Weight gain associated with antidiabetic medications

Diabetes has emerged as the major epidemic of modern times, with obesity, particularly central obesity, being a major risk factor for Type 2 diabetes and its attendant cardiovascular disease. Furthermore, weight reduction has been shown to prevent Type 2 diabetes in people with prediabetes and to improve glycemic control and reduce cardiovascular disease risk in the diabetic population. Weight gain is a major problem that faces physicians striving to achieve adequate glycemic, blood pressure and lipid control for their diabetic patients. The use of antidiabetic agents, particularly insulin, insulin secretagogs and thiazolidinediones, has long been associated with weight gain, not only complicating the management of diabetes but also sending mixed messages to patients who are being asked to lose weight. This article presents the effects of antidiabetic medications on bodyweight, explaining the potential mechanisms of weight gain and also discusses the available therapeutic options that could achieve better glycemic control without adverse effects on bodyweight or, even better, cause weight loss.

KEYWORDS: antidiabetic medications ■ insulin ■ sulfonylurea ■ thiazolidinedione ■ weight gain

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Obesity in diabetic populations

Most people with Type 2 diabetes are either overweight or obese, with up to 90% of people with diabetes being overweight at diagnosis [1]. These patients continue to gain weight over time, with the exception of the postdiagnosis period where patients are educated and encouraged to lose weight for better control of their illness [1]. While risk factors for diabetes include increased age, hypertension, sedentary lifestyle, family history of diabetes and ethnic minorities (**Box 1**) [2], obesity is one of the most important risk factors for insulin resistance, Type 2 diabetes and cardiovascular disease (CVD) [3]. Central obesity clusters with other cardiovascular risk factors in people with diabetes and is a major component of the metabolic syndrome [3,4]. CVD risk factors include insulin resistance, low high-density lipoprotein cholesterol, increased triglyceride levels, small dense low-density lipoprotein cholesterol, systolic hypertension, absence of nocturnal decline in pulse and blood pressure, increased oxidative stress and endothelial dysfunction, among others (**Box 2**) [3,4].

A high prevalence of CVD risk factors associated with obesity has been demonstrated in large studies. In the Swedish National Diabetes Register, a cross-sectional analysis involving 44,042 Type 2 diabetes patients, with a 6-year prospective study of 4468 Type 2 diabetes patients, obese patients with diabetes (37%) had high frequencies of hypertension (88%) and hyperlipidemia (81%), as well as microalbuminuria (29%) [5]. Interestingly, control of blood pressure, a major risk factor for CVD in this population, to a goal of 130/80 mmHg was only achieved in 11% of patients [5]. Data for various ethnic minorities demonstrated a high prevalence of obesity and poor control of CVD risk factors in patients with diabetes [6,7]. In studies conducted in 2001 and 2004, less than 5% of diabetic patients achieved blood pressure, glycemic and lipid control simultaneously [6,7].

Type 2 diabetes patients generally gain weight throughout the course of the disease. This weight gain is associated with worsening glycemic control and further increases CVD risk factors [8]. For example, in a follow-up study of 1292 women with coronary heart disease (CHD), higher levels of bodyweight within the 'normal' range, as well as modest weight gain after 18 years of age, increased risks of CHD significantly, with a 5–11 kg increase in bodyweight associated with a 25–65% increase in CHD risk [9]. This risk is increased further with the aggregation of other CVD risk factors, such as hypertension and dyslipidemia associated with weight gain [8]. Weight gain has deleterious effects on glycemic control and other CVD risk factors, including hypertension and dyslipidemia, thus limiting the ability of the diabetic patients to comply with the treatment regimens [8]. Weight gain also sends mixed

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Box 1. Risk factors for Type 2 diabetes.

- Age >45 years
- Overweight (e.g., BMI ≥25 kg/m^2)
- Lifestyle (physical inactivity, high-caloric, high-fat intake)
- Family history of Type 2 diabetes (parents or siblings)
- Ethnic minorities
- Gestational diabetes
- Hypertension
- Dyslipidemia (low HDL-cholesterol, high triglyceride levels)
- Impaired fasting glucose (≥100 to ≤125 mg/dl)
- Impaired glucose tolerance (2 h plasma glucose ≥140 mg/dl)
- Spouse with Type 2 diabetes mellitus

messages to the patients who are advised to lose weight as a major component of their treatment plan in order to gain better glycemic control.

Antidiabetic medications & weight gain

Major therapeutic classes of medications used for Type 2 diabetes, such as insulin, sulfonylureas (SUs) and thiazolidinediones, have been associated with weight gain [10,11], with the potential to offset the beneficial effects of glycemic control [8]. Landmark trials, such as the UK Prospective Diabetes Study (UKPDS) [12], clearly established the beneficial effects of tight glucose control on microvascular complications in Type 2 diabetes. In this study, weight gain was significantly higher in the intensive group (mean: 2.9 kg) compared with the conventionally treated arm ($p < 0.001$) and patients assigned insulin had a significantly higher weight gain (4.0 kg) compared with those assigned chlorpropamide (2.6 kg) or glibenclamide (1.7 kg) [12].

Weight reduction & prevention of Type 2 diabetes

Weight reduction has been shown to reduce the rate of diabetes in high-risk prediabetic populations [13,14]. Two major large-scale trials from Finland and the USA (the Finnish Diabetes Study and the Diabetes Prevention Program) have shown consistent results in terms of prevention of Type 2 diabetes with lifestyle changes that included weight loss of approximately 6.8 kg over 36 months [15,16]. The magnitude of prevention of Type 2 diabetes with lifestyle interventions was almost twice that achieved with medications such as metformin [16]. These strategies have been shown to be beneficial in people with prediabetes and the metabolic syndrome, and have resulted in significant reduction and improvement in metabolic outcomes and cardiovascular risk [17]. As such, they have been made into recommendations by major medical associations [18].

Benefits of weight loss in diabetes

The degree of caloric restriction and the magnitude of weight loss in the diabetic population have independent effects on improvements in glycemic control and insulin sensitivity [19], particularly with the use of low carbohydrate diets leading some to discontinue antidiabetic medications altogether for selected patients [20]. Weight loss improves glycemic control in diabetes and, more importantly, decreases the overall mortality in this patient population above and beyond glycemic control [21]. In the American Cancer Society's (ACS) Cancer Prevention Study, a prospective analysis with a 12-year mortality follow-up of 4970 overweight diabetic patients aged 40–64 years, intentional weight loss was reported by 34% of the cohort. After adjustment for initial BMI, sociodemographic factors, health status and physical activity, weight loss was associated with a 25% reduction in total mortality and a 28% reduction in CVD and diabetes mortality. In this study, weight loss of 9.1–13.2 kg was associated with the greatest reductions in mortality (~33%) [21]. These data collectively indicate that weight loss is not only beneficial in terms of glycemic control, but is also associated with reduced mortality from CVD, the major cause of death in diabetes.

Antidiabetic medications & weight gain

Insulin secretagogs

Antidiabetic agents, such as SU, repaglinide and nateglinide, are collectively termed insulin secretagogs; they act mainly by increasing insulin secretion through stimulation of SU receptors [22]. Studies involving SU generally demonstrate a tendency towards weight gain [8]. For example, in the European GlUcose control in Type 2 diabetes: Diamicron MR versus glimEpiride (GUIDE) study, the first large-scale, head-to-head comparison of two SUs designed for once-daily administration used under conditions of everyday clinical practice, 845 patients with Type 2 diabetes were randomized to either gliclazide or glimepiride in a double-blind, 27-week, parallel-group design [23]. A_{1c} was reduced to a similar degree in the two groups (by 1.1 and 1%, respectively)

and bodyweight increased by approximately 0.6 kg in the two groups [23]. Similarly, weight gain was also observed in patients treated with repaglinide and nateglinide. In a randomized, parallel-group, open-label, multicenter 16-week clinical trial comparing efficacy and safety of repaglinide monotherapy and nateglinide monotherapy in Type 2 diabetic patients previously treated with diet and exercise [24], final A_{1c} values were lower for repaglinide monotherapy than nateglinide monotherapy (7.3 vs 7.9%). Mean final reductions of A_{1c} were significantly greater for repaglinide monotherapy than nateglinide monotherapy (-1.57 vs -1.04%; p = 0.002). Mean weight gain at the end of the study was 1.8 kg in the repaglinide group compared with 0.7 kg for the nateglinide group [24]. These studies demonstrate that insulin secretagogs are associated with weight gain in the diabetic population. While the exact mechanisms of weight gain with insulin secretagogs are largely unknown, decreased glycosuria and defensive snacking to avoid hypoglycemia are proposed as putative explanations [8].

Finally, it is important to note that there is a differential effect on bodyweight between various generations of SU, with glyburide being top of the list for weight gain compared with others. This feature is mainly related to the higher incidence of hypoglycemia and defensive snacking. Glimepiride and glipizide, however, were noticed to be more weight neutral [25].

Thiazolidinediones

Thiazolidinediones (TZDs) are insulin sensitizers that reduce insulin resistance in peripheral tissues and also decrease hepatic blood glucose production. These agents work by activating the peroxisome proliferator-activated receptor-γ, a nuclear receptor that regulates the production of proteins involved in glucose and lipid homeostasis [26]. The mechanisms of enhanced insulin sensitivity with TZDs include altered free fatty acid influx to skeletal muscles and regulation of adipose differentiation leading to the production of small, compact and more insulin-sensitive fat cells with decreased epinephrine receptors. Other mechanisms include increasing adiponectin and decreasing free fatty acids and TNF-α [27]. Weight gain with the use of TZDs is thought to be a class effect, with the magnitude of weight gain correlating, in part, with improved metabolic control; more increase in bodyweight is observed in patients responding better to TZD therapy [28].

Weight gain of 3.8 kg over a 3-year period with the use of pioglitazone was observed in the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) study, that involved 5238 with Type 2 diabetes [29]. Weight gain was also observed with rosiglitazone. In a randomized, double-blind, controlled clinical trial involving 4360 participants with rosiglitazone, metformin and glyburide as initial treatment for newly diagnosed Type 2 diabetes, patients were treated for a median of 4 years, with rosiglitazone being associated with increased bodyweight of 4.8 kg [30]. Rosiglitazone was also used in the prediabetic population in the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial [31]. In this landmark study, rosiglitazone at 8 mg daily for 3 years was associated with a 60% reduction in new onset diabetes. It also increased the likelihood of conversion to normoglycemia in the prediabetic population [32]. Rosiglitazone in the DREAM trial was associated with an average of 3.3 kg weight gain over the 36-month period of the study [32]. A significant decrease in waist-to-hip ratio with a significant increase in hip circumference was demonstrated in the rosiglitazone group compared with placebo, indicating that weight gain occurred in the hip area as opposed to the waist [31]. These findings are consistent with the notion that fat cells in the gluteal area are more insulin sensitive compared with intra-abdominal fat [3].

Box 2. Cardiovascular disease risk factors in diabetes.

- Hypertension
- Insulin resistance
- Diabetic dyslipidemia:
  - Low high-density lipoprotein cholesterol levels
  - High triglyceride levels
  - Small, dense low-density lipoprotein particles
- Cigarette smoking
- Male gender
- Postmenopausal state
- Absent nocturnal drop in blood pressure and heart rate
- Salt sensitivity
- Elevated C-reactive protein and other inflammatory markers
- Increased cardiovascular oxidative stress
- Impaired endothelial function
- Procoagulant state
- Hyperuricemia
- Left ventricular hypertrophy

A possible mechanism of weight gain with the use of TZDs is edema caused by reduced renal excretion of sodium and altered intestinal ion transport leading to fluid retention. TZD-induced edema can also result from increased microvascular permeability secondary to enhanced production of VEGF by TZDs [33]. Furthermore, in the DREAM trial genetic analysis of 4197 participants, indicated that variation at the *NFATC2* locus contributes to edema among individuals who receive rosiglitazone, an effect that was more pronounced among the European participants of this multinational study [34].

Finally, depending on the individual and on the treatment regimen employed, weight gain associated with TZD treatment may vary greatly with the greatest increases observed when these agents are combined with SU or insulin. On the other hand, when TZDs are used in combination with metformin, weight might be reduced, or remain unchanged [35].

Insulin & weight gain

The majority of patients with Type 2 diabetes will require insulin therapy at some time in order to achieve adequate glycemic control. This is due to the progressive nature of Type 2 diabetes where an estimated 50% loss of β-cell function occurs by diagnosis with a further decline in the insulin secretory capacity over time [36]. In the UKPDS, untreated patients with Type 2 diabetes experienced a 4% decline per year in β-cell function [36]. Despite the need for insulin administration for better glycemic control, insulin therapy is generally delayed. A prospective study involving nearly 4000 patients with Type 2 diabetes who had newly started SU/metformin therapy were followed for 54.6 months, during which time 41.9% of the subjects added insulin. Over half of the SU/metformin patients attained but failed to maintain A_{1c} levels of 8%, yet continued SU/metformin therapy for an average of nearly 3 years, sustaining a glycemic burden equivalent to nearly 32 months of A_{1c} levels of 9% [37]. Several barriers to initiation of insulin therapy have been cited, including weight gain and fear of hypoglycemia, among others. These have been demonstrated in the Diabetes Attitudes, Wishes and Needs (DAWN) study, where data were obtained from surveys of patients with Type 2 diabetes not taking insulin (n = 2061) and diabetes care providers (nurses = 1109; physicians = 2681) in 13 countries in Asia, Australia, Europe and North America [38]. Healthcare providers were generally reluctant to prescribe insulin because of concerns about developing hypoglycemia and weight gain. These concerns, especially those related to insulin-mediated weight gain, frequently become a psychological barrier to insulin initiation [39].

Mechanisms of weight gain with insulin therapy

Weight gain associated with insulin use appears to be related to insulin dosage and improved glycemic control (**Box 3**) [8]. Patients on insulin therapy generally gain 2–3 kg over a period of 6–12 months, which is less pronounced with combination therapy compared with insulin monotherapy due to decreased insulin dosage and/or the weight-reducing effects of metformin in combination therapy [40]. Potential mechanisms of weight gain with insulin therapy (**Box 3**) include correction of glycosuria, leading to reduced energy loss, and the catch-up process of regaining weight associated with better glycemic control [8,11,39,41]. Furthermore, anabolic effects of insulin and increased lipogenesis in muscle and adipose tissues may also lead to weight gain [11]. While insulin plays a role in signaling satiety in the CNS and reducing food intake, this mechanism is impaired in Type 2 diabetes [8]. Enhanced lipogenesis due to loss of first pass effect of insulin injected subcutaneously as opposed to endogenously secreted into portal circulation, is an additional mechanism proposed for weight gain associated with insulin therapy [8,11].

Basal insulin analogs

Compared with neutral protamine Hagedorn (NPH), insulin detemir and insulin glargine have a relatively delayed and prolonged absorption time and a more predictable glucose-lowering effect [42]. This reduces the risk of nocturnal hypoglycemia and may offer benefits in reference to weight gain. However, in a 26-week open-label study comparing basal regimens of glargine or NPH among insulin-naive US inner city ethnic minority Type 2 diabetic patients, there were no differences in basal glycemic control or nocturnal hypoglycemia between glargine and NPH, although glargine precipitated greater weight gain [43]. Insulin detemir has been shown in several studies to induce less weight gain than NPH. For example, in a 26-week, multinational, open-label, parallel-group trial involving 505 subjects with Type 2 diabetes, patients receiving insulin detemir had significantly less weight gain compared with those receiving NPH insulin (1.0 and 1.8 kg, respectively; p = 0.017) [44]. The difference in

weight gain between insulin detemir and NPH appears to be more noticeable when insulin detemir is administered in the evening. This has been demonstrated in a multicenter, randomized, three-arm, parallel-group, open-label trial conducted across 91 centers in the USA and Europe in patients with poorly controlled Type 2 diabetes (n = 504). At 20 weeks the mean weight gains observed were 0.7 and 1.6 kg ($p < 0.001$) for the insulin detemir and the NPH groups, respectively [45]. Evidence suggests that insulin detemir and insulin glargine appear to have a similar effect on glycemic control, with weight-sparing effects conferred by insulin detemir [46]. Analysis of five open-label trials demonstrated that once-daily use of insulin detemir results in significantly less weight gain and fewer hypoglycemic episodes than glargine, while maintaining clinically appropriate A_{1c} levels in Type 2 diabetic patients currently receiving once-a-day dosing [47]. Mechanisms of the weight-sparing effects of detemir are not understood at present; however, reduced subject variability in glycemia with detemir, compared with NPH and glargine insulin, reduces hypoglycemic potential and defensive snacking, one of the mechanisms of weight gain [8,11].

Other mechanisms proposed for the favorable effects on weight with insulin detemir include reduced peripheral lipogenesis and CNS effects of improved satiety [8,48]. Finally, it is important to note that although the absolute weight gain was numerically higher with glargine versus detemir, weight gain with glargine does not differ from detemir when adjusted for the reduction in A_{1c}. Individuals treated with detemir, however, require a higher daily dose of insulin compared with individuals treated with glargine in order to achieve the same A_{1c} reduction. Therefore, at equipotent dose, the weight gain was not significantly different between the two basal insulin preparations glargine and detemir [49].

Box 3. Potential mechanisms of insulin-associated weight gain.

- Reduced energy loss due to correction of glycosuria
- Increased lipogenesis due to loss of first pass effect of insulin injected subcutaneously
- Decreased satiety associated with insulin leading to increased food intake
- Anabolic effects of insulin
- Defensive snacking due to fear of hypoglycemia
- Genetic predisposition

Biguanides

Meformin is the only biguanide approved for use in the USA. It was reintroduced in 1994 after being withdrawn decades earlier for the fear of lactic acidosis that was more substantial with fenformin, another biguanide medication [50]. Metformin is widely used and is considered a first-line therapy for diabetes management by major societies such as the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Metformin is an insulin sensitizer that decreases free fatty acid release from adipose tissue. It also decreases hepatic glucose output, hence its beneficial effects on fasting plasma glucose levels [50]. Metformin has consistently demonstrated a weight loss effect in drug-naive patients as well as in those taking other antidiabetic drugs [8,50,51]. It is the only antidiabetic medication that has been shown to decrease CVD risk, including mortality, in overweight diabetic patients, as demonstrated in the UKPDS [52]. In this study, the investigators concluded that since intensive glucose control with metformin appears to decrease the risk of diabetes-related end points in overweight populations and is associated with less weight gain and fewer hypoglycemic attacks than are insulin and SUs, it may be the first-line pharmacological therapy of choice in these patients [52]. These conclusions were implemented a decade later in the recommendations by the ADA and EASD. At present, both the ADA and EASD recommend metformin for patients with Type 2 diabetes as the first-line therapy together with lifestyle changes, such as diet and exercise [53]. Weight loss associated with metformin has been demonstrated in several studies and ranges between 2.5 and 4.3 kg over a 1–5-year period [8,54]. For example, in drug-naive Type 2 diabetic patients treated with pioglitazone monotherapy versus metformin monotherapy for 52 weeks, there was an increase in bodyweight of 1.9 kg in the pioglitazone group and a decrease of 2.5 kg in the metformin group. Glycemic control was similar in both groups, as evidenced by similar A_{1c} reduction with pioglitazone and metformin monotherapies [54]. While it is tempting to attribute weight loss to gastrointestinal side effects, substantial evidence to that effect is lacking. The exact mechanism of weight loss with metformin is unknown, although several mechanisms have been proposed. Such mechanisms include enhanced secretion of glucagon-like peptide-1 (GLP-1) and leptin levels [55], as well as inhibition of dipeptidyl peptidase IV (DPP-IV) activity [56]. Another possible mechanism may be control of food intake as a result of the effect on satiety [57].

Newer therapeutic agents: effects on bodyweight

Newer therapeutic agents, such as GLP-1 agonists, DPP-IV inhibitors and amylin analogs, have evolved as potentially effective therapeutic interventions in Type 2 diabetes with pleotropic effects above and beyond glycemic control, including a favorable profile regarding bodyweight [58,59]. Exenatide, the first GLP-1 analog, has been shown to reduce bodyweight apart from glycemic control in Type 2 diabetic patients inadequately controlled with SU and/or metformin [60]. Amylin analogs, such as pramlintide, have also been shown to reduce bodyweight in obese patients [61], as well as diabetic patients treated with insulin [62]. Other agents, such as DDP-IV inhibitors, appear to be weight neutral with a decreased risk of hypoglycemia and equivalent glycemic control compared with SU [63]. Finally, sodium glucose cotransporter inhibitors, such as dapagliflozin, exhibit a dose-dependent reduction in A_{1c} achieved through the inhibition of reabsorbtion of glucose at the proximal tubule by the sodium glucose cotransporter-2 receptor. These agents lead to mild osmotic diuresis and renal elimination of glucose, resulting in reduced bodyweight. Nevertheless, further studies are needed to better characterize the weight loss associated with these agents and to determine whether it is only caused by glucose leak through the kidney or whether other mechanisms are also involved [64].

Conclusion

Weight gain is associated with the use of several antidiabetic medications, including insulin and insulin secretagogs, and is generally a barrier to achieving adequate glycemic control. Potential mechanisms of insulin-associated weight gain include correction of glycosuria leading to reduced energy loss as well as the anabolic effects of insulin and increased lipogenesis in muscle and adipose tissues. Accumulating evidence indicates that the use of detemir appears to reduce the risk of weight gain, compared with NPH and glargine insulin. Mechanisms of the favorable effects on body weight with detemir are not clearly understood; however, with detemir there is reduced within-subject variability in glycemia leading to reduction in hypoglycemic episodes and defensive snacking, compared with NPH and glargine insulin. Metformin use is associated with modest weight loss. In combination with insulin or SU, metformin appears to offset the weight gain associated with these agents. Incretins, such as GLP-1 analogs, as well as amylin analogs, cause weight reduction, while DPP-IV inhibitors are weight neutral. These newer therapeutic modalities have favorable effects on bodyweight while achieving glycemic goals, thus providing attractive alternatives to insulin and insulin secretagogs.

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Executive summary

- Type 2 diabetes patients generally gain weight throughout the course of the disease. This weight gain is associated with worsening glycemic control and further increases cardiovascular disease risk factors.
- Major therapeutic classes of medications used for Type 2 diabetes, such as insulin, sulfonylureas and thiazolidinediones (TZDs), have been associated with weight gain.
- Weight reduction has been shown to reduce the rate of new diabetes in high-risk prediabetic populations.
- Benefits of weight loss in diabetic patients include improvement in glycemic control leading, in some cases, to discontinuation of antidiabetic medication, and decreases in cardiovascular disease risk.
- While the exact mechanisms of weight gain with insulin secretagogs are largely unknown, decreased glycosuria and defensive snacking to avoid hypoglycemia are proposed as putative explanations.
- Weight gain with TZDs is thought to be a class effect, mainly related to improved metabolic control, and more increase is observed in patients responding better to TZD.
- Edema, a possible mechanism of weight gain with TZDs, is caused by reduced renal excretion of Na^+, altered intestinal ion transport and increased microvascular permeability mostly related to enhanced production of VEGF.
- Potential mechanisms of weight gain related to insulin usage include improved glycemic control, correction of glycosuria, the anabolic effect of insulin and an increase in lipogenesis.
- Other antidiabetic medications from different classes, such as biguanides, glucagon-like peptide-1 analogs and amylin analogs, are associated with weight loss, the mechanism of which is not completely understood at present.

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