Body Weight Considerations in the Management of Type 2 Diabetes

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ABSTRACT

Obesity is one of the main risk factors for type 2 diabetes (T2D), representing a major worldwide health crisis. Modest weight-loss (≥ 5% but < 10%) can minimize and reduce diabetes-associated complications, and significant weight-loss can potentially resolve disease. Treatment guidelines recommend that intensive lifestyle interventions, pharmacologic therapy, and/or metabolic surgery be considered as options for patients with T2D and obesity. The benefits and risks of such interventions should be evaluated in the context of their weight-loss potential, ability to sustain weight change, side effect profile, and costs. Antihyperglycemia therapies have considerable effects on patient weight, prompting careful consideration of weight-loss or weight-neutral therapies for patients with T2D who also have obesity. Metformin, sodium glucose co-transporter 2 inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), α-glucosidase inhibitors, and amylin mimetics promote weight-loss. Dipeptidyl peptidase-4 inhibitors and fixed-ratio insulin/GLP-1 RA combination therapies (IDegLira, iGlarLixi) appear to be weight-neutral. Thiazolidinediones, insulin secretagogues (sulfonylureas, meglitinides), and insulins are associated with weight gain. Sulfonylureas are additionally associated with a higher risk of serious hypoglycemia from hyperinsulinemia, making them less suitable for the treatment of patients who are overweight or have obesity. Patients are often overtitrated on basal insulin, resulting in an increased risk of hypoglycemia and weight gain without achieving glycemic goals. Given these observations, the effects of antihyperglycemia agents on weight should be considered when individualizing T2D therapy.

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Keywords: Antihyperglycemia therapy; GLP-1 RA; Insulin; Lifestyle; Obesity; Type 2 diabetes; Weight-loss; Weight management
INTRODUCTION

The increasing prevalence of both obesity and type 2 diabetes (T2D) represents major public health crises worldwide. Obesity increases the risk of multiple diseases, and is believed to account for 80 – 85% of the risk for developing T2D [1]. In 2015, diabetes affected around 30 million people in the USA alone (9.4% of the population), of which 90 – 95% of cases were type 2 [2]. As expected, given its relationship to disease risk, a high proportion of people diagnosed with diabetes in the US are overweight [body mass index (BMI) \( \geq 25 \text{ kg/m}^2 \)] or have obesity (87.5%; BMI \( \geq 30 \text{ kg/m}^2 \)) [2].

For patients with T2D, prevention of weight gain, and modest weight reduction of as little as 5%, can reduce diabetes-associated complications and significantly improve cardiovascular risk factors [3, 4]. However, weight gain during antidiabetes therapy is common and has been cited as a reason for delaying treatment intensification—particularly with insulin-based regimens [5]. A combination of clinician perceptions and attitudes, patient concerns about weight gain and potential hypoglycemia, and the increasing complexity of treatment options contribute to reluctance in therapy escalation, leading to clinical inertia [5–7]. Overcoming clinical inertia is paramount in the effective treatment of diabetes, and communication between clinicians and patients about antihyperglycemia therapies may help dispel some of the concerns associated with treatment progression [7]. Given that the benefits and detriments may be prioritized differently by patients and their clinicians (for example, a change in body weight might present a significant concern to a patient, but be considered a normal part of therapy to the clinician), it is important that clinicians consider not only the antihyperglycemia effects of selected medications, but also the effect they may have on body weight.

This review presents an overview of the relationship between T2D and obesity, and discusses the effects of widely used classes of antihyperglycemia agents on body weight. The information in this article is based on previously conducted studies and does not include any new report of findings not previously published by any of the authors.

RELATIONSHIP BETWEEN OBESITY AND T2D

While the underlying cause of T2D is multifactorial, the cardinal features are a decline in insulin production by pancreatic \( \beta \)-cells and peripheral insulin resistance [8]. A number of factors play a major role in the development of both obesity and T2D (Fig. 1), and studies have identified a wide range of potential links between the two conditions relating to insulin resistance, pro-inflammatory cytokines, endothelial dysfunction, deranged fatty acid metabolism, and cellular processes such as mitochondrial dysfunction and endoplasmic reticulum stress [3, 9, 10].

Excess adiposity and fat distribution have a strong relationship with hyperinsulinemia and T2D; fat distribution may be equally, or more, important than adiposity in determining development of T2D [11]. Increased upper body fat—visceral fat in particular—is associated with metabolic syndrome, T2D, and cardiovascular disease. Though the mechanism behind this has not been fully elucidated, it is likely to be related to differences in functional subtypes of adipose tissue. Overall, visceral fat is more metabolically active than subcutaneous fat, producing a range of adipose-specific cytokines (such as adiponectin) as well as pro-inflammatory cytokines that contribute to metabolic syndrome and insulin resistance [9, 12].

STRATEGIES USED FOR WEIGHT-LOSS IN T2D

The primary clinical goals of weight-loss in patients with T2D are achievement of glycemic targets, improvement of lipid profile, and normalization of blood pressure [13]. The American Diabetes Association (ADA) recommends a glycated hemoglobin \( \text{A}_{1c} \) (A1C) target of < 7.0% for most adults with T2D. However, these goals...
must be individualized for each patient according to their needs. More stringent A1C goals (such as target A1C < 6.5%) may be suitable for younger patients, or for patients with a short duration of diabetes, provided they are achieved without significant hypoglycemia or significant adverse events. Conversely, less stringent A1C goals (such as target A1C < 8.0%) may be suitable for older patients, or those patients with extensive comorbidities, high risk of hypoglycemia, or a long duration of diabetes. “Over-basalization” (a commonly used term amongst health care providers when referring to detrimentally high amounts of basal insulin [14]) can occur when the basal insulin dose is increased but A1C remains uncontrolled due to a lack of postprandial glucose control. Over-basalization is associated with increased weight gain and hypoglycemia risk [14] and is an important consideration for weight-loss strategies in patients using basal insulin to manage their T2D.

Sustained weight-loss (≥ 5% after one year) has been shown to improve glycemic control in patients with obesity [8, 15, 16]. In addition, there is strong and consistent evidence that modest, sustained weight-loss can delay the progression from prediabetes to T2D [16]. Recent treatment guidelines from the ADA and The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) recommend weight-loss through lifestyle modification or nonsurgical energy restriction promoting weight-loss with the goal of reducing body weight by 5–10% in patients with T2D and a BMI ≥ 25 kg/m² [8, 13]. The use of weight-loss medication is recommended as an option for eligible patients with a BMI ≥ 27 kg/m² [8, 13]. Recommendations for bariatric surgery differ between guidelines, with AACE recommending it as an option for patients with a BMI ≥ 35 kg/m², and ADA recommending it for patients with a
BMI ≥ 40 kg/m² (≥ 37.5 kg/m² in Asian Americans) [8, 13].

Nutrition education at diagnosis and throughout the care process is advocated by the ADA and the AACE/ACE to support lifestyle modification and achieve weight-loss [8, 13, 17], and is an annually renewable benefit in insurance plans in the US [18, 19]. ADA guidelines state that lifestyle intervention programs should be intensive and involve frequent follow-ups [8]. Despite these recommendations, data from the National Health and Nutrition Examination Survey (NHANES) indicate that only 54.6% of patients reported receiving any diabetes education, and in a study investigating the effects of diabetes and nutrition education on health outcomes, only 13.4% had received an educational visit of any kind [20, 21]. Clinical data indicate that lifestyle interventions can achieve long-term results overall, despite the tendency for patients to regain weight over time [22]. In the Look AHEAD (Action for Health in Diabetes) trial of intensive lifestyle interventions, a 6% decrease in body weight was achieved after 9.6 years of follow-up [23]. Participants also showed improved glucose control over the follow-up period [23, 24].

The National Institutes of Health obesity guidelines suggest the use of weight-management medications as an adjunct to lifestyle modifications in patients with a BMI ≥ 30 kg/m² (or ≥ 27 kg/m² in patients with concomitant risk factors and/or diseases); however, insurance coverage and patient selection criteria for weight-loss medication have been prohibitive and a barrier to therapy options [8, 25]. Five agents (or combinations) are currently approved by the US Food and Drug Administration (FDA) for long-term weight management in patients with T2D: orlistat (a lipase inhibitor); lorcaserin (a selective serotonin receptor agonist); phentermine/topiramate (a sympathomimetic amine anorectic in combination with an antiepileptic); naltrexone/bupropion (an opioid antagonist in combination with an aminoketone antidepressant); and liraglutide at a dose of 3 mg (a glucagon-like peptide-1 receptor agonist [GLP-1 RA]) [8]. Data from clinical trials show average one-year weight-losses with these agents; the percentage of subjects losing sufficient body weight (≥ 5%) was 35–73% with orlistat, 38–48% with lorcaserin, 45–70% with phentermine/topiramate, 36–57% with naltrexone/bupropion, and 51–73% with liraglutide [8, 26–32].

The ADA recommends metabolic/bariatric surgery as a treatment option for T2D in eligible patients with a BMI ≥ 40 kg/m² (≥ 37.5 kg/m² in Asian Americans) regardless of the extent of glycemic control and in patients with a BMI 30.0–34.9 kg/m² (27.5–32.4 kg/m² in Asian Americans) with inadequately controlled hyperglycemia despite optimal medical therapy [8]. The effects of bariatric surgery on T2D are profound and may include temporary disease remission. In a large meta-analysis (N = 135,246), patients with T2D and severe obesity who underwent bariatric surgery achieved a 58% reduction in excess body weight, and 78% of patients no longer showed clinical manifestations of T2D after two years. The overall A1C reduction was 2.1% [33].

Addressing excess weight can have a significant impact on outcomes in diabetes care. Lifestyle, pharmacologic, and surgical interventions all have the potential to reduce weight sufficiently to improve glycemic control, and each is associated with its own risks and benefits [8, 13]. Discussion regarding the pros and cons of each strategy should be an integral part of managing T2D in overweight patients.

EFFECTS OF ANTIHYPERGLYCEMIA DRUGS ON BODY WEIGHT

The effects of antihyperglycemia therapy on clinical outcomes (including body weight) vary both between and within the drug classes (Fig. 2) [13]. The ADA recommends choosing glucose-lowering medications that are weight-neutral or that promote weight-loss when treating patients with T2D who are overweight or have obesity with a hierarchy of choice [8]. In the following section we will review the drug classes associated with weight-loss, as well as those that are weight-neutral, and those that are associated with weight gain. In addition to the
effects on weight, potential adverse events and dosing schedules also impact patients on a daily basis, and should be considered when individualizing therapy (Table 1).

### Drug Classes Associated with Weight-Loss

**Metformin**

Metformin is the first-line recommended treatment for T2D. It has a low risk of hypoglycemia and promotes slight weight-loss and euglycemia with only mild gastrointestinal side effects [8, 13, 34]. Metformin has been shown to reduce A1C levels by ~1% compared with placebo [35]. Approximately 50% of the studies conducted in drug-naïve patients to date have shown significant reductions in body weight with metformin relative to baseline or comparators, and weight changes of +1.5 to –2.9 kg in insulin-naïve patients have been reported [36]. The mechanisms behind weight-loss with metformin are not fully understood, but are likely related, at least in part, to its anorectic effects [37].

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**Fig. 2** Profiles of antidiabetic medications. **AGI** alpha-glucoosidase inhibitor, **ASCVD** atherosclerotic cardiovascular disease, **BCR-QR** bromocriptine qui release, **CHF** congestive heart failure, **COLSVEL** colesevelam, **DPP-4i** dipeptidyl peptidase 4 inhibitor, **FDA** US Food and Drug Administration, **GI Sx** gastrointestinal side effects, **GLN** glinides, **GLP-1 RA** glucagon-like peptide-1 receptor agonist, **MET** metformin, **PRAML** pramlintide, **SGLT-2i** sodium glucose co-transporter 2 inhibitor, **SU** sulfonylurea, **TZD** thiazolidinedione Reprinted with permission from American Association of Clinical Endocrinologists © 2018 AACE. Garber AJ, Abrahamson MJ, Barzilay JI, et al. AACE/ACE comprehensive type 2 diabetes management algorithm 2018. Endocr Pract. 2018;24:91–120
### Table 1 Mechanisms of action, effects on body weight, side effects, and dosing schedule of antidiabetes drug classes

| Drug Class                          | Mechanism of action                                                                 | Effect on body weight (change in kg) | Disadvantages                                           | Dosing schedule                                      |
|-------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------|---------------------------------------------------------|-------------------------------------------------------|
| **Associated with weight-loss**     |                                                                                     |                                     |                                                         |                                                       |
| Metformin                           | Activate AMP-kinase; ↓ hepatic glucose production                                    | + 1.5 to − 2.9<sup>a</sup>          | GI side effects                                         | Divided doses with meals                               |
| α-glucosidase inhibitors            |                                                                                     |                                     |                                                         |                                                       |
| Acarbose                            | Inhibit intestinal α-glucosidase activity                                            | − 0.43 to − 1.80                    | GI side effects                                         | Three times daily before all major meals               |
| Miglitol                            | Slow intestinal carbohydrate digestion/absorption                                   |                                     |                                                         |                                                       |
| **GLP-1 RAs**                       |                                                                                     |                                     |                                                         |                                                       |
| Short-acting:                       | Activate GLP-1 receptors; ↑ insulin secretion (glucose dependent)                  | − 1.14 to − 6.9                     | GI side effects; Effect on heart rate; Injectable       | Exenatide: within 1 h prior to morning and evening meals |
| Liraglutide, exenatide              | ↓ glucagon secretion (glucose dependent)                                            |                                     | Acute pancreatitis; Black box warning for risk of thyroid c-cell tumors (albiglutide, exenatide extended-release, dulaglutide) |
| Long-acting:                        | Slow gastric emptying (short-acting agents)                                        |                                     |                                                         |                                                       |
| Lixisenatide                        | ↑ satiety (short-acting agents)                                                    |                                     |                                                         |                                                       |
| Albiglutide, exenatide extended-release, dulaglutide, semaglutide |                                                                                     |                                     |                                                         |                                                       |
| **Amylin mimetics**                 |                                                                                     |                                     |                                                         |                                                       |
| Pramlintide                         | Activate amylin receptors; ↓ glucagon secretion; Slows gastric emptying; ↑ satiety | − 2.57<sup>c</sup> [51]            | GI side effects; Hypoglycemia; Injectable               | Before all major meals                                 |

<sup>a</sup> - glucosidase inhibitors

<sup>b</sup> - Lixisenatide: once daily within 1 h before the first meal of the day

<sup>c</sup> - Albiglutide, exenatide extended-release, dulaglutide: once weekly, any time of day, with or without food

<sup>d</sup> - Semaglutide: once weekly

<sup>e</sup> - Exenatide: within 1 h prior to morning and evening meals

<sup>f</sup> - Semaglutide: once weekly
| Mechanism of action | Effect on body weight (change in kg) | Disadvantages | Dosing schedule |
|---------------------|-------------------------------------|---------------|----------------|
| **SGLT2 inhibitors** | 0.9 to 2.5 [48, 54, 56, 60] | Genitourinary infections, Polyuria, Volume depletion/hypotension/dizziness, Boxed warning for association with lower limb amputation in patients with established CVD (canagliflozin), Risk of diabetic ketoacidosis, Risk of fractures | Canagliflozin: once daily before the first meal of the day, Dapagliflozin/empagliflozin: once daily, taken in the morning, with or without food |
| Canagliflozin, dapagliflozin, empagliflozin | Inhibit SGLT2 in the proximal nephron, Block glucose reabsorption in the kidney → increased glucosuria | 0.09 to 1.11 [38, 40, 41, 48] | Angioedema/urticaria, Acute pancreatitis, ↑ heart failure hospitalizations (saxagliptin, alogliptin) |
| **Weight-neutral** | 2.0 to 2.7 [67–71] | Nausea, Vomiting, Diarrhea | Once daily |
| **DDP-4 inhibitors** | 2.0 to 2.7 | Nausea | Once daily |
| Sitagliptin, saxagliptin, linagliptin, alogliptin | Inhibit DPP-4 activity, increasing postprandial incretin (GLP-1, GIP) concentration, ↑ insulin secretion (glucose dependent), ↓ glucagon secretion (glucose dependent) | 0.09 to 1.11 | Angioedema/urticaria, Acute pancreatitis, ↓ heart failure hospitalizations (saxagliptin, alogliptin) |
| **Fixed-ratio combination therapy** | 1.99 to 2.31 [33, 38, 73] | Hypoglycemia | Once daily with first meal of the day |
| IDegLira, iGlarLixi | Complementary mechanisms of its components; basal insulin targets FPG, GLP-1 RA lowers PPG | -2.0 to +2.7 | Nausea, Vomiting, Diarrhea |
| **Associated with weight gain** | 1.99 to 2.31 | Hypoglycemia | Once daily with first meal of the day |
| **Sulfonylureas** | Close KATP channels on β-cell plasma membrane, ↑ insulin secretion | 1.99 to 2.31 | Hypoglycemia |
| Glyburide, glipizide, glimepiride | | | |

Δ Adis
α-Glucosidase Inhibitors

α-Glucosidase inhibitors delay the absorption of carbohydrates in the gastrointestinal tract, which subsequently slows the spike in post-prandial glucose. They demonstrate A1C-lowering effects (reductions of ~1% versus placebo) and a low risk of hypoglycemia; they demonstrate cardiovascular benefit in patients with impaired glucose tolerance and T2D, and are associated with weight-loss [8, 13, 35]. Weight change associated with α-glucosidase inhibitors ranges from −0.43 to −1.80 kg [38–41]. α-Glucosidase inhibitors may also cause dose-related gastrointestinal side effects, such as flatulence and diarrhea [42].
Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs)

GLP-1 RAs reduce postprandial glucose levels by a variety of mechanisms. They activate GLP-1 receptors in the pancreas to stimulate insulin secretion and suppress glucagon secretion [43, 44]. They also act on GLP-1 receptors in the central nervous system to decrease appetite. Further, they act on the gastrointestinal tract to slow gastric motility and emptying; this delays intestinal glucose absorption, which reduces postprandial glucose excursions and also leads to reduced appetite and enhanced satiety [43, 44]. These agents show efficacy in reducing A1C (reductions of ~0.8% to 1.9% compared with baseline), have a low risk of hypoglycemia due to their glucose-dependent mechanism of action, and are usually associated with reductions in weight and blood pressure [13, 45]. The most common side effects with GLP-1 RAs are transient, mild-to-moderate gastrointestinal adverse events (such as nausea and vomiting) [46, 47]. GLP-1 RAs are an injectable therapy, with injection requirements ranging from twice daily to once weekly, depending on the formulation. Clinical trial data show that GLP-1 RA therapy is associated with weight change ranging from $-1.14$ to $-6.9$ kg [38–41, 48, 49].

Amylin Mimetics

Pramlintide, which is indicated for patients who use meal-time insulin therapy and have failed to reach glycemic targets [50], has A1C-lowering effects (reductions of ~0.33% versus placebo), and is associated with gastrointestinal side effects, an increased risk of hypoglycemia with insulin therapy (unless insulin dose is decreased concomitantly), and the need for multiple daily injections [51, 52]. In clinical diabetes trials, pramlintide consistently and significantly lowered body weight compared with placebo (between-group differences of 1.5 to 2.5 kg; $P < 0.01$) [52]. Weight-loss efficacy is likely related to enhanced satiety and slowed gastric emptying, and studies have shown reduced food and caloric intake in non-diabetic individuals with obesity [52, 53]. In patients with obesity who do not have diabetes, significant reductions in weight (weighted mean difference $-2.27$ kg) and waist circumference (weighted mean difference $-2.02$ cm) have been achieved [51]). The effects of pramlintide on weight appear to be independent of gastrointestinal side effects [52].

Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors

SGLT2 inhibitors prevent glucose reabsorption in the proximal tubules of the kidneys, resulting in an increase in urinary glucose excretion [54, 55]. They have A1C-lowering efficacy (reductions of ~0.69% compared with placebo) with a low incidence of hypoglycemia, and are associated with weight-loss and systolic blood pressure reduction [8, 13, 54, 56]. Adverse events associated with SGLT2 inhibitors include increased urogenital infections and bone fractures [13, 54, 57–59]. Meta-analyses have revealed a greater loss of body weight in patients treated with SGLT2 inhibitors (−0.9 to −2.5 kg) compared with placebo and oral antidiabetes drugs including metformin, sulfonylureas, and dipeptidyl peptidase 4 (DPP-4) inhibitors [54, 60]. Weight-loss with SGLT2 inhibitors is associated with significant decreases in total body fat, waist circumference, index of central obesity, and visceral adiposity [57, 61]. The increased renal excretion of glucose is thought to induce weight-loss through both the induced calorie deficit and fluid loss resulting from increased osmotic diuresis [62].

Weight-Neutral Agents

Dipeptidyl Peptidase 4 (DPP-4) Inhibitors

DPP-4 inhibitors have A1C-lowering properties (reductions of ~0.75% versus placebo) with a low risk of hypoglycemia, are weight-neutral, and are well tolerated, with reported adverse event rates of hypersensitivity and skin-related reactions similar to placebo in pooled analyses [13, 35, 63]. The range of weight change associated with DPP-4 inhibitor therapy is $-0.09$ to $+1.11$ kg [38, 40, 41, 48]. In patients already on metformin, the addition of a DPP-4 inhibitor resulted in a more favorable weight profile versus the addition of a sulfonylurea, meglitinide,
or thiazolidinedione (TZD), but not versus the addition of a GLP-1 RA [40, 64].

**Fixed-Ratio Combination Therapy**

Once-daily GLP-1 RA/basal insulin titratable fixed-ratio combinations [insulin glargine and lixisenatide (iGlarLixi) and insulin degludec and liraglutide (IDegLira)] produce greater A1C reductions (≈ 0.72%) compared with basal insulin alone, with a higher likelihood of achieving A1C < 7.0% than with using each individual agent on its own [65]. Fixed-ratio combination therapies also help to mitigate the weight gain associated with basal insulin use without increasing hypoglycemia risk, and have a significantly lower frequency of gastrointestinal adverse events compared with GLP-1 RAs alone, likely reflecting the gradual increase in GLP-1 RA dose that parallels titration of the basal insulin component [46, 66].

Clinical trial data from patients receiving fixed-ratio combination therapies showed a weight change of −0.3 kg to −0.7 kg for iGlarLixi and −2.7 to +2.0 for IDegLira [67–71]. These differences in weight are due to the use of either liraglutide or lixisenatide in the combination with insulin [71, 72].

The safety and efficacy profiles of fixed-ratio combinations, combined with their ease of use, decreased injection burden, and potential to address over-basalization, make them particularly useful in patients who are overweight or have obesity, or who wish to avoid weight gain, and those who require intensification of basal insulin therapy.

**Drug Classes Associated with Weight Gain**

**Sulfonylureas**

Sulfonylureas show high efficacy in lowering A1C (reductions of ≈ 1.25% versus placebo), but are associated with weight gain and hypoglycemia [13, 35]. Sulfonylureas are considered to have the highest risk of severe hypoglycemia of the available T2D therapies [13]. Meta-analyses have demonstrated that when added to other agents, sulfonylureas are associated with weight gain ranging between 2.01 and 2.3 kg versus placebo [38, 40, 73]. Due to associated hypoglycemia, weight gain, and possible cardiovascular risk, together with their diminished efficacy over time, sulfonylureas should be avoided in patients with obesity [74].

**Thiazolidinediones (TZDs)**

TZDs show relatively high efficacy in reducing A1C (reductions of ≈ 1.25% versus placebo), are associated with weight gain and a low risk of hypoglycemia, and induce durable antihyperglycemia effects [8, 13, 35]. Weight gain seen with TZDs ranges from 2.30 to 4.25 kg [38–41, 48], and is thought to be related to a number of mechanisms, including fluid retention and redistribution of adipose tissue [75].

**Meglitinides (glinides)**

Glinides have A1C-lowering properties (reductions of ≈ 0.75% versus placebo), a shorter half-life, and a similar side effect profile, but with a lower risk of hypoglycemia, compared with sulfonylureas [13, 35, 74]. In addition, their relatively short half-life means they must be administered frequently [74]. Weight gain is similar to that seen with sulfonylureas (0.91 to 2.67 kg), which suggests glinides should also be avoided in patients with obesity [38, 40, 41].

**Insulin and Insulin Analogs**

Insulin remains the most effective glucose-lowering agent—especially in patients with elevated A1C. A significant proportion of patients with T2D require insulin therapy as their disease progresses because of β-cell failure. Compared with most other antihyperglycemia therapies, there is a substantial risk of hypoglycemia with insulin—especially with regimens that include prandial insulin [13]. Weight gain with insulin ranges between 1.56 and 5.75 kg, which is substantially greater than with other agents [39–41, 48, 76]. Although all insulin therapy is associated with weight gain, the extent of weight gain varies between the different insulins and regimens. In meta-analyses, weight gain with insulin analog therapy was found to positively correlate with insulin dosage [77] and to be greater with biphasic (premixed) insulin than with basal insulin alone [48, 76, 78]. However, weight gain is similar with premixed
insulin and combination basal/prandial insulin [79].

In terms of different basal insulin formulations, insulin detemir (versus insulin glargine) has been associated with a lower increase in body weight when used in combination with oral antidiabetes drugs or with prandial insulin [79]. However, a pooled analysis found that, due to the lower A1C-lowering efficacy of insulin detemir, weight gain per mean A1C change was similar with both insulin analogs [80]. A recent meta-analysis including the latest generation of insulin analogs showed that treatment with insulin glargine 300 U/ml resulted in a comparable change in body weight to treatment with insulin detemir, NPH insulin, or insulin degludec, but significantly lower weight gain when compared with premixed insulin [81].

Guidelines recommend intensification to target postprandial glucose where A1C remains above target despite basal insulin being titrated to an acceptable fasting plasma glucose or if basal insulin dose exceeds 0.5 U/kg/day [8, 13]. Intensification can be achieved by adding either a rapid-acting insulin analog (basal plus or basal bolus), premixed insulin, or a GLP-1 RA [8, 13]. Alternatively, a once-daily, fixed-ratio combination of basal insulin in combination with a GLP-1 RA provides the advantage of drug delivery through a single daily injection with a lower risk of hypoglycemia. The weight-related advantages of GLP-1 RAs mentioned here should also be considered when intensifying therapy.

CONCLUSIONS

Current major guidelines recommend that when choosing antihyperglycemic treatments for patients who are overweight or have obesity, wherever possible, consideration should be given to medications that promote weight-loss or that are weight-neutral [8]. Given the benefits of weight-loss and the potential risks of weight gain in patients with T2D, the effect of antihyperglycemia agents on body weight is an important factor to take into account when individualizing patient therapy. Future developments should focus on increasing the number of agents for T2D that promote weight-loss, thus providing more options for patients.

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