggested that such symptoms may play a role in the weight neutrality or weight loss seen with metformin therapy.²⁹

Several trials have been conducted to determine the role of metformin in the treatment of early and prediabetes. Metformin was part of the Diabetes Prevention Program, in which it was compared to lifestyle for prevention of diabetes in patients with impaired glucose tolerance.³⁰ Individuals treated with metformin lost 2.5% of their basal body weight compared with a 7.5% loss in the lifestyle group. The ADA algorithm published in 2006 recommended metformin as the best choice for initial therapy in type 2 diabetes and recommended that it be started along with lifestyle therapy at the time of diagnosis.⁶

Thiazolidinediones

Thiazolidinediones are a class of drugs that activate the peroxisome proliferator-activated receptor- γ (PPAR- γ). Activation of this receptor decreases insulin resistance and promotes glucose uptake by the cell in patients with type 2 diabetes. Drugs that are currently available in this class include rosiglitazone and pioglitazone.

The improved glucose control seen with these drugs may result in weight gain and in some cases substantial weight gain.³¹⁻³⁵ The cause of this weight gain is unclear. Decreased glycosuria may play a role, but these drugs appear to also have a direct effect on the PPAR receptors on the adipocyte and thus stimulate adipogenesis.³⁶ Most of the increase in adipose tissue is in the subcutaneous fat depot, and visceral fat may actually decrease. Flux in fluid balance may also occur in patients, as signified by peripheral edema. In a study by Phillips et al.³² of monotherapy with rosiglitazone, weight gain of 7.2 lb was seen when compared to placebo; A1C decreased 1.5% from a baseline of 9.0%. The greatest increase in weight is usually seen when these agents are combined with insulin secretagogues or insulin and in patients who are markedly hyperglycemic. Raskin et al.³⁵

reported a weight gain of 11.7 lb in a study in which 8 mg of rosiglitazone was added to insulin therapy. Hollander et al.³⁷ saw a lesser weight gain of 7.0 lb in a 6-month study of 4 mg of rosiglitazone in patients on insulin therapy; A1C decreased 0.4% from a baseline of 8.5%. In the ADOPT trial, an increase of 5.2 lb was seen in the rosiglitazone arm at 1 year, and A1C fell by 0.5%. At study end, mean weight gain was 10.6 lb.²⁵

α -Glucosidase Inhibitors

α -Glucosidase inhibitors include the drugs acarbose and miglitol. Their method of action is to delay the breakdown of polysaccharides by blocking a series of enzymes in the gut, thereby decreasing the postprandial glucose spike.³⁸ Because of their mechanism of action, they are taken with each meal. The major side effects—flatulence and loose stools—are the result of the delayed uptake of carbohydrate, which allows increased opportunity for bacterial fermentation.

Variable effects on weight have been seen with this drug.^{39–41} In a 3-month dose titration study of acarbose in patients with type 2 diabetes, no weight gain was seen in the three treatment groups when compared to placebo.⁴¹ In a 6-month type 1 diabetes study of acarbose, an A1C decrease of 0.48% was observed, with a weight increase of 0.44 lb compared to a 0.22-lb weight gain in the placebo group.⁴²

Dipeptidyl peptidase-IV (DPP-IV) Inhibitors

DPP-IV inhibitors are one of the newest classes of drugs to be introduced for the control of blood glucose. To understand the mechanism of action of these drugs, it is important to understand the role of glucagon-like peptide 1 (GLP-1), which is secreted in the gut after food ingestion. GLP-1 stimulates insulin production by the β -cell, regulates glucagon secretion, may slow gastric emptying, and can affect the appetite center in the hypothalamus, resulting in feelings of satiety. DPP-IV is an enzyme in the blood that inactivates the GLP-1 peptide. DPP-IV inhibitors slow the breakdown of GLP-1 and thereby extend its metabolic effects.^{43,44} Several drugs in this class are in development, and sitagliptin has recently been approved by the U.S. Food and Drug Administration (FDA). Viligliptin,

another DPP-IV inhibitor, is currently being evaluated by the FDA. Trials of both drugs have been shown to lower blood glucose.^{45–47} Six-month studies with sitagliptin, both as monotherapy and in combination with metformin and pioglitazone, have shown average A1C decreases of 0.6–8.0%.

Both sitagliptin and viligliptin have been shown to have a neutral effect on weight gain. Moreover, both drugs can be considered insulin secretagogues. The usual effect of this class on weight gain may be offset by the other effects of GLP-1. Hypoglycemia is also rare with these drugs and also may play a role in diminution of expected weight gain.

Exenatide

Exenatide is a GLP-1 mimetic and is given as an injection. It is a synthetic version of extendin-4, a protein secreted in saliva of the Gila monster. It mimics some of the actions of naturally secreted GLP-1 by binding to and stimulating the GLP-1 receptors.⁴⁸

Combination studies in patients with type 2 diabetes on oral agent monotherapy and combination oral agent therapy have shown reduction in A1C and in weight.^{49–51} Ratner et al.⁴⁹ reported a weight loss of 6.6 lb accompanied by a 1.1% decrease in A1C in a 30-week study of exenatide in patients on metformin. The weight loss is progressive and occurs regardless of baseline weight, although the greatest weight loss is seen in the most obese patients. An 82-week extension study of a partial cohort of patients from the initial 1-year study found a mean decrease of 10.1 lb associated with sustained A1C reduction. A 28-week trial that compared the addition of exenatide or glargine to patients already on oral agents found an equal decrease in A1C, with weight gain in the insulin cohort of 2.8 lb and weight loss in the exenatide cohort of 4.6 lb.⁵² An 82-week extension study of a partial cohort of patients from the initial 1-year study found a mean decrease of 9.9 lb.⁵³ However, when overall trial data are analyzed, a responder pattern in terms of weight loss is seen in the extension studies, and not all treated patients lose weight.⁵⁴

Exenatide is resistant to the effect of DPP-IV and thus can exert a prolonged possible supraphysiological effect on the GLP-1 receptors, especially on the central nervous

system-mediated effects on appetite. Nausea is the most common side effect of exenatide but apparently does not correlate with weight loss.

Pramlintide

Pramlintide is an analog of amylin, a hormone cosecreted by the β -cell with insulin. Amylin has been shown to suppress prandial glucagon production and slow gastric emptying. Abnormalities in the production of amylin in conjunction with insulin abnormalities have been seen in both type 1 and type 2 diabetes.^{55,56} Pramlintide is given as an injection at each meal and has been shown to decrease postprandial glucose. It has been studied extensively in patients with type 1 or type 2 diabetes and has been shown to produce significant lowering of A1C in both groups.^{57–59}

Decrease in body weight has been seen in studies of both type 1 and type 2 diabetic patients.^{58,59} In a 1-year study in patients with type 2 diabetes on insulin therapy, Hollander et al.⁵⁷ found that patients on pramlintide lost an average of 3.1 lb, associated with a 0.8% improvement in A1C compared to the group treated with placebo. Ratner et al.⁵⁹ also found similar effects in a 13-week study in patients with type 1 diabetes. In this group, treated patients had a 1.05% decrease in A1C along with a decrease in weight. Because of the effect of pramlintide on weight loss in patients with diabetes, it has been studied as a weight-loss drug in non-diabetic obese individuals with some success. Its mechanism of action for weight loss may relate to its effect on gastric emptying and thereby satiety. Studies on food intake in patients treated with pramlintide have shown a reduction in caloric intake.⁶⁰

Obesity Drugs

Weight loss is considered an important aspect of therapy for patients with diabetes. Excess weight places greater direct demand on the β -cell and also aggravates insulin resistance. Numerous studies have shown that weight loss in patients with diabetes can result in improvement in glucose levels.^{61–63}

Weight loss appears to be more difficult for patients with diabetes than for those without diabetes. This phenomenon has been shown in studies of lifestyle therapy, drug therapy, and even bariatric surgery. The Look Ahead trial, a 11.5-year study of

lifestyle, behavioral, and drug therapy in patients with type 2 diabetes on variable treatment regimens may show different results.⁶⁴ An interim report of its results has shown a fairly impressive weight loss of 8% of basal body weight and a decrease in mean A1C from 7.25 to 6.6% at 1 year in the treatment group, whereas the control group lost 0.4% of basal body weight with a decrease in A1C of 0.15%.

A limited number of drugs have been approved by the FDA for the treatment of obesity. Phentermine is the oldest and most commonly prescribed anti-obesity drug. It has been studied in two small 3- and 4-month studies for weight loss in patients with type 2 diabetes.^{65,66} Weight loss of up to 7.9–8.3 lb was reported, but no effect was found on glucose as measured by fasting blood glucose level. Sibutramine, a central nervous system appetite suppressant, and orlistat, a lipase inhibitor, have both been studied in patients with type 2 diabetes. Rimonabant, a cannabinoid antagonist, has also been studied in patients with type 2 diabetes. It has been approved in the European Community and approval is pending in the United States.

The three drugs studied in patients with type 2 diabetes work by quite different mechanisms. Orlistat blocks triglyceride uptake in the gut and may cause loose stools and flatulence.⁶⁷ It has been studied along with lifestyle therapy in combinations with sulfonylureas, metformin, and insulin in 12-month trials in patients with type 2 diabetes.^{68–70} Similar decreases in both A1C and weight were observed. In a 1-year study by Hollander et al.⁶⁹ in patients treated with sulfonylureas, a 0.48% decrease in A1C from baseline was seen, in conjunction with a weight loss of 13.6 versus 9.5 lb in the placebo group.

Sibutramine, a serotonin and noradrenaline reuptake inhibitor, influences satiety and may increase thermogenic energy. Side effects of this drug include increases in blood pressure and tachycardias. Studies have shown sibutramine to cause weight loss and an accompanying decrease in glucose level.^{71–73} In a study reported by Serrano-Rios et al.,⁷¹ a mean weight loss of 9.9 lb and a decrease in A1C of 1.0% from a baseline of 9.0% was seen.⁷¹ In a study by McNulty et al.,⁷³ although overall mean A1C reduction was seen

in the group treated with sibutramine versus the group treated with placebo, the improvement in glucose control was found only in patients who lost 5 or 10% of basal body weight and was not seen when the intention-to-treat group was analyzed.

Rimonabant, a selective cannabinoid (CB1) receptor inhibitor, decreases appetite and affects energy balance. Although CB1 receptors have been identified on numerous body organs, the major effect of this drug appears to be on the central nervous system. Rimonabant has been shown to cause significant weight loss and decrease in A1C in a year-long study in patients with type 2 diabetes who were on either metformin or sulfonylurea therapy.⁷⁴ Average weight loss was 8.1 lb over the placebo group and was associated with a decrease in A1C of 0.7% from a baseline of 8.5%. No differences in weight loss or A1C change were seen between the metformin group and the group on sulfonylureas. More recent data have become available from a 6-month study in drug-naïve patients that also showed similar results: a mean A1C decrease of 0.8% from a baseline of 7.9% in the treated group as opposed to a 0.3% decline in A1C for the placebo group.⁷⁵ Mean body weight declined by 14.7 lb in the rimonabant group versus 5.9 lb in the placebo group. In terms of side effects of the cannabinoid inhibitor, there may be minor risk for increase in development or aggravation of depression.

Summary

Weight gain is an undesirable result of treatment for patients with type 1 or type 2 diabetes. Multiple medications are now available to lower blood glucose, but as the goal of near-normal glycemia is sought, weight gain often ensues. Unfortunately, weight gain can be associated with poor cardiovascular outcomes and other morbidity and leads to increasing insulin resistance in both type 1 and type 2 diabetes.^{76–78} Concerns about weight gain should not discourage advancement of therapy, however.

The choice of treatment for patients depends on the degree of progression of their diabetes. Insulin is always the first choice for the treatment of type 1 diabetes, but there are multiple treatment choices for patients with type 2 diabetes. The ADA consensus al-

gorithm for the treatment of type 2 diabetes⁷ suggested starting drug treatment at diagnosis and also introducing insulin earlier in the progression of disease. The focus of this algorithm is glycemic control and not weight. Metformin, however, is recommended as the drug of choice for initiation of therapy, and it does have a favorable effect on weight. The second tier of the algorithm suggests the choices of basal insulin, sulfonylurea, or a thiazolidinedione in addition to metformin as the second step in treatment. All three of these agents are associated with variable weight gain.

The consensus algorithm does not include the newer drugs, such as pramlitide, extenatide, sitagliptin, or inhaled insulin. Do these drugs offer advantages over the older drugs? All four appear to have a neutral effect on weight gain or to actually cause weight loss. Pramlitide has been studied both in type 1 and type 2 diabetes and has been associated with modest weight loss. Extenatide has been shown to cause weight loss in patients along with sustained decrease in A1C. Less weight gain has been seen with inhaled insulin in patients on basal-bolus therapy, and the DPP-IVs have been associated with weight neutrality.

The decision to initiate or add any drug to the diabetes regimen rests on a number of factors, including efficacy, side effects, weight considerations, patient acceptance, and cost. Therapy must always be directed to the individual patient. Weight gain does not have to be an inevitable result of diabetes treatment. Optimization of therapy to limit weight gain requires understanding the effect of the drug in question on weight and its effect on efficacy. In climbing the ladder of increasingly complex diabetes therapy for patients with type 2 diabetes, successful combination therapy may be best attained through the synergy of adding a weight-loss promoting or weight-neutral drug to one that promotes weight gain. The importance of implementing nutrition therapy to neutralize decreases in glycosuria is also a key point in limiting weight gain for all patients.

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Note of disclosure: Dr. Hollander has received honoraria for speaking engagements from Merck, Pfizer, and Sanofi-Aventis and has served on advisory boards for these companies and for Roche Pharmaceuticals, all of which manufacture pharmaceutical products for the treatment of diabetes.