

Weight Management for Patients with Type 2 Diabetes: Impact of Newer Antidiabetic Therapies on Body Weight

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CASE STUDY

JB is a 61-year-old, non-Hispanic Caucasian man diagnosed with type 2 diabetes (T2D) in June 2015. His body mass index (BMI) at diagnosis was 31.* To control his blood glucose, JB was prescribed metformin combined with a sulfonyleurea, which has reduced his fasting plasma glucose and glycated hemoglobin (HbA_{1c}) levels. He received dietary advice to help him lose weight; however, after initial success, JB has been unable to keep the weight off in the long term. Although he felt well, he also had elevated blood cholesterol and is receiving a statin.

In March 2018, JB attended a scheduled clinic appointment. His HbA_{1c} was 7.6% and his BMI was 30.8. JB tells you he has read that some diabetes medicines can cause weight gain, and he is concerned that the drugs he is taking are making it more difficult for him to lose weight.

What advice would you give him, and would you make any changes to his diabetes medications?

*Calculated as weight in kilograms divided by height in meters squared.

Note: This is a hypothetical case study for educational purposes.

INTRODUCTION

Obesity is linked to insulin resistance, development of metabolic syndrome, and progression to diabetes, as well as increased risk of morbidity, including cardiovascular disease,

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and mortality in patients with T2D.¹⁻³ Even modest weight loss (~5% of body weight) in overweight or obese patients with T2D has been shown to improve blood glucose control as well as blood pressure and lipid levels, delay progression of diabetes, and reduce the need for glucose-lowering medication.⁴⁻⁷ Consequently, guidelines from the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) recommend that weight loss should be considered for any patient with T2D who is overweight or obese.^{4,5} However, patients with diabetes who are overweight or obese often struggle to achieve sustained weight loss with lifestyle modification alone. In the opinion of the author, this is because the body has a goal to return to its maximal weight, and these patients must constantly work against this goal to first reduce and then maintain a lower weight.

Maintenance of weight reduction was assessed in the Action for Health in Diabetes (Look AHEAD) study, which compared intensive lifestyle intervention with usual care in a large cohort of overweight and obese patients with T2D.^{6,7} Although weight loss was significantly greater in the group receiving intensive intervention at all time-points up to 8 years, weight loss started to drop off after the first year, even in this group. At 1 year, there was a mean 8.6% reduction from baseline in weight in the intensive lifestyle intervention group, declining to 4.7% at year 8.^{6,7} The tendency for weight regain is likely to be at least partly due to physiological adaptations that favor weight gain in response to a reduced-calorie and reduced-fat diet.⁸ Therefore, primary care physicians should consider the psychological implications associated with advising their patients on losing weight and ensure that realistic expectations are set. Physicians should also encourage improved health and lifestyle rather than making weight loss the main focus.

Moreover, for many patients with T2D, lifestyle modifications are unlikely to be enough to achieve glycemic targets, and guidelines recommend that pharmacotherapy should also be employed to improve glycemic control.^{4,5} With a wealth of different agents available, it is now possible to tailor therapy to the needs of the individual. This is particu-

larly important for patients who are struggling to lose weight, because several commonly used antidiabetic medications can actually promote weight gain: namely, insulin, sulfonylureas, and thiazolidinediones.^{4,5,9} In addition, concomitant medications may also be associated with an increase in body weight. For example, antipsychotic and antiepileptic medications, including some that are used to manage diabetic neuropathy, may contribute to an increase in weight.¹⁰⁻¹² Furthermore, other medications commonly prescribed in primary care, such as beta-blockers and selective serotonin reuptake inhibitors, may also lead to weight gain.^{13,14}

The aim of this article is to review the impact on body weight of new classes of antiglycemic therapies and provide practical guidance on the most appropriate strategies for glycemic control in the overweight or obese patient with T2D.

EFFECT OF TYPE 2 DIABETES THERAPIES ON BODY WEIGHT

Therapies associated with weight gain

Sulfonylureas and thiazolidinediones effectively reduce blood glucose and HbA_{1c} levels, and may be used as add-on therapy in patients with T2D who do not achieve targets with metformin alone. However, they are also associated with weight gain.⁹ In addition, insulins, which may be used in patients with T2D who require additional control, are also associated with weight gain. For example, in the United Kingdom Prospective Diabetes Study (UKPDS), insulin therapy was associated with a 4-kg increase in weight, and sulfonylureas with an increase of 1.7 to 2.6 kg, over 10 years.¹⁵ Similar results were observed in other prospective studies involving patients with T2D,^{16,17} with treatment combinations containing insulin associated with a mean 3.2-kg increase in weight; thiazolidinediones, with a 3.1-kg increase; and sulfonylureas, with a 0.7-kg increase, over 5 years.¹⁶ Moreover, weight gain can be additive when different agents are used. Pioglitazone was associated with an increase in body weight of 0.9 to 2.6 kg, depending on dosage, in monotherapy studies (16 to 26 weeks), with larger increases seen when used in combination with insulin (2.3 to 4.1 kg) and sulfonylureas (2 to 4.1 kg).¹⁷ Insulin acts through a number of mechanisms, including lowering blood glucose levels by increasing uptake of glucose into fat and muscle cells.⁹ Sulfonylureas promote the release of insulin from beta cells in the pancreas. These mechanisms of action by insulin and sulfonylureas improve glycemic control, but can also lead to weight gain by decreasing excretion of glucose in the urine (glycosuria).⁹ In addition, insulin and sulfonylureas are associated with a risk of hypoglycemia, and patients concerned about this may increase food intake as a protective

strategy.⁹ Unlike other insulins, insulin detemir is associated with modest weight loss (~0.5 kg over 26 weeks) rather than weight gain.¹⁸ Weight increase with pioglitazone may result from increases in both water retention and fat storage.¹⁷

Therapies associated with weight neutrality or loss

Metformin is usually the first-line treatment option for T2D, due to its well-established efficacy and safety profile determined through decades of use in Europe and since 1995 in the United States.^{5,19} Metformin is generally considered to have a neutral effect on weight,⁹ although in the Diabetes Prevention Program Outcomes Study, it was found to induce weight loss over the trial period (2 years; mean 2.1% decrease from baseline) and the open-label extension period (7 to 8 years; mean 2% decrease from baseline),²⁰ most likely resulting from reduced food intake.²¹ However, if HbA_{1c} targets are not met with lifestyle modifications and metformin alone, additional antihyperglycemic agents may be required.

Newer therapies for T2D, including glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, and amylin mimetics, may be considered for overweight and obese patients because they provide glycemic control while having either a neutral effect on body weight or an overall weight reduction effect.^{9,16,17,20,22-28} The effects of the various therapies on body weight are summarized in the **TABLE**.

GLP-1 is an incretin hormone that is secreted from the intestinal L cells and is involved in increasing glucose-dependent insulin secretion as well as the regulation of food intake.^{9,22,29} Native GLP-1 is rapidly (half-life, <2 min) degraded in the body by the enzyme DPP-4.²⁹ Injectable analogs of GLP-1 (GLP-1 receptor agonists) used for T2D treatment are resistant to degradation by DPP-4.²⁹ These include albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, and semaglutide.^{22,30,31} GLP-1 receptor agonists reduce HbA_{1c} by up to 1.9% and also induce weight loss by up to 3.7 kg by promoting reduced food intake^{9,22,30} (in these studies, background medications differed and may have contributed to weight changes). GLP-1 receptor agonists have recently been shown to reduce the risk of cardiovascular events and all-cause mortality in patients with T2D at high risk of cardiovascular events while they were taking standard therapy.³² The most common side effects associated with GLP-1 receptor agonists include gastrointestinal effects, such as nausea, diarrhea, and vomiting.^{19,30}

Decreased food intake with GLP-1 receptor agonists is thought to result from their effects in inhibiting gastric emptying and promoting a feeling of satiety⁹ via a variety of central effects in the hypothalamus. Animal studies have

TABLE Type 2 diabetes therapies and their effects on body weight

Associated with weight gain	Weight-neutral or modest weight decrease	Associated with weight loss
Insulin (3.2-kg increase over 5 years ¹⁶ ; 4-kg increase over 10 years ¹⁵)	MET (~2-kg reduction over 10 years ²⁰)	GLP-1RA (~1- to 4-kg reduction over 26–52 weeks ^{9,22})
SU (0.7-kg increase over 5 years ¹⁶ ; 1.7- to 2.6-kg increase over 10 years ¹⁵)	DPP-4i (overall considered weight-neutral ^{22,23})	SGLT-2i (~2- to 4-kg reduction over 26–52 weeks ^{9,24})
TZD (3.1- to 4-kg increase over 3–5 years ^{16,17})	AGI (no effect ^{25,26} or ≤1.2-kg reduction ²⁷)	Amylin analog (~1- to 2-kg reduction over 26–52 weeks ²⁸)

Abbreviations: AGI, alpha-glucosidase inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; MET, metformin; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.

indicated that weight loss with GLP-1 receptor agonists is mediated by the arcuate nucleus in the hypothalamus, which is involved in energy intake and expenditure.^{29,33} A separate pathway for increased energy expenditure may involve stimulation of the ventromedial nucleus in the hypothalamus, resulting in increased metabolism in brown adipose tissue.^{29,34} Other proposed mechanisms for weight loss with GLP-1 receptor agonists include increased metabolism in white adipose tissue and neuroprotective effects, including reduction of hypothalamic inflammation induced by a high fat diet.²⁹ Moreover, treatment with a GLP-1 receptor agonist has been shown to inhibit the increase in leptin receptors normally seen during weight loss, resulting in increased circulating levels of leptin, which acts to reduce appetite.³⁵ It should be noted, however, that despite the beneficial effects of the GLP-1 receptor agonists on body weight, they are not approved for weight reduction in patients with T2D.⁴ In 2010, a higher dosage (3 mg daily) of liraglutide was approved by the US Food and Drug Administration (FDA) in combination with a reduced-calorie diet and increased physical exercise for weight management.³⁶ However, this dosage is not indicated for the treatment of T2D (usual dosage in T2D is 1.2 mg daily, to a maximum of 1.8 mg daily).³⁶

SGLT-2 mediates reabsorption of filtered glucose in the kidneys.³⁷ There are several marketed SGLT-2 inhibitors, including canagliflozin, dapagliflozin, empagliflozin, and the recently FDA-approved ertugliflozin. These agents are administered orally and promote increased glycosuria, thereby lowering blood glucose.³⁷ SGLT-2 inhibitors are associated with HbA_{1c} reductions of 0.5% to 1%, with additional beneficial effects in patients with T2D, including reductions in blood pressure (placebo- or comparator-corrected decreases: systolic, up to -7 mm Hg; diastolic, up to -3 mm Hg) and body weight (~2 to 4 kg).^{9,24,38} In addition, cardiovascular outcomes studies have shown that, like the GLP-1 receptor agonists, SGLT-2 inhibitors are associated with a reduction in cardiovascular events^{39,40} and have also reduced all-cause mortality in patients with T2D at high risk of cardiovascular events.⁴⁰

Side effects associated with SGLT-2 inhibitors include genital mycotic infection and urinary tract infection.^{9,19,38}

Weight loss associated with SGLT-2 inhibitor therapy is considered to result from increased glucose excretion. However, the typical observed weight loss is less than expected, considering the number of calories excreted.⁴¹ It is thought that glycosuria may promote increased food intake, and combining an SGLT-2 inhibitor with a calorie-restricted diet may provide greater weight loss.⁴¹

DPP-4 inhibitors (including linagliptin, saxagliptin, and sitagliptin) are orally administered agents that reduce DPP-4-mediated degradation of GLP-1, resulting in an increase in endogenous GLP-1 levels.²² Glycemic efficacy of DPP-4 inhibitors (HbA_{1c} reductions of 0.5% to 1%) is typically less than that of GLP-1 receptor agonists.^{22,23} Overall, DPP-4 inhibitors are considered to have a neutral effect on weight.^{22,23} Compared with GLP-1 receptor agonists, DPP-4 inhibitors are associated with fewer gastrointestinal symptoms.²²

Alpha-glucosidase inhibitors (including acarbose and miglitol) delay breakdown of carbohydrates in the small intestine, and lower postprandial glucose and insulin levels.²⁷ HbA_{1c} reductions are typically in the region of 0.5% to 0.8%.^{25–27} Clinical trials have reported no or a moderate (≤1.2-kg reduction) effect on body weight.^{25,27} A reduction in BMI of 0.17 was reported in a meta-analysis of alpha-glucosidase inhibitor trials; however, no significant effect on body weight was found.²⁶ Gastrointestinal effects are typically the most common side effects reported with these drugs.

The pancreatic beta-cell hormone amylin is involved in regulation of food intake, presenting a therapeutic strategy for T2D. The injectable, pramlintide, is currently the only amylin analog available. HbA_{1c} reductions of 0.1% to 0.6% and weight loss ranging from 1 to 2 kg in patients with T2D have been reported with pramlintide.²⁸

GUIDELINE RECOMMENDATIONS FOR BODY WEIGHT MANAGEMENT IN TYPE 2 DIABETES

Overall, guidelines from the ADA and AACE/ACE are similar

in their approach to treatment of patients with T2D who are overweight or obese; however, there are several differences in the proposed treatment algorithms, as noted in the text that follows.

Glycemic targets and treatment algorithms for improving glycemic control

ADA guidelines recommend a HbA_{1c} target of <7% for nonpregnant adults with T2D or a HbA_{1c} target of <6.5% for those who can achieve this target without adverse effects or significant hypoglycemia.⁴² AACE/ACE guidelines suggest an optimal HbA_{1c} target of ≤6.5%; if this is not achievable without adverse outcomes (eg, in patients with concurrent serious illness at risk of hypoglycemia), higher targets should be employed.⁵

The treatment algorithm in the 2018 ADA guidelines suggests 3 starting points for therapy (in addition to lifestyle modification), depending on HbA_{1c} at diagnosis: initiating metformin if HbA_{1c} is <9%; initiating dual therapy with metformin and another agent if HbA_{1c} is ≥9%; and moving directly to metformin plus insulin therapy if HbA_{1c} is ≥10%.¹⁹ If the target is not reached on monotherapy or dual therapy, one of the following treatment options can be considered: sulfonylurea, SGLT-2 inhibitor, thiazolidinedione, GLP-1 receptor agonist, DPP-4 inhibitor, or basal insulin. Rather than stating an order of preference for initiating the additional agents, ADA guidelines leave this to the physician to decide, based on drug-specific effects and patient factors, such as glucose-lowering efficacy, the individual's risk of hypoglycemia, effects on weight, cardiovascular effects, cost, preferred route of administration (oral or subcutaneous injection), and potential adverse effects.¹⁹

In the 2018 AACE/ACE guidelines, in addition to lifestyle therapy, patients with HbA_{1c} <7.5% should be started on monotherapy; those with HbA_{1c} ≥7.5%, on dual or triple therapy; and those with HbA_{1c} >9% and with symptoms at entry, on insulin (with or without an additional agent). The 2018 AACE/ACE guidelines state that the choice of therapies should be individualized.⁵ However, in contrast to ADA guidelines, recommendations are given on the choice of therapeutic options, which are listed in hierarchical order based on strength of recommendations. Metformin is the preferred agent for initiating monotherapy.⁵ For dual therapy, metformin should be used plus another agent, in the following order of preference: GLP-1 receptor agonist, SGLT-2 inhibitor, DPP-4 inhibitor, thiazolidinedione, basal insulin, colesevelam (a bile acid sequestrant), bromocriptine (a dopamine-receptor agonist), alpha-glucosidase inhibitor, and, last, sulfonylurea. Recommendations for triple therapy are similar, except that DPP-4 inhibitors come after basal insulin in order of preference.⁵ Caution is advised with regard

to the use of thiazolidinediones, sulfonylureas, and basal insulin, due to their potential for adverse effects.⁵

Recommended approaches for managing weight loss

Both ADA and AACE/ACE guidelines agree that weight loss management should be employed if patients are overweight or obese, due to the known benefits of weight reduction (eg, improved glycemic control, lipid levels, and blood pressure).^{4,5}

The 2018 ADA recommendations for overweight or obese patients are as follows⁴: At each routine visit, BMI should be calculated. A BMI ≥25 to 29.9 is classified as overweight (≥23 to 27.4 for patients of Asian origin); a BMI above these levels is classified as obesity.^{43,44} All patients with BMI ≥25 (≥23 for patients of Asian origin) who are ready to lose weight should receive advice on lifestyle modification, including dietary, behavioral, and physical exercise recommendations. Weight-loss medications may be considered for selected patients with BMI ≥27, and bariatric surgery may be considered for those with BMI ≥30 (27.5 for patients of Asian origin). Medications approved for weight loss include phentermine, orlistat, lorcaserin, phentermine/topiramate, naltrexone/bupropion, and liraglutide 3 mg daily.⁴

AACE/ACE guidelines are slightly different from ADA guidelines; they propose a “complications-centric” model for weight management, in which weight-loss medications or surgery may be considered for patients with elevated BMI if additional complications (such as diabetes) are present.^{5,45} Addition of weight-loss medication may be considered for patients with BMI ≥27 and complications, and for those with BMI ≥30 regardless of the presence of complications. Bariatric surgery can be used for adults with BMI ≥35 and comorbidities, particularly if therapeutic goals have not been reached using other treatments.

Both ADA and AACE/ACE guidelines highlight that the choice of antidiabetic medications for patients with T2D should involve consideration of the effect of these agents on the patient's weight (**TABLE**).^{4,5} From this perspective, therapies that have a weight-neutral or weight-reducing effect (metformin, GLP-1 receptor agonists, SGLT-2 inhibitors, DPP-4 inhibitors, alpha-glucosidase inhibitors) are preferred over those that promote weight gain (sulfonylureas, insulin, thiazolidinediones).^{4,5,19} However, the physician should also consider the HbA_{1c} target: if this is not reached with metformin plus 2 other glucose-lowering agents, insulin may need to be employed. The side-effect profiles of the chosen agents should also be considered.^{5,19} Recommendations for weight management in patients with T2D, based on the ADA and AACE/ACE guidelines, are summarized in the **FIGURE**.

FIGURE Approaches for glycemic and weight control for patients with type 2 diabetes, based on ADA and AACE/ACE guidelines^{4,5,19,42}

Guideline:	ADA (2018)	AACE/ACE (2018)	
HbA _{1c} goal:	<7% ^a	≤6.5% ^b	
All patients to receive lifestyle therapy			
Weight-loss program if BMI:	≥25	≥25	Order of preference (based on AACE/ACE recommendations) for dual/triple therapy based on effects on body weight:
Weight-loss medication ^c if BMI:	≥27	≥27	
Bariatric surgery ^c if BMI:	≥30	≥35	
Pharmacotherapy (if HbA _{1c} goal not met with lifestyle therapy alone)			
Monotherapy (MET) Initiate if entry HbA _{1c} :	<9%	<7.5%	Weight loss: GLP-1RA SGLT-2i Weight neutral: DPP-4i AGI Weight gain: TZD Basal insulin SU
If goal not met by 3 months, move to dual therapy			
Dual therapy (MET + 1 agent) Initiate if entry HbA _{1c} :	≥9%	≥7.5%	
If goal not met by 3 months, move to triple therapy			
Triple therapy (MET + 2 agents) Initiate if entry HbA _{1c} :	N/A	>9% (without symptoms)	
If goal not met by 3 months, move to insulin therapy			
Insulin therapy (MET and/or 1 agent) Initiate if entry HbA _{1c} :	≥10% (or BG ≥300 mg/dl, or with symptoms)	>9% (with symptoms)	

Abbreviations: AACE/ACE, American Association of Clinical Endocrinologists/American College of Endocrinology; ADA, American Diabetes Association; AGI, alpha-glucosidase inhibitor; BG, blood glucose; BMI, body mass index; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated hemoglobin; MET, metformin; N/A, not applicable; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.

^aGoal <6.5% for patients without adverse treatment effects or significant hypoglycemia.

^bGoal >6.5% in cases of serious illness and at risk of hypoglycemia.

^cDepending on patient factors.

BMI units are kg/m². Lower BMI thresholds may be appropriate for some ethnicities (eg, patients of Asian origin).

2018 ADA guidelines do not make recommendations about starting with triple therapy.

CASE STUDY FOLLOW-UP

JB's primary care physician should inform him that although metformin is weight-neutral, sulfonylureas are associated with weight gain. Because JB's HbA_{1c} level (7.6% at his most recent clinic appointment) has not met the target of ≤7.5% (according to 2018 AACE/ACE guidelines), JB's physician should consider escalating him to triple therapy. The additional therapeutic agent should be one that is associated with weight loss, such as a GLP-1 receptor agonist or an SGLT-2 inhibitor. According to current guidelines, potential for side effects should also be considered. JB should therefore be advised to visit the clinic in 3 months.

If triple therapy improves JB's HbA_{1c} level but does not lead to weight loss by the next clinic visit, weight-loss medication

could also be considered. If triple therapy does not control the HbA_{1c} level, JB remains at risk of microvascular and macrovascular complications of diabetes; injectable insulin therapy should be considered.

Note: This is a hypothetical case study for educational purposes.

IMPLICATIONS FOR PRIMARY CARE

T2D remains a significant cause of morbidity and mortality in the United States. Most patients with T2D are overweight or obese, and a weight reduction of even 5% to 10% can have significant health benefits, improving glycemic control, potentially reducing the risk of cardiovascular events, and also reducing pressure on weight-bearing limbs. Primary care

physicians can play a key role both in counseling patients on the benefits of weight reduction and in helping them to find the best approach for them to lose weight. Physiological processes that make the patient's own body want to return to its maximal weight mean that it can be very difficult for a patient to sustain weight loss in the long term. Specific weight-loss medication and bariatric surgery should be considered in a minority of motivated patients if they are really struggling to keep the weight off. Although none of the agents approved for the management of blood glucose levels are indicated to help patients with T2D lose weight, several of the available agents are either weight-neutral or induce weight loss and should be considered when selecting the most appropriate management strategy in overweight or obese patients with T2D. ●

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