

## REVIEW

# Diabetes: how to manage overweight and obesity in type 2 diabetes mellitus

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### Abstract

The prevalence of obesity worldwide continues to increase substantially. Obesity is a chronic disease that can lead to other health conditions, including type 2 diabetes mellitus (T2DM). A variety of treatment options are available to treat T2DM. With its prevalence increasing, it is essential that healthcare professionals assess how their patients' current diabetes treatment is being managed to avoid further weight gain in those with overweight or obesity.

**Keywords:** insulin, medications, obesity, overweight, type 2 diabetes mellitus, weight gain, weight loss.

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## Introduction

Obesity is a serious, preventable chronic disease that affects millions of people worldwide, and its prevalence continues to increase. Obesity is defined as having a BMI greater than or equal to 30 kg/m<sup>2</sup>, whereas overweight is defined as having a BMI greater than or equal to 25 kg/m<sup>2</sup>. The underlying cause of overweight or obesity is generally due to an energy imbalance between calories consumed *versus* expended, which may lead to weight gain.

The World Health Organization estimates that more than 1.9 billion adults are overweight, with over 650 million of those classified as having obesity.<sup>1</sup> Obesity can lead to other health conditions, including type 2 diabetes mellitus (T2DM), cardiovascular disease, musculoskeletal disorders and certain cancers. With the increasing prevalence of obesity, it is important that healthcare professionals assess how their patients' current disease states are being managed with medications, and if any of those medications are exacerbating the issues surrounding weight in their patients. This concept especially holds true for the management of patients with T2DM.

Weight loss, or prevention of weight gain, is an important goal in the management of patients with prediabetes or with T2DM. It has been demonstrated that even a modest reduction in weight of as little as 5% may reduce complications associated with diabetes and improve cardiovascular risk factors.<sup>2,3</sup> There is also strong evidence suggesting that the management of obesity

can delay the progression from prediabetes to T2DM and has been proven beneficial in patients who already have T2DM.<sup>4-7</sup> Additional weight gain in these patients can lead to adverse consequences, including a worsening of insulin resistance and development of cardiovascular disease. The standards for care for patients with T2DM require comprehensive education in self-management and, typically, intensive treatment programmes.<sup>8</sup>

## Methods

Utilizing the PubMed database, we queried primary and tertiary literature on the management of diabetes. Search terms related to anti-hyperglycaemics used in the treatment of T2DM, effects on weight in patients with overweight and obesity classifications and other diabetes-related complications. In addition, relevant practice guidelines and expert consensus recommendations for diabetes mellitus and weight management were referenced.<sup>3,8-10</sup>

## Results

### Mechanisms for overweight and obesity in patients with diabetes mellitus

Whilst many factors play a role in the development of T2DM, the main features include a decline in insulin production by pancreatic beta cells and the presence of insulin resistance.<sup>9</sup> Studies have demonstrated a variety of possible links between obesity and T2DM, including insulin resistance,

proinflammatory cytokines, endothelial dysfunction, irregular fatty acid metabolism, dysregulation of gastric emptying and appetite suppression, and other cellular processes.<sup>2,10,11</sup> Excess weight and fat distribution are related to hyperinsulinaemia and T2DM. It has been suggested that fat distribution plays a major role in determining the development of T2DM.<sup>12</sup> Evidence further suggests that the link between the two is related to several ‘levels and factors of influence’ or social determinants of health, including lifestyle, socioeconomic, behavioural, community and psychosocial factors such as diet, physical activity and access to healthcare.<sup>13</sup>

## Lifestyle considerations in patients with overweight or obesity

Achieving and maintaining a healthy weight incorporates healthy eating and physical activity. Modest and sustained weight loss can improve not only glycaemic control in patients with diabetes but also other cardiometabolic factors, including blood pressure and lipid control. Throughout the literature, there is a significant number of studies that show benefit in glycaemic control with lifestyle interventions.<sup>4,14,15</sup> Whilst there are debates about which type of diet is best, it has been identified that significant weight loss can be achieved with lifestyle interventions that reduce total calories by 500–750 kcal/day.<sup>8</sup> Counselling on nutrition at diagnosis and throughout the care process is emphasized by the American Diabetes Association and the American Association of Clinical Endocrinologists/American College of Endocrinology to support lifestyle modification and achieve weight loss.<sup>8,9,16</sup>

In addition to dietary changes, routine physical activity is essential for overall health in individuals with prediabetes and diabetes. It is especially important in those patients who need to lose weight. Aerobic exercises, such as walking, jogging and swimming, can improve insulin sensitivity and moderate to vigorous exercise can substantially improve cardiovascular outcomes in patients with diabetes.<sup>17</sup>

## The effect of anti-hyperglycaemics on body weight

The management of diabetes mellitus includes medications that can cause weight gain, weight loss or are weight neutral. As described in current practice guidelines, patients with T2DM and overweight or obesity will benefit from a selection of medications that not only entail efficacy in glycaemic control but consideration of the medication’s effect on weight. Choosing anti-hyperglycaemic agents that promote weight loss, or at a minimum maintain weight neutrality, is preferred in these patients.<sup>8</sup>

### Weight gain

Whilst these medications are used with the intent to improve glycaemic control, the benefits of better glycaemic control are

sometimes offset by the weight gain that occurs. Common medications associated with weight gain include insulin secretagogues, thiazolidinediones and insulin.

### *Insulin secretagogues*

The classes of medications in this group include sulfonylureas and meglitinides (glinides). These agents mainly act by increasing insulin secretion either in a glucose-independent or glucose-dependent manner. Sulfonylureas have demonstrated a high efficacy in lowering haemoglobin A1c but are known to cause weight gain and hypoglycaemia.<sup>16,18–20</sup> Studies have also demonstrated that, when added to other anti-hyperglycaemics, sulfonylureas can be associated with a weight gain of up to 2.3 kg as compared to placebo.<sup>21,22</sup> Meglitinides have a similar side-effect profile as sulfonylureas but are generally less effective with regards to A1c lowering. Due to associated adverse effects, including weight gain, as well as possible diminished effectiveness over time, sulfonylureas and meglitinides are not the preferred choices in patients with obesity.

### *Thiazolidinediones*

Thiazolidinediones (TZDs) are known as insulin sensitizers that reduce insulin resistance in peripheral tissues and help to decrease hepatic blood glucose production.<sup>23</sup> Mechanistically, TZDs activate the peroxisome proliferator-activated receptor- $\gamma$ , which is a nuclear receptor that regulates the production of proteins involved in glucose and lipid homeostasis. Weight gain of up to 4.25 kg can be seen with the use of TZDs and is generally thought to be related to fluid retention and possible redistribution of adipose tissue.<sup>21,24,25</sup> Whilst TZDs provide a good option for glucose lowering in patients with T2DM, in addition to weight gain, these agents should be avoided in patients with cardiovascular disease and bone issues.

### *Insulin*

Whilst generally associated with type 1 diabetes mellitus, insulin is also used in a large proportion of patients with T2DM when pancreatic beta cell failure occurs as the disease progresses.<sup>26</sup> Weight gain with the use of insulin ranges between 1.56 and 5.75 kg.<sup>24,27–30</sup> All types of insulins have been associated with weight gain, but the extent of weight gain varies based on the type of insulin and specific insulin regimen.<sup>26</sup> The potential weight gain associated with insulin therapy can be attributed to an increase in caloric intake due to a fear of hypoglycaemia, a reduction in glycosuria, and an increase in fatty acid storage in adipose tissue.<sup>29</sup> Meta-analyses have demonstrated weight gain to be positively correlated with insulin dose and a greater weight gain seen with premixed insulins than with basal insulin alone.<sup>31,32</sup>

### Weight neutral/weight loss

Presently, there are medications available for the management of T2DM that offer weight neutrality or are associated with the potential for weight loss. Common medications associated with

weight neutrality include those in the dipeptidyl peptidase IV (DPP-IV) inhibitor drug class. Biguanides, glucagon-like peptide 1 (GLP1) receptor agonists (RA), sodium–glucose cotransporter 2 (SGLT2) inhibitors, alpha-glucosidase inhibitors and amylinomimetics offer weight loss (Table 1).

#### *DPP-IV inhibitors*

The medications included in the DPP-IV inhibitor drug class function to reduce degradation and prolong the action of active incretins such as GLP1 and gastric inhibitory polypeptide. In facilitating this mechanism, DPP-IV inhibitors offer a balance in hyperglycaemic management related to glucose-dependent insulin release, which in turn results in a reduced hypoglycaemic risk. The weight neutrality classification of DPP-IV inhibitors is thought to be explained mechanistically by two counterbalancing effects. First, there is a reduced need for caloric intake from fast-acting carbohydrates to correct hypoglycaemic events, which otherwise may be a property of weight gain. Furthermore, the weight loss potential of reducing the degradation and prolonging the action of active incretins is limited and does not meet the same level of effects as otherwise seen with their GLP1 RA counterparts. Clinical evidence has demonstrated variability in weight outcomes when using DPP-IV inhibitors. In a meta-analysis including 13 trials, DPP-IV inhibitors showed a small increase in body weight of 0.5 kg when compared to placebo.<sup>33</sup> Additional clinical evidence has demonstrated variability in body weight changes of –1.4 kg to +1.8 kg dependent on variability in comparator groups and heterogeneity amongst trials.<sup>34,35</sup> The culmination of evidence has resulted in the DPP-IV inhibitors being considered as having a weight neutral effect, which may be favourable in patients who would benefit from weight management or mitigation from additional weight gain.

#### *Biguanides*

Metformin, an insulin sensitizer used as a first-line anti-hyperglycaemic agent in the management of T2DM and the only FDA-approved biguanide, demonstrates mechanisms that support weight loss through hepatic, central nervous system (CNS), gastrointestinal and gut microbiome effects. Historically, reductions in caloric intake directly or indirectly related to common, dose-dependent gastrointestinal adverse effects with metformin were believed to be the primary mechanisms for weight loss. Nausea, diarrhoea, bloating and alteration in taste (dysgeusia) were attributed to short-term weight loss in patients with obesity without diabetes.<sup>36</sup> A study by Lee et al. showed a dose-dependent reduction in food quantity consumption (an anorectic effect) with metformin, resulting in an 8.8±0.3 kg weight loss in patients with non-insulin-dependent diabetes over 24 weeks.<sup>37</sup> In the CNS, metformin has been proposed to mediate appetite regulatory signals through incretins (such as GLP1), leptin and peripheral metabolites. Other proposed mechanisms for weight loss facilitated by metformin include reduced hepatic gluconeogenesis and modification in the gut microbiome.<sup>38</sup>

Respectively, these mechanisms will reduce hyperinsulinaemia and facilitate short-chain fatty acids in decreasing the release of free fatty acids from adipocytes and suppressing appetite-regulating incretins.<sup>36</sup>

The broad culmination of clinical evidence describing the weight loss potential of metformin has been shown to be dependent on background therapy. The UKPDS study demonstrated that metformin added to insulin secretagogue therapy saw minimal changes in weight (+1 kg).<sup>39</sup> However, in newly diagnosed or treatment-naive patients with diabetes mellitus, a weight loss of –0.64 kg to –3.8 kg was seen with the use of metformin.<sup>40,41</sup> The degree of weight loss was greater when adjunct diet modifications were made.<sup>41</sup> In addition to changes in total body weight, additional clinical evidence suggests that weight loss with metformin is specific to body fat *versus* lean body mass. One study by Wang et al. found statistically significant reductions in percent body fat (–4.45%) and body fat mass (–3.51 kg) in a patient population with newly diagnosed T2DM at 6 months of treatment.<sup>42</sup>

Generally, metformin is considered highly effective for the management of hyperglycaemia with A1c reductions of 0.6–1.6% and, when implemented early in the diagnosis of T2DM, could benefit from other cardiometabolic effects, including total body weight and body fat reductions.<sup>41</sup>

#### *GLP1 receptor agonists*

GLP1 RAs function to heighten the activity of the human incretin hormone, GLP1. Under normal physiological conditions, GLP1 is a hormone produced in the L cells of the small intestines, the alpha cells of the pancreas, and various structures of the CNS. Each site of GLP1 action facilitates not only a glycaemic effect but also those that promote body weight reductions. GLP1 RAs will potentiate human GLP1 activity in the pancreas and distal small intestines to stimulate glucose-dependent insulin secretion and reduce glucagon secretion. The glucose-dependent nature reduces hyperinsulinaemia and additional weight gaining effects. Within the CNS, GLP1 activity on vagal afferent neurons will induce slowing of gastric emptying, promoting satiety. At the brainstem and hypothalamus sites within the CNS, GLP1 facilitates suppression in appetite and, subsequently, a reduction in food consumption, leading to reduced calorie intake.<sup>43</sup>

Collectively, practice guidelines recommend GLP1 RAs be used to manage a patient with diabetes mellitus who would also benefit from weight loss. This recommendation has been supported by a number of randomized controlled trials (RCTs) and meta-analyses that have demonstrated significant weight loss with GLP1 RA use. In 2017, a meta-analysis that evaluated weight change from baseline in 37 studies found a total weighted mean difference (WMD) of –1.59 kg ( $p<0.001$ ) amongst GLP1 RAs. There was variability amongst individual GLP1 RA agents dependent on factors such as monotherapy use or their use as add-on therapy. Lixisenatide had the

**Table 1. Weight effects of FDA-approved anti-hyperglycaemics for diabetes mellitus.**

Drug class	Weight gain			Weight neutral			Weight loss		
	Generic drug name	Effect on body weight (Δ in kg)	Drug class	Generic drug name	Effect on body weight (Δ in kg)	Drug class	Generic drug name	Effect on body weight (Δ in kg)	
Sulfonylureas	Glimepiride <sup>77</sup>	-0.2 to +2.0	Dipeptidyl Peptidase IV Inhibitor <sup>32-34</sup>	Alogliptin Linagliptin Saxagliptin Sitagliptin	No effect	Biguanides	Metformin <sup>35-40</sup>	-0.64 to -8.8	
	Glipizide <sup>78</sup>	+0.5							
	Glyburide <sup>79</sup>	-0.4 to + 3.8							
Meglitinides	Nateglinide <sup>80</sup>	+1.0 to +3				Glucagon-like peptide 1 receptor agonists	Dulaglutide <sup>56</sup>	-3.1 to -4.7	
	Repaglinide <sup>81</sup>	+0.3 to +5.5					Exenatide ER <sup>91</sup>	-1.1 to -2.9	
Thiazolidinedione	Pioglitazone <sup>82</sup>	+0.9 to +4.1				Sodium-glucose cotransporter 2 Inhibitors	Liraglutide <sup>92</sup>	-3.3 to +0.3	
	Rosiglitazone <sup>83</sup>	+0.8 to +5.4					Lixisenatide <sup>93</sup>	-0.1 to -2.7	
Insulin	Basal: Insulin degludec <sup>84</sup> Insulin detemir <sup>85</sup> Insulin glargine <sup>86</sup> Insulin neutral protamine Hagedorn <sup>86</sup>	+1.9 to +3.0				α-Glucosidase inhibitors	Semaglutide <sup>94,95</sup>	-1.2 to -6.0	
		-0.3 to +1.2					Canagliflozin <sup>96</sup>	-3.3 to +0.1	
		+0.1 to +3.9					Dapagliflozin <sup>97</sup>	-3.3 to +0.1	
		-0.0 to + 1.9					Empagliflozin <sup>98</sup>	-1.4 to -3.9	
							Ertugliflozin <sup>99</sup>	-1.6 to -3.2	
							Acarbose <sup>69-72</sup>	-0.4 to -3.5	
	Bolus: Insulin aspart <sup>87</sup> Insulin glulisine <sup>88</sup> Insulin lispro <sup>89</sup> Insulin regular <sup>90</sup>	+0.1 to +2.7					Amylinomimetics	Pramlintide <sup>73-76</sup>	-1 to -2
		-0.3 to +2.2							
		+0.8 to +2.3							
		+0.4 to +2.4							

lowest WMD at  $-0.21$  kg whilst liraglutide demonstrated the greatest weight change from baseline of  $-2.51$  kg ( $p < 0.001$ ). Furthermore, long-acting GLP1 RAs dosed weekly had a greater WMD from baseline at  $-1.67$  kg *versus*  $-1.32$  kg for those agents administered daily. Notably, semaglutide was not included in this evaluation.<sup>44</sup>

Of the available GLP1 RAs, the top three agents demonstrating good efficacy for weight loss as recognized by the American Diabetes Association and European Association for the Study of Diabetes are semaglutide, liraglutide and dulaglutide.<sup>9</sup>

### Semaglutide

#### Oral

A systematic review assessing the weight loss potential of oral semaglutide across the eight-study PIONEER programme found dose-dependent changes in body weight ranging from  $-1$  to  $-4.7$  kg. Weight loss of oral semaglutide was greater in comparison to empagliflozin 25 mg daily, liraglutide 1.8 mg daily and sitagliptin 100 mg daily.<sup>45</sup> Additionally, after 52 weeks, patients treated with oral semaglutide observed significantly higher proportions of body weight loss of 5% or more *versus* placebo (oral semaglutide: 39.4% with 14 mg/day; 28.1% with 7 mg/day and 17.2% with 3 mg/day compared to 5.2% in the placebo group;  $p < 0.001$ ).<sup>46</sup>

#### Injectable

Weekly semaglutide received subcutaneously in patients with obesity and T2DM was evaluated in a post hoc efficacy analysis of the phase III RCTs as part of the SUSTAIN programme. Weight loss was found to be consistent across all BMI subgroups with a potential of 2.5–5.7 kg weight reduction when semaglutide was dosed at 0.5 mg weekly and 2.0–7.9 kg reduction for semaglutide 1 mg weekly, both considered therapeutic doses of the product.<sup>47</sup> In Sustain 10, a trial that compared the efficacy and safety of semaglutide 1 mg weekly to liraglutide 1.2 mg daily in patients with obesity and T2DM found an estimated treatment difference of  $-3.83$  kg ( $p < 0.0001$ ) favouring semaglutide at 30 weeks. Statistically significant differences favouring semaglutide 1 mg weekly were also noted in the proportion of patients with weight loss of  $\geq 5\%$  and  $\geq 10\%$ .<sup>48</sup>

### Liraglutide

Seven phase III RCTs evaluated the potential for weight change with liraglutide in obese patients with liraglutide after 52 weeks. Liraglutide 1.8 mg daily demonstrated a higher potential for weight loss of at least 5% or more (24.4%) and maximum weight reductions of  $-4.3\%$  compared to active oral anti-hyperglycaemics and exenatide extended release.<sup>49</sup> The weight-loss potential of liraglutide 1.8 mg daily was further evaluated against other active comparators (oral anti-hyperglycaemics, basal insulin or multiple-dose insulin regimens) and consistently resulted in greater body weight reductions (2.8–5 kg) over at least 26 weeks in patients with

T2DM,<sup>50–52</sup> and one trial demonstrated 40.4% of patients achieving at least a 5% weight loss after 56 weeks of therapy.<sup>53</sup>

### Dulaglutide

A statistical assessment of six trials evaluating dulaglutide efficacy and safety in patients with obesity and T2DM found dose-dependent weight loss; however, the extent of weight loss varied based on background and/or comparator therapy. Overall, dulaglutide at a dose of 1.5 mg weekly saw a potential weight loss of 0.86–3.18 kg. The weight loss was identified to be at the greatest potential in patients with higher initial BMIs and when added to background metformin, which resulted in 24–34% of patients losing at least 5% of body weight *versus* those on dulaglutide monotherapy (12–17%) or other background anti-hyperglycaemics (9–18%).<sup>54</sup> The weight-loss potential was further evaluated for dulaglutide when patients were GLP1 RA-naive ( $-3.2$  kg) or those that switched from another GLP1 RA ( $-1.6$  kg). Subgroup evaluation hypothesized the greatest weight reduction in patients with a shorter duration of diabetes mellitus diagnosis and preserved renal function.<sup>55</sup>

In 2020, dulaglutide received FDA approval for expanded dosing of dulaglutide to 4.5 mg weekly. In two expanded dosing trials, there was evidence of additional weight loss potential in patients with obesity and T2DM not controlled on background metformin. Weight reductions for dulaglutide 3 mg weekly ranged from 3.9 to 4 kg (estimated treatment difference was  $-0.9$  to  $-2.4$  kg). Additionally, superior weight loss was demonstrated as early as 12 weeks and sustained to 56 weeks in individuals receiving dulaglutide 4.5 mg weekly. Body weight reductions achieved at this new maximum dose ranged from 4.1 to 4.7 kg (estimated treatment difference  $-1.6$  to  $-2.6$  kg).<sup>56,57</sup>

### SGLT2 inhibitors

In the setting of hyperglycaemia, the SGLT2 receptor found in the proximal convoluted tubule of the kidneys has increased expression. This results in exaggerated glucose reabsorption at the SGLT2 receptor potentiating the hyperglycaemic state. In addition to glycaemic effects, SGLT2 inhibitors reversibly block the SGLT2 receptor, resulting in reduced reabsorption of filtered glucose from the tubular lumen and lowering of the renal threshold for glucose, increasing glucose urinary excretion by  $\sim 75$  g with an associated energy deficit of  $\sim 300$  kcal daily, lending to adipose tissue mass reductions.<sup>58</sup> Another proposed mechanism for weight loss with the use of SGLT2 inhibitors is explained by extracellular volume loss due to increased polyuria and osmotic diuretic effects.<sup>59</sup>

Practice guidelines recognize SGLT2 inhibitors in patients with T2DM and the potential for patients to benefit from weight loss with a recommendation for use in place of or in addition to GLP1 RAs. In a meta-analysis by Cai et al., 51 studies were evaluated to describe weight changes from baseline amongst different SGLT2 inhibitors.<sup>44</sup> The meta-analysis found a total WMD of  $-2.01$  kg ( $p < 0.001$ ) amongst SGLT2 inhibitors. Weight

loss potential was similar regardless of use as monotherapy or when used as an add-on to other anti-hyperglycaemics. Dapagliflozin had the lowest WMD at  $-1.92$  kg, whilst canagliflozin demonstrated the greatest weight reduction from the baseline of  $2.3$  kg ( $p < 0.001$ ). Ertugliflozin was not included in the analysis.<sup>44</sup>

Currently, there are four FDA-approved SGLT2 inhibitors; however, canagliflozin, dapagliflozin and empagliflozin have been on the market the longest and have robust evidence available related to weight reductions.

### Canagliflozin

A systematic review and meta-analysis assessing the effect of canagliflozin use on body weight after 12 months of canagliflozin 100 and 300 mg resulted in a weight loss of 3.08% and 3.45%, respectively.<sup>60</sup> Other trials assessing canagliflozin 100 and 300 mg in patients with diabetes found a dose-dependent weight loss from baseline to 26 weeks of 1.9 kg and 2.9 kg.<sup>61</sup> This effect was further sustained in the analysis evaluating the effect after 56 weeks.<sup>62</sup> When canagliflozin 100 or 300 mg were added to oral anti-hyperglycaemics, such as metformin or a secretagogue, weight reductions of 2.0–3.6 kg and 3.1–4.4 kg, respectively, were demonstrated over 52 weeks.<sup>63,64</sup>

### Dapagliflozin

Dapagliflozin 10 mg daily has demonstrated total body weight changes of  $-2.96$  to  $-3.5$  kg over 24 weeks in patients with overweight or obesity and T2DM. In addition to body weight changes, changes in adiposity markers were noted. A waist circumference decrease of 1.52 cm ( $p = 0.0143$ ) and a change in body fat mass of  $-2.22$  kg resulted. Bolinder et al. noted in their study that more than 30.5% of patients enrolled achieved a body weight decrease of 5% or greater.<sup>65,66</sup>

### Empagliflozin

A meta-analysis of 10 studies evaluating empagliflozin in patients with T2DM demonstrated a body weight loss of  $-1.85$  kg compared to placebo.<sup>67</sup> A randomized controlled trial looked to evaluate the effect of empagliflozin on adiposity indices in patients with T2DM. In addition to finding body weight results up to  $-1.7$  to  $-1.9$  kg, changes in waist circumference of  $-1.3$  cm and percent total body of  $-0.2$  to  $-0.3\%$  were noted.<sup>68</sup> When evaluating empagliflozin as monotherapy in patients with T2DM, body weight changes of  $-1.8$  to  $-2.3$  kg and  $-2.0$  to  $-2.6$  kg were demonstrated when administering empagliflozin 10 mg daily and 25 mg daily, respectively, versus placebo or sitagliptin.<sup>69</sup>

### $\alpha$ -Glucosidase inhibitors

$\alpha$ -Glucosidase inhibitors (AGIs), such as acarbose, competitively inhibit enteric  $\alpha$ -glucosidase delaying the hydrolysis of oligosaccharides and disaccharides to glucose and other monosaccharides at the brush border of the small intestine.

The mechanism induces a prolonged absorption of carbohydrates resulting in a dose-dependent reduction in postprandial serum insulin. This insulin-sparing mechanism, along with improved insulin sensitivity with long-term use of AGIs, supports body weight reductions seen in clinical trials.<sup>70–72</sup>

As demonstrated with other anti-hyperglycaemics that offer weight-loss potential, clinical evidence regarding the weight reductions with acarbose suggests variability dependent on the comparator group and underlying concomitant medication use. A study that evaluated acarbose use in a patient population with T2DM and limited changes to lifestyle demonstrated a 0.46 kg loss after 12 months.<sup>70</sup> A median weight reduction of 3.5 kg was achieved when acarbose 100 mg three times daily was added to a sulfonylurea in a group of patients with T2DM.<sup>71</sup> When weight loss efficacy was compared between acarbose and DPP-IV inhibitors in a meta-analysis of randomized controlled trials, acarbose demonstrated superiority ( $p < 0.05$ ). There was a mean difference of  $-1.23$  kg favouring acarbose.<sup>72</sup> A pooled study of post-marketing surveillance studies from around the world found an absolute reduction in body weight of  $-1.16 \pm 2.57$  kg ( $-0.98 \pm 2.11$  kg in patients with overweight and  $-1.67 \pm 3.02$  kg in patients with obesity). Overall, 6.68% and 9.98% of patients with overweight and obesity, respectively, achieved a body weight reduction of at least 5% over the 3-month study period.<sup>73</sup>

### Amylinomimetics

Pramlintide, a synthetic analogue of human amylin, functions to mimic the function of the 37-amino acid neuroendocrine peptide hormone and acts on the hindbrain at the amylin receptor to reduce postprandial hyperglycaemia. This anti-hyperglycaemic mechanism is facilitated through reduction in glucagon release, delayed gastric emptying and centrally mediated appetite suppression. Consequently, pramlintide has demonstrated a decrease in food intake and body weight both in animal and human studies.

In two studies in patients with overweight and type 1 diabetes mellitus, the addition of pramlintide to insulin therapies significantly reduced body weight ( $-0.5$  kg in both studies) in comparison to placebo, where weight gain was seen over 52 weeks. The nadir for weight loss with the add-on of pramlintide was  $-1$  and  $-1.3$  kg, respectively.<sup>74,75</sup> In a patient population with obesity and concomitant T2DM treated with pramlintide 120  $\mu$ g once daily via subcutaneous route saw a mean weight loss of  $-1.6$  kg over 16 weeks. This was in comparison to a placebo group, which gained on average 0.7 kg ( $p < 0.001$ ). Overall, 68% of study participants in the pramlintide group had some degree of weight loss.<sup>76</sup> Another pooled post hoc analysis of two RCTs assessed body weight reductions in an insulin-treated patient population with add-on pramlintide versus placebo. Patients in the pramlintide group had a mean body weight reduction of 1.8 kg versus 0.14 kg in the placebo group ( $p < 0.0001$ ). The pramlintide group was more likely to

experience  $\geq 5\%$  body weight reduction than with placebo ( $p=0.0005$ ).<sup>77</sup>

## Clinical application

Clinical guidelines and trial evidence have emphasized the role of managing excess weight as described by classifications of overweight or obesity to be an area of focus for patients with diabetes. The benefits of weight loss in this patient population have demonstrated improved glycaemic control and reduced anti-hyperglycaemic needs. In addition, deliberate weight loss in patients with obesity and T2DM has been associated with a risk reduction of cardiovascular disease outcomes and all-cause mortality with effect sizes dependent on the percentage of weight reduction. Selecting anti-hyperglycaemic agents, for example, GLP1 RA and SGLT2 inhibitors, that avoid the potential adverse effects of weight gain, for example,

sulfonylureas, are preferred when determining the best agent to treat hyperglycaemia in patients with T2DM.

## Conclusion

Clinical guidelines have supported the selection of anti-hyperglycaemics that may also be leveraged to contribute to weight management in patients with overweight or obesity and with diabetes. As demonstrated in the clinical evidence, agents with the greatest weight loss potential include those in the GLP1 RA, SGLT2 inhibitor, biguanide, AGI and amylinomimetic drug classes. In addition to lifestyle modifications with diet and physical activity, the preference for anti-hyperglycaemic agents that not only support the achievement of glycaemic targets but also weight-loss goals should be considered in the clinical decision-making process of an individual patient.

## Key practice points

- Obesity is a chronic disease with increasing prevalence worldwide.
- Additional weight gain in patients with prediabetes or type 2 diabetes mellitus (T2DM) can lead to adverse consequences.
- Weight loss or the prevention of weight gain is an important goal in the management of patients with prediabetes or T2DM.
- Selection of therapy to treat T2DM should consider the use of medications that have a favourable cardiovascular profile and a beneficial, or at least neutral, effect on weight.

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