Revisiting weight reduction and management in the diabetic patient: Novel therapies provide new strategies

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Abstract

Weight gain has been so synonymous with diabetes care that overweight/obesity is considered an intractable aspect of diabetes and its management. A healthy body mass index (BMI) is paramount, however, in preserving the cardiometabolic profile, slowing the course of the disease and extending the life expectancy of patients. It is also key to fostering a healthy and productive society at large. Two trends in care press us to challenge our assumptions about weight control in this population by reconsidering traditional approaches to the management of diabetes. First, new anti-diabetes drug classes have emerged that are more “weight-friendly” than previously available treatments and “gentler” on the faltering β cell. Second, novel anti-obesity agents are proving efficacious in patients with diabetes. This paper presents the composite of newer and older anti-obesity and anti-diabetic drugs. It makes recommendations for anti-diabetic regimens and processes of care that engender weight loss, or neutralize or minimize weight gain, while getting many patients to their glycated hemoglobin (HbA1c) goal. Anti-obesity agents that can be safely and effectively incorporated into these regimens for the patient needing supplemental support are reviewed in detail.

Introduction

In 2013, the American Medical Association officially recognized obesity as a disease [1], emphasizing the gravity of recent health statistics demonstrating that the high prevalence of obesity has caused an increase in the morbidity associated with weight-related diseases, including diabetes. An estimated 382 million individuals worldwide had diabetes in 2013, representing ~8.3% of the world’s population. If current trends continue, it is anticipated that 592 million individuals — or 10.1% of the world’s population — will have diabetes by 2035 [2].

Of the large number of patients diagnosed with type 2 diabetes mellitus (T2DM), 85% are classified as overweight (body mass index [BMI] ≥25 kg/m²) or obese (BMI ≥30 kg/m²) [3]. Efforts to control diabetes can actually exacerbate the problem, as anti-diabetic pharmacotherapy is commonly associated with weight gain that is often substantial [4]. The large-scale United Kingdom Prospective Diabetes Study showed that after an initial weight loss with dietary instruction, patients with T2DM showed a considerable weight gain with the hypoglycemic therapies, sulfonylureas and insulin [5]. Although these patients had received intensive blood-glucose control, one wonders if macrovascular disease had not been exacerbated by the patients’ weight gain [5]. Evidence shows the benefits of weight loss, including improved glycemic control and reductions in cardiovascular risk factors [6,7].

Since the United Kingdom Prospective Diabetes Study [5], evidence supporting treatment of both diabetes and obesity has grown. Even minor elevations in blood glucose can increase endothelial dysfunction and inflammation, leading to adverse cardiovascular and microvascular outcomes [8-11]. Cardiovascular morbidity and mortality correlate with increasing severity and duration of hyperglycemia with no apparent glycated hemoglobin (HbA1c) threshold, with similar trends observed for microalbuminuria and polyneuropathy [9,11-14]. It has also been shown that initiating intensive therapy shortly after diabetes has been diagnosed can reduce micro- and macrovascular complications; patients who achieve an HbA1c level of ≤7% see additional benefit [5,15,16]. Weight management is essential for the health of overweight and obese patients — especially those with diabetes — as weight loss in these patients is associated with improved insulin sensitivity; lower blood pressure (BP), cholesterol and triglycerides and a reduction in markers of inflammation and endothelial dysfunction [17].

As the diabetes armamentarium has expanded, it has included some agents that lower HbA1c and prevent hyperglycemia without promoting weight gain (weight-neutral effects) and others that engender weight loss. Such regimens can

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History

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reduce complications and risks for patients with obesity as well as diabetes. Indeed, the authors believe a goal of diabetes management includes achieving glycemic control while avoiding hypoglycemia and weight gain, both of which may increase the risk of cardiovascular disease [6,18]. The goal of neutral or positive weight effects may be difficult to achieve in patients who require insulin, but strategies such as a eucaloric diet, incretin therapy (with or without other non-insulin therapies) and decreased reliance on basal/bolus insulin therapy can effectively minimize weight gain in insulin-treated patients. While lifestyle modification remains a fundamental component of first-line therapy for diabetes, pharmacotherapy has advanced to a level that allows patients to avoid the weight gain historically seen with this therapeutic option and to actually achieve weight loss. Best practices in the care of diabetes should therefore utilize these tools and strategies.

Similar to the expanding tool chest of anti-diabetes agents, new anti-obesity drugs are approved for use in the patient with diabetes. With newer anti-diabetic and anti-obesity therapies available, weight gain is no longer inevitable for patients with diabetes. The goal of this review is to help physicians reconsider optimal combinations of interventions when treating diabetes in concert with overweight or obesity.

Weight effect “weighs in” on choice of anti-diabetic agent

In patients with diabetes and obesity, glucose-lowering ability should be considered hand-in-hand with the effects of the anti-diabetic agent on weight. The glycemia-lowering efficacy, safety and impact on weight for major classes of therapies used in diabetes treatment are reviewed below and summarized in Table 1 and Figure 1. Of the currently available anti-diabetic drugs, three classes — glucagon-like peptide-1 (GLP-1) agonists, sodium-glucose co-transporter 2 (SGLT-2) inhibitors and metformin — have weight reduction capabilities (Figure 1). Accordingly, these three classes should be considered preferentially to avoid weight gain in patients with diabetes.

Sulfonylureas

Sulfonylureas lower blood glucose by stimulating insulin secretion in a glucose-independent manner [19]. Treatment with sulfonylureas has been shown to decrease HbA1c by <1.5% [20,21]. However, in the context of obesity, sulfonylureas as a class should be avoided, in light of associated hypoglycemia, weight gain, cardiovascular risk and correlation with β-cell apoptosis, as well as their diminished efficacy with time [22-30].

A frequent side effect of sulfonylurea therapy is weight gain. The amount of weight gain varies among the sulfonylurea class; use of glinazide for 5 years was associated with a weight gain of 0.7 kg [31], while 1.5–2.5 kg of weight gain may occur with other sulfonylureas [5,32,33]. The weight gain is most likely a result of increased appetite associated with efforts to avoid hypoglycemia [5]. The major adverse side effect seen with sulfonylureas is hypoglycemia, which can be asymptomatic — though no less dangerous — in close to 50% of patients with T2DM [34-36]. Hypoglycemia may result in severe episodes of coma or seizure that may be long-lasting and life threatening. Longer-acting agents such as chlorpropamide, glyburide, glibenclamide and sustained-release glipizide are associated with a higher risk of hypoglycemia than immediate-release glipizide, glimepiride or gliclazide [20,37,38].

Glinides

Like sulfonylureas, glinides lower glycemia by stimulating insulin secretion, although they bind to different sites on sulfonylurea receptors [39,40], and must be administered more frequently due to a shorter half-life [20,41,42]. Two glinides are currently available in the USA, repaglinide (PRANDIN®) and nateglinide (STARLIX®). Repaglinide has efficacy similar to metformin or sulfonylureas, decreasing HbA1c by <1.5%. Nateglinide is somewhat less effective, decreasing HbA1c by ~1.0% [43-45], although it is apparently associated with a lower risk of hypoglycemia than sulfonylureas [43,45]. The association with weight gain is similar to that of sulfonylureas, and in the context of obesity, glinides as a class should be avoided.

Incretins

Incretin-based therapies — GLP-1 agonists and dipeptidyl-peptidase-4 (DPP-4) — have multiple effects on glucose homeostasis, including glucose-dependent insulin release and glucagon suppression [46]. Save for exenatide once weekly (QW), incretin therapies start working with the first doses, may improve β-cell function, have a low risk of inducing hypoglycemia and have beneficial or neutral effects on body weight [46,47]. DPP-4 inhibitors, such as saxagliptin (ONGLYZA®), sitagliptin (JANUVIA®), linagliptin (TRADJENTA®), vildagliptin (GALVUS®) and alogliptin (NESINA®), reduce HbA1c by 0.5–1% and have neutral effects on weight [47]. GLP-1 agonists such as exenatide (BYETTA®) and liraglutide (VICTOZA®) reduce HbA1c by 1–1.5% and result in a reduction in body weight [46,47]. Newer once-weekly GLP-1 agonists (albiglutide [TANZEUM®] and dulaglutide [TRULICITY®]) have similar, if not exactly the same, benefits as the other GLP-1 agonists [48,49].

GLP-1 agonists suppress hypothalamic centers for appetite or increase satiety and slow gastric emptying [47,50]. Both of these mechanisms may be associated with the adverse effect of nausea and/or vomiting [47]. Tolerability can be increased by advising patients to stop eating when feeling “full” and to avoid very high-fiber or high-fat meals. Moreover, by virtue of the weight-loss benefit associated with reduced insulin resistance, GLP-1 receptor agonists treat 7 of the 8 elements of hyperglycemia outlined in DeFronzo’s Ominous Octet [26]. Both DPP-4 inhibitors and GLP-1 agonists have potential beneficial effects on cardiovascular risk factors such as BP and lipids (cholesterol, high- and low-density lipoproteins [HDL, LDL] and triglycerides) [46,47,51-56].
### Table 1. Obesity and anti-diabetic medications and their effects on HbA1c and weight.

<table>
<thead>
<tr>
<th>Obesity medications</th>
<th>HbA1c change</th>
<th>Weight change</th>
<th>Most common adverse events</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorcaserin</td>
<td>Decrease</td>
<td>Decrease</td>
<td>Headache, back pain, nasopharyngitis, nausea(^a) &gt;10% dry mouth, constipation, paresthesia; &gt;5% dysgeusia, insomnia</td>
<td>[128,130]</td>
</tr>
<tr>
<td>Phentermine/topiramate ER</td>
<td>Decrease</td>
<td>Decrease</td>
<td>&gt;10% nausea, headache, constipation; &gt;5% vomiting, dizziness, insomnia, dry mouth and diarrhea</td>
<td>[142-145]</td>
</tr>
<tr>
<td>Naltrexone/bupropion</td>
<td>Decrease</td>
<td>Decrease</td>
<td>Gastrointestinal symptoms: &gt;10% oily spotting, flatus with discharge, fecal urgency, fatty oily stool, increased defecation; &gt;5% fecal incontinence</td>
<td>[126,127]</td>
</tr>
<tr>
<td>Orlistat</td>
<td>No effect</td>
<td>Decrease</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

### Anti-diabetic medications

| GLP-1 agonists               | Decrease     | Decrease      | >10% nausea, hypoglycemia, diarrhea, constipation, vomiting, headache, decreased appetite; >5% dyspepsia, fatigue, dizziness, abdominal pain and increased lipase (vildagliptin) | [46,108,146] |
| DPP-4 inhibitors             | Decrease     | Neutral       | Headache, nasopharyngitis, urinary tract infection, upper respiratory tract infection; elevated liver enzymes | [46,47,165-169] |
| SGLT-2 inhibitors            | Decrease     | Decrease      | Urinary tract infections, yeast infections, hypovolemic symptoms | [80,81,107] |
| Metformin                    | Decrease     | Decrease      | Moderate gastrointestinal symptoms (diabetes, nausea/vomiting, flatulence), low risk of lactic acidosis | [60,61,63,170] |
| TZD                          | Decrease     | Increase      | >10% upper respiratory tract infection; >5% headache, sinusitis, myalgia and pharyngitis Adverse events of special interest: Moderate bone loss, may exacerbate fluid retention, heart failure | [69,71,75,76] |
| \(\alpha\)-Glucosidase inhibitors | Decrease   | Neutral       | Moderate gastrointestinal symptoms (flatulence, diarrhea and stomachache) | [97,99,171,172] |
| Colesevelam                  | Decrease     | Neutral       | Mild gastrointestinal symptoms (constipation) | [91,173] |
| Bromocriptine-QR             | Decrease     | Neutral       | Moderate gastrointestinal symptoms (>10% nausea, rhinitis, headache, asthma, dizziness, constipation, sinusitis; >5% diabetes, amylloypa, dyspepsia, vomiting, infection, anorexia) | [93,95,174] |
| Sulfonylurea                  | Decrease     | Increase      | Hypoglycemia, increased hypoglycemia risk with renal impairment, asthma, headache, dizziness, nausea, diarrhea, epigastric fullness, heartburn | [5,21,37,38,175-177] |
| Glinides                     | Increase     | Neutral       | Mild hypoglycemia, upper respiratory tract infection, sinusitis, constipation, arthralgia, headache, vomiting | [43,162,163] |
| Ranolazine                   | Decrease     | Neutral       | Dizziness, headache, constipation, nausea | [102,103,180] |
| Pramlintide                  | Decrease     | Decrease      | Mild-to-moderate nausea, vomiting, anorexia, headache, and mild-to-moderate hypoglycemia | [100,101] |
| Insulin                      | Decrease     | Increase      | Hypoglycemia | [5,178,179] |

\(^a\)Common adverse events are reported based on clinical studies in patients with T2DM.

Abbreviations: DPP-4 = Dipeptidyl-peptidase-4; ER = Extended release; GLP-1 = Glucagon-like peptide-1; HbA1c = Glycated hemoglobin; QR = Quick release; SGLT-2 = Sodium-glucose co-transporter 2; T2DM = Type 2 diabetes mellitus; TZD = Thiazolidinedione.

Incretins should be used to replace sulfonylureas and glinides, primarily for their efficacy, ability to preserve \(\beta\) cells and the likelihood that they will decrease adverse cardiovascular outcomes [57,58]. Despite the relatively high cost of incretins, we posit that if the cost of hypoglycemia is taken into consideration (e.g. emergency room visits, hospital admissions, home glucose testing and other impacts on quality of life), the differences in true cost between incretins and sulfonylureas are more modest than they initially appear. This is especially true, given that any cost savings associated with the use of sulfonylureas are quickly nullified, since they lose effectiveness in 1–3 years due to \(\beta\)-cell apoptosis [57,59]. Moreover, starting with sulfonylureas is an illogical process based on clinical studies in patients with T2DM. Lorcaserin Decrease Decrease Headache, back pain, nasopharyngitis, nausea

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**Biguanides**

Metformin (brand names include GLUMETZA\(^\text{®}\), GLUCOPHAGE\(^\text{®}\), FORTAMET\(^\text{®}\) and RIOMET\(^\text{®}\)) decreases hepatic glucose output and lowers fasting glycemia [60,61]. Metformin remains the drug most often recommended by guidelines for monotherapy. It has an established safety record, is weight-neutral and may impart cardiovascular benefits [62]. When administered as monotherapy, metformin has been found to lower HbA1c by ~1.5% [61]. The most common adverse effects of metformin are gastrointestinal impairments [61]; lactic acidosis occurs rarely (4 cases per 100,000 treated patient-years). Lactic acidosis is of concern due to its potentially fatal outcome [63], but cautious use of metformin, even in mild-to-moderate chronic renal impairment, has been advocated [64]. Metformin does not cause hypoglycemia and has been used safely in patients with prediabetes [60,65]; it is either weight-neutral or elicits modest weight loss [60,61]. In the large-scale United Kingdom Prospective Diabetes Study, a beneficial effect of metformin therapy on cardiovascular disease (CVD) was observed [66]. Moreover, during the 10-year follow-up of the Diabetes Prevention Program Outcomes Study, the original lifestyle group experienced weight loss, but then had a partial weight gain. The group of patients who were taking metformin lost a mean of 2.5 kg during the program.
and kept most of the weight off during the follow-up period [67].

**Thiazolidinediones**

Thiazolidinediones (TZDs) are agonists of the peroxisome proliferation-activated receptor γ (PPAR-γ), which regulate glucose homeostasis and lipid metabolism [68]. Pioglitazone (ACTOS®) has beneficial effects on insulin sensitivity and can improve β-cell function and reduce poor cardiovascular outcomes [68-70]. TZDs lower HbA1c by ~1–1.5%; however, the effects may not occur for up to 3 months after initiation of therapy [71].

Hypoglycemia is an unlikely adverse effect, and pioglitazone can be used in patients with renal disease or renal failure. TZDs may cause bone loss and increase fracture risk in women, however, and therefore, use of anti-osteoporotic drugs in at-risk women must be considered [72]. Pioglitazone is contraindicated in class III or IV congestive heart failure or hepatic impairment with alanine aminotransferase >3 times the upper limit of normal [71,73,74]. Weight gain is a possible side effect with pioglitazone, but studies have shown that this effect can be minimized with education [75], control of meal portion sizes [76] and concurrent use of a GLP-1 agonist [77]. The purported association of pioglitazone with bladder cancer has been recently discounted by the negative results of the 10-year randomized, prospective Kaiser-Permanente trial, acknowledged in the 2015 American Diabetes Association (ADA) diabetes guideline update [78].

**SGLT-2 inhibitors**

Currently, there are three SGLT-2 inhibitors approved as treatments for T2DM: canagliflozin (INVOKANA®), dapagliflozin (FARXIGA™) and empagliflozin (JARDIANCE®) [79]. SGLT-2 inhibitors reduce the reabsorption of filtered glucose from the kidney tubules back into the bloodstream, thereby lowering plasma glucose levels [80]. SGLT-2 inhibitors are associated with decreased HbA1c, fasting plasma glucose (FPG) and postprandial glucose, as well as improved BP and β-cell function [80,81]. Furthermore, they have been associated with reductions in body weight [80]. When we consider the mechanism of action of SGLT-2 inhibitors, the weight-loss effect that occurs is to be expected, as glucose excretion as a consequence of SGLT-2 inhibition results in a loss of calories [79]. Combining SGLT-2 inhibitors with GLP-1 agonists produces an added weight-loss benefit [82]. Moreover, by virtue of the weight-loss benefit associated with reducing insulin resistance, SGLT-2 inhibitors treat five of the eight elements of hyperglycemia outlined in DeFronzo’s Ominous Octet [26].

Side effects of SGLT-2 inhibitors include a modest increased risk of urinary tract infections, increased risk of genital yeast infections and hypovolemic symptoms [80]. The likelihood of these effects can be minimized by advising patients to drink liquids and maintain fastidious bathroom habits, as well as by adjusting diuretic and anti-hypertensive therapies. Additionally, because the mechanism of action of SGLT-2 inhibitors is independent of the action of insulin and diminishes as patients’ plasma glucose concentrations decrease, the intrinsic risk of hypoglycemia is low [79]. These agents may be used to take patients off sulfonylureas and glinides; additionally, insulin doses may be reduced by ~20% when starting an SGLT-2 inhibitor, thus maximizing potential weight reduction [83].

Those who worry about the effects of long-term hyperglycemia on kidney function can find solace in findings that lifespan is not reduced in families with a genetic absence of SGLT-2 [84,85]. In addition, a drug that controls blood sugar, and
reduces BP, microalbuminuria, hyperfiltration and weight theoretically points to renal safety and potential benefit over time.

Insulin

Insulin is very effective at lowering glycemia, but it is associated with hypoglycemia and weight gain of 2–4 kg [5,20]. Current standard therapy in patients with type 1 diabetes is a basal/bolus insulin regimen in which patients maintain basal glycemic control with long-acting insulin analogs, and post-prandial control with rapid-acting insulin. As a result, there is less risk of hypoglycemia or weight gain [86].

Using insulin to maintain glycemic control in patients with T2DM and obesity can prove difficult [87]. Weight gain due to a diet high in calories, fat and simple carbohydrates can necessitate increases in basal doses of insulin to maintain control of blood glucose, storing all the calories they shouldn’t be eating in the first place. Correspondingly, patients have increased appetite prior to meals and may consume excess calories. The cycle of weight increases, recurrent hypoglycemia and overeating that leads to inappropriate insulin correction and, as a result, poor control, creates a challenge for healthcare providers in treating diabetes and obesity. Figure 2 demonstrates this vicious cycle.

As noted above, numerous agents should appear in the paradigm of care before considering basal insulin. Additionally, basal insulin therapy should be delayed until the patient and medical team feel certain the patient can adhere to a eucaloric diet. Once patients have removed simple carbohydrates from their diet and are controlling their calories by eating moderate amounts of high-fiber foods, complex carbohydrates, lean proteins and heart-healthy fats, insulin may be considered [88].

In fact, implementation of this diet can often prevent use of insulin in the first place [89]. If basal insulin is still required, it will be used in conjunction with the non-insulin therapies, with a predicted >90% likelihood of being able to avoid bolus insulin [83,87], which carries 85% of the risk of hypoglycemia seen with basal/bolus therapy [90].

Other available anti-hyperglycemic options

Colesevelam (WELCHOL®) can reduce HbA1c levels by 0.5% in patients receiving metformin or a sulfonylurea [91]. The most common adverse events (AEs) are gastrointestinal disturbances, the risk of hypoglycemia is low (incidence is ~3%) [91,92] and colesevelam is weight-neutral [91].

Bromocriptine-QR (quick release; CYCLOSET®) reduces HbA1c by 0.5–0.9%, presumably by inducing a dopamine surge in the hypothalamus, thereby increasing peripheral insulin sensitivity [93-95]. No undue hypoglycemia was observed in Phase III studies, and bromocriptine-QR is weight-neutral [93]. The most common AE was nausea, but the incidence decreases after the initial titration period [95]. Although hypotension and cardiac valve fibrosis were safety concerns with bromocriptine, a 1-year safety study in patients with diabetes showed a 40% reduction in cerebrovascular accident, myocardial infarction, hospitalization for congestive heart failure or acute coronary syndrome or coronary revascularization, ostensibly due to a reduction in sympathetic tone [93,94].

In glucose-intolerant/insulin-resistant rodents, bromocriptine plus exendin-4 therapy normalized glucose intolerance without raising plasma insulin levels, suggesting a synergistic effect between dopamine agonism and GLP-1 analog therapy [96]. In clinical practice, physicians have noted weight loss with bromocriptine-QR co-treatment, suggesting that bromocriptine-QR may increase sensitivity to GLP-1 therapy.

α-Glucosidase inhibitors (acarbose [PRECOSE®], miglitol [GLYSET®]) work by decreasing the rate of absorption of glucose from the gastrointestinal tract [20], and have been found to decrease HbA1c by −0.5–0.8% [20,97]. They are weight-neutral, without a risk of hypoglycemia [20,97], and may delay or prevent diabetes progression [98]. The use of these agents remains limited, however, due to the high incidence of gastrointestinal adverse effects [20,97-99].

Pramlintide (SYMLIN®) is an amylin analogue indicated as adjunctive therapy with insulin, with or without sulfonylurea or metformin [100,101]. In patients with diabetes treated with insulin glargine with or without oral anti-diabetic agents, pramlintide was found to lower HbA1c levels by 0.7%, while patients receiving placebo had reductions of 0.36% (p < 0.05) [100]. Impressively, despite being used in combination with insulin, pramlintide was associated with weight loss (1.6 kg). Common side effects included nausea and hypoglycemia, both of which were characterized as mild to moderate [100].

Ranolazine (RANEXA®) is a first-in-class anti-angina drug with cardioprotective properties that also lowers glucose [102]. In patients with diabetes and non-ST segment elevation acute coronary syndromes, ranolazine reduced HbA1c by 1.2%. There was no significant difference in the number of cases of serious hypoglycemia between ranolazine- and placebo-treated patients [102], and treatment was weight-neutral [103]. Ranolazine is currently awaiting approval for an indication for its use in diabetes.

The new paradigm of diabetes care: Importance of body weight management

Treating the patient with diabetes begins with dietary counseling. Most patients are overweight at the first visit; for normal weight patients, it is paramount to employ pharmacological and overall strategies to avoid weight gain and fully attend to weight management issues from the start of care. A practical recommendation for most patients is a “no concentrated
sweet” diet with hard fruits at mealtime, to decrease the rate of absorption of fruit sugars and still provide “sweetness” [104], keeping in mind that the best “diet” is ultimately the diet to which a patient will adhere.

Our overarching philosophy for patients requiring pharmacotherapy is early combination therapy with agents that will not promote hypoglycemia while engendering weight loss or that will at least be weight-neutral. We do not advocate “first-, second-, third-line” therapeutic hierarchies or competition between classes. The American Diabetes Association/ European Association for the Study of Diabetes (ADA/EASD) cautions against risks of weight gain and hypoglycemia. Despite this, it recommends delaying combination therapy until HbA1c is >9.0 [6,62,87]. In 2013, the American Association of Clinical Endocrinologists (AACE) issued new treatment algorithms for patients with T2DM [29], which emphasize quality of glycemic control and safety, stating that “minimizing risk and severity of hypoglycemia, minimizing risk and magnitude of weight gain” are priorities [29]. More consistent with our approach than the ADA guidance, AACE advocates early combination therapy — when HbA1c is >7.5 [29]. The guidelines are in agreement that sulfonylureas be given the lowest priority, for the reasons discussed above.

Choosing “weight-friendly” anti-diabetes agents and processes of care

A patient-centric, evidence-based practice approach is fundamental, and some combinations of medications can be particularly advantageous [87,105,106]. For instance, patients can lose between 3.5 and 6.0% of body weight when using an incretin or SGLT-2 inhibitor [107,108], and a synergistic benefit can be attained when using these agents successively or simultaneously [109]. Likewise, a DPP-4 inhibitor along with an SGLT-2 inhibitor can elicit the same glycemic and weight benefits as a GLP-1 agonist. Because a large-scale study of combination use of these agents has not yet been published, the 2015 ADA/EASD consensus paper [62] has noted that an evidence-based recommendation for the combination of SGLT-2 inhibitors and GLP-1 agonists cannot be made at this time. A post hoc analysis demonstrated benefits including weight loss and lower HbA1c when canagliflozin was added to a DPP-4 inhibitor or GLP-1 agonist. The combination was generally well tolerated in patients with T2DM [82]. Additionally, a small UK observational study suggests that patients who were prescribed both dapagliflozin and a GLP-1 agonist had greater weight loss than those taking dapagliflozin alone [110]. The weight gain associated with pioglitazone may be mitigated by including a GLP-1 agonist or SGLT-2 inhibitor in the regimen [111]. Additionally, synergistic weight loss with bromocriptine-QR in addition to a GLP-1 agonist has been observed.

For patients requiring add-on medications to their existing regimens, a GLP-1 agonist and/or SGLT-2 inhibitor is recommended before initiating insulin therapy. We strongly encourage delaying basal insulin therapy, based on associated increased risks of hypoglycemia and concomitant weight gain. In those patients who require basal insulin, the need for bolus insulin can be obviated [83,87], and thus the additional risks of hypoglycemia and weight gain are reduced in the vast majority of patients by preserving β-cell function. Use of GLP-1 agonists results in weight reduction with minimal hypoglycemic risk [112]. A DPP-4 inhibitor could also be added to the regimen instead of, or prior to, advancing care to insulin use; a weight-neutral response and smaller HbA1c reduction would be expected with a DPP-4 inhibitor compared with a GLP-1 agonist. Combining GLP-1 agonists with basal insulin has proven effective, allowing 40–80% of patients to reach FPG targets [113], thereby obviating the need for bolus insulin. An additional 20–30% of patients achieve control of FPG levels with SGLT-2 inhibitors and basal insulin. The addition of metformin, pioglitazone or bromocriptine-QR to basal insulin therapy is successful in reaching target levels in some patients who are refractory to GLP-1 agonist or SGLT-2 inhibitor treatment. It is estimated that >90% of patients on basal and three non-insulin therapies will not need bolus therapy, which we see as highly favorable, since it has been shown that 85% of hypoglycemic risk in basal/bolus therapy is due to bolus insulin [90].

A “no concentrated sweet” diet and three-drug therapy for 3 days to quickly reverse hyperglycemia in patients with HbA1c >9.0 is successful in most instances. If the patient is adherent to the diet yet remains symptomatic after 3 days, basal insulin may be started. Non-insulin agents, particularly incretins and SGLT-2 inhibitors, are generally continued when starting basal insulin.

Accordingly, insulin therapy should be reserved for select patients and situations. This includes patients with type 1 diabetes, including those who are ketosis-prone and absolute insulin-deficient patients; initial T2DM patients who have progressed to become ketosis-prone; absolute insulin-deficient patients (i.e. latent autoimmune diabetes in adults); those patients with “Flatbush diabetes” [114], whose reduction in β-cell function is so severe that they present in diabetic ketoacidosis; and those individuals who, for reasons of safety, tolerability or specific comorbidities cannot use one or more of the non-insulin agents discussed.

Lifestyle management of insulin-associated weight gain requires a strict eucaloric or hypocaloric diet. For those already adhering to such a diet, additional calorie reductions should be implemented, along with proportionally decreased insulin doses [87,88].

For patients with obvious hypoglycemia or a history of lacking hypoglycemia awareness, even greater insulin reduction is needed. One strategy for patients receiving basal or basal plus bolus insulin is decreasing insulin doses by 25% if hypoglycemia episodes are experienced, and an additional 25% if the patient starts a “no concentrated sweet” diet [83,88]. The estimated new insulin dose can be further reduced by 25% if a GLP-1 agonist is added, or by 20% if an SGLT-2 inhibitor is added. Using this protocol, patients using ≤40 units of insulin daily can stop insulin at the first visit. Others on >40 units/day can have progressive decreases in insulin — with the expected progressive weight loss from additive GLP-1, SGLT-2 and improved insulin sensitivity engendered by metformin, pioglitazone or bromocriptine-QR [88].
Strategies for body weight management in patients with diabetes

Current guidelines recommend weight loss therapy for all patients with T2DM who are obese or overweight with indicators of cardiovascular risk [115], a strategy followed in our practice, as well. The three types of therapy to be considered, in order of intensity, are lifestyle modification, pharmacotherapy and bariatric surgery (Table 2).

Lifestyle modification

Current guidelines recommend reducing calorie intake by 500–750 kcal/day, to attain a target for total caloric consumption of 1200–1500 kcal/day for women and 1500–1800 kcal/day for men [115]. Mediterranean or low-carbohydrate diets are the authors’ frequent recommendation to patients [116]; however, recent studies have shown the best practice is the recommendation of any diet that a patient will follow for successful weight loss and management [117]. Thus, an individualized diet plan created for the patient as a “one-size-fits-all” approach to diet is not advisable. The AHA/ACC/TOS Obesity Guidelines recommend any one of the following prescriptions for food and calorie intake reductions [115]:

1. 1200–1500 kcal/day for women and 1500–1800 kcal/day for men (kilocalorie levels are usually adjusted for the individual’s body weight);
2. A 500- or 750-kcal/day energy deficit or
3. One of the evidence-based diets that restricts certain food types (such as high-carbohydrate foods, low-fiber foods or high-fat foods) in order to create an energy deficit.

Practitioners may find it helpful to counsel patients that eliminating even 125 kcal/day can engender a 1 lb/month weight loss — without the onerous chore of counting every calorie consumed [118]. For example, our advice to patients includes having 2 fewer pieces of bread each day (or an equivalent amount of kcals), which can yield ~2 lbs of weight loss monthly. Though more recent work by Hall et al. provides a more conservative estimate of effect of calorie reduction on weight loss achieved, the authors find the estimate by Rosenbaum et al. to serve patients well [118,119].

Weight loss may be facilitated by the incorporation of ≥150 min of moderate-intensity activity per week (≥30 min/day, most days of the week) [115]. Even a moderate-pace walk (1.5 miles in 30 min) can result in a 2 lb/week weight loss [115,120]. A comprehensive lifestyle modification program that includes behavior therapy and interventions to help patients understand not only what to eat and what not to eat, but how to best make lasting changes, can improve adherence to diet and exercise recommendations. The behavior change process employs self-monitoring (use of a diary or record of food intake and physical activity), goal setting and problem solving [121,122]. Very clear and measurable goals are key for behavioral change; these should involve small changes that are possible to achieve without a great deal of effort, rather than large changes that are less likely to become permanent. Programs generally include on-site counseling by a trained interventionist, although electronically delivered or commercially available programs can also be used [115].

Pharmacotherapy for obesity

Diet and exercise alone may be insufficient to engender and maintain weight loss in the diabetic state, as adaptive mechanisms are turned on to counteract weight loss and management [117]. Thus, an individualized diet plan created for the patient as a “one-size-fits-all” approach to diet is not advisable. The AHA/ACC/TOS Obesity Guidelines recommend any one of the following treatments for food and calorie intake reductions [115]:

- Pharmacotherapy
- Bariatric surgery
- Lifestyle modification

Table 2. A guide for selecting treatment for obesity.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>BMI (kg/m²)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>25.0–26.9</td>
</tr>
<tr>
<td>Lifestyle modification</td>
<td>Indicated with comorbidities</td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td>Not indicated</td>
</tr>
<tr>
<td>Bariatric surgery</td>
<td>Not indicated</td>
</tr>
</tbody>
</table>

Data taken from [115,181].
Abbreviation: BMI = body mass index.
Lorcaserin (BELVIQ®)

Lorcaserin is a selective 5-HT2C (serotonin) receptor agonist approved for weight loss in obese patients or patients with a BMI of ≥27 kg/m² with a weight-related comorbidity [128]. Lorcaserin is thought to regulate satiety by facilitating release of α-melanocyte-stimulating hormone from hypothalamic pro-opiomelanocortin/cocaine neurons [129]. The efficacy of lorcaserin has been demonstrated in patients with and without T2DM. In patients with T2DM, the Behavioral Modification and Lorcaserin for Overweight and Obesity Management in Diabetes Mellitus (BLOOM-DM) study evaluated lorcaserin for weight management for 1 year in patients with overweight and obesity; weight change was −5.5% with lorcaserin twice daily (BID) vs. −1.7% with placebo (completer population) [130]. Patients receiving lorcaserin achieved significantly greater weight loss (37.5% of patients had reductions of ≥5% of body weight with lorcaserin 10 mg BID vs. 16.1% with placebo) and had significantly greater reductions in both HbA1c (−0.9 with lorcaserin 10 mg BID vs. −0.4 with placebo) and FPG (−27.4 mg/dl with lorcaserin 10 mg BID vs. −11.9 mg/dl with placebo) [130]. Significant reductions in FPG were seen in patients taking lorcaserin beginning at week 2 (prior to significant changes in weight), suggesting some beneficial effects of lorcaserin on glycemic control may be weight-independent [131]. Of note, among patients who were weight loss non-responders (weight loss <5% at week 12), those receiving lorcaserin had greater reductions in HbA1c than those receiving placebo after 1 year [131].

A 2-year trial of lorcaserin in patients without diabetes (Behavioral Modification and Lorcaserin for Overweight and Obesity Management [BLOOM]) demonstrated weight gain when lorcaserin recipients were re-randomized to placebo at 1 year, suggesting a need for long-term use to sustain weight-loss benefit [132]. Common AEs in patients with T2DM include headache, back pain, nasopharyngitis and nausea [130]. Although hypoglycemia was seen more often with lorcaserin than with placebo, the rates were comparable (7.4% lorcaserin 10 mg BID vs. 6.3% placebo), and lorcaserin has proved to be very well tolerated in clinical practice [128]. In addition, experience shows that hypoglycemic risk can be mitigated by decreasing the dose of hypoglycemic agents as a patient loses weight.

In the past, serotonergic pathways were targeted by the non-specific serotonergic agonists fenfluramine and dexfenfluramine, but these products were withdrawn from the market in 1997 due to 5-HT2B receptor-mediated cardiac valvulopathy [133]. Lorcaserin has a functional selectivity for 5-HT2C receptors ~100 times greater than its selectivity for 5-HT2B receptors [134], and after 1 year of treatment, echocardiographic analysis of 5249 patients on lorcaserin found similar risks of FDA-defined valvulopathy in patients treated with lorcaserin and placebo [135].

Phentermine/topiramate extended-release (QSYMIA®)

The phentermine/topiramate extended-release (ER) fixed combination is approved for chronic weight management in obese patients or patients with BMI ≥27 kg/m² with a weight-related comorbidity [136]. The sympathomimetic effect of phentermine acts to suppress appetite, and the anxiolytic and migraine medication topiramate acts to prolong satiety. The mechanism by which the combination of these drugs promotes weight loss is unknown. Approved dosages of the drugs in combination are lower than the recommended doses of topiramate ER for neurologic indications and phentermine for weight loss [137]. Dosing is slowly uptitrated to a potential maximum dose of phentermine 15 mg/topiramate ER 92 mg. If by 24 weeks of total therapy the patient has not lost ≥5% of baseline body weight, it is unlikely that benefit will be derived from further treatment. However, because sudden discontinuation of treatment could precipitate a seizure, phentermine 15 mg/topiramate ER 92 mg should be dosed every other day for a minimum of 1 week prior to discontinuation [136].

Two Phase III clinical trials of phentermine/topiramate ER demonstrated 1-year mean weight loss of 10.9% (at 15/92 mg dose vs. 1.6% with placebo) in the EQUIP trial [138], and 9.8% mean weight loss (at 15/92 mg dose vs. 7.8% at 7.5/46 mg dose vs. 1.2% with placebo) in the CONQUER trial [139]. Progression to T2DM was reduced by 54 and 76% in patients receiving mid- (7.5/46 mg) and high-dose (15/92 mg) phentermine/topiramate ER, respectively, compared with placebo (completer population) [140]. Phentermine/topiramate ER has not been studied in patients with T2DM who are being treated with insulin or sulfonylureas [141]. Adverse events commonly associated with phentermine/topiramate ER include paresthesia, dizziness, dysgeusia, insomnia, constipation and dry mouth [136]. In addition, even at lower doses, our experience is that patients discontinue the drug or express concerns about a “mental fog” associated with topiramate use that inhibits normal daily functioning.

Naltrexone/bupropion (CONTRAVER®)

Naltrexone is an opioid antagonist, and bupropion is a relatively weak inhibitor of the neuronal reuptake of dopamine and norepinephrine. Naltrexone and bupropion have effects on two separate areas of the brain involved in the regulation of food intake: bupropion acts to reduce food intake via adrenergic and dopaminergic signaling at the hypothalamus; naltrexone attenuates the orexigenic β-endorphin signals while facilitating unopposed α-melanocyte-stimulating hormone satiety signals [142,143]. Naltrexone/bupropion is indicated for obese patients or patients with BMI ≥27 kg/m².
with at least one weight-related comorbidity [144]. In the Phase III Contrave Obesity Research (COR-I and COR-II) studies, there was a significant reduction in weight with naltrexone plus bupropion treatment (6.1 and 6.4%, respectively) as compared with placebo (1.3 and 1.2%, respectively) at 56 weeks [142,145]. In patients with T2DM, compared with placebo, naltrexone/bupropion yielded greater weight reduction (5.0 vs. 1.8%, respectively) and greater HbA1c reduction (0.6 vs. 0.1%, respectively) [143,144]. The most common AEs are nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth and diarrhea [144]. In addition, the CONTRAVE prescribing information contains a black box FDA warning for suicidal thoughts and behavior as well neuropsychiatric reactions [144].

Liraglutide (SAXENDA®)

Liraglutide (3 mg) is a GLP-1 receptor agonist indicated for weight management in obese patients and in patients with a BMI of ≥27 kg/m² with a weight-related comorbidity [146,147]. A lower dose of liraglutide (1.8 mg) is marketed under the name VICTOZA®, indicated for treatment of T2DM [147,148]. Weight loss with this agent (under either brand name) is due to GLP-1 agonism in the central nervous system, which increases satiety and thus reduces food intake and body weight [146,149]. It also slows gastric emptying, providing patients with a feeling of stomach fullness earlier than usual, which also leads to decreased food intake [150] and, in a mouse model, increased thermogenesis [151].

The efficacy of liraglutide for weight loss and maintenance has been demonstrated in ~4800 patients with and without T2DM [147]. In patients with T2DM and overweight or obesity, 1-year treatment with liraglutide resulted in a 3.7% greater weight loss than with placebo, with more liraglutide-treated patients achieving weight loss ≥5% (liraglutide, 49% vs. placebo, 16%). In another 1-year study in patients with overweight or obesity but without T2DM, liraglutide treatment resulted in a 4.5% greater weight loss than with placebo, and more patients achieved weight loss ≥5% (liraglutide, 62% vs. placebo, 34%) [146]. In a third study of weight maintenance, patients who were overweight (with at least one comorbidity) or obese were treated with liraglutide or placebo following a 12-week, low-calorie diet run-in period, and were only randomized if they achieved body weight loss ≥5% [108]. One year following randomization, liraglutide-treated patients achieved greater weight loss (liraglutide, 6.2% vs. placebo, 0.2%; \( p < 0.0001 \)), and more patients lost ≥5% of body weight from the time of randomization [108]. Not surprisingly, liraglutide treatment also produced statistically significant improvements vs. placebo in HbA1c, FPG and fasting insulin [108].

In clinical trials, the most common AEs (reported in ≥5% of patients) associated with liraglutide were nausea, hypoglycemia, diarrhea, constipation, vomiting, headache, decreased appetite, dyspepsia, fatigue, dizziness, abdominal pain and increased lipase [146]. From a practical clinical point of view, stopping sulfonylureas and glinides altogether, reducing insulin doses by 25% and re-titrating as needed can minimize the hypoglycemic risk seen in these studies. Though captured as a side effect, decreased appetite is desired for weight reduction, and dyspepsia, nausea and vomiting can be minimized if patients follow instructions to stop eating at the first sense of stomach fullness as they partake in a meal. Usual office therapies are effective in addressing loose stools (adding fiber) and constipation (encouraging fluids and fiber in the diet). FDA labeling includes a caution to avoid liraglutide use in patients with a history of pancreatitis; our practice is to stop liraglutide in those patients with new abdominal pain until it is proven that the patient does not have pancreatitis. However, a recently published assessment from the FDA and European Medicines Agency (EMA) reassures us that evidence is lacking regarding a causal relationship between GLP-1 therapy and pancreatitis or pancreatic cancer [152]. This conclusion is supported by other recent data, as well [153,154].

Bariatric surgery

Bariatric surgery may be considered in patients with a BMI of ≥40 kg/m², or ≥35 kg/m² if serious weight-related health complications are also present [115]. In the USA, roux-en-Y gastric bypass (GBP) and laparoscopic adjustable gastric banding (LAGB) are the most common procedures [155]. A systematic review and meta-analysis of 621 studies that measured the impact of bariatric surgery on T2DM showed that following surgery, patients with diabetes had a mean weight loss of 64.4% for all procedures. Furthermore, 78.1% of patients were no longer diabetic, and diabetes improved or regressed in 86.6% of patients [156].

Emerging data suggest that patients with mild to moderate, class 2 obesity (BMI 35.0 – 39.9 kg/m²), and patients with class 1 obesity (BMI 30.0 – 34.9 kg/m²) [115] along with diabetes or other obesity-related comorbidities, can benefit from LAGB, a finding supported by the International Diabetes Federation and the FDA [157]. Durable reductions in weight, HbA1c and BP were seen in long-term follow-up (mean of 6.9 years) of severely obese patients following laparoscopic GBP [158]. However, 19% of patients relapsed to diabetes, a tendency related to preoperative duration of diabetes and preoperative level of HbA1c [158]. A meta-analysis of bariatric surgery techniques by the Cochrane group could find no definitively superior technique among GBP, laparoscopic-assisted GBP and LAGB [159]. This same analysis found, however, that surgical interventions yielded improvements in diabetes outcomes and health-related quality of life in randomized-controlled trials of bariatric surgery vs. non-surgical interventions [159]. Thus, despite the inherent risks, bariatric surgery can provide benefit to patients with diabetes. Moreover, additional studies of patients who received an endoscopic duodenal-jejunal bypass liner in lieu of these surgical procedures [160] demonstrate that similar results are possible without surgical intervention.

Recommendations: Weight loss agents

We recommend use of the newer anti-obesity medications in patients who would benefit from additional weight loss, if GLP-1 renin–angiotensin system (RAS)/SGLT-2 inhibitors are
being used for diabetes management but are insufficient. We find the fewest side effects with lorcaserin, but most patients can tolerate naltrexone/bupropion. However, in a patient receiving other anti-depressant therapy, naltrexone/bupropion should be avoided. Thus, lorcaserin is our preferred weight-reduction medication for patients with a history of depression, although these patients should be monitored for the emergence or worsening of depression when being treated with lorcaserin [128]. In our clinical practice, few patients seem to tolerate topiramate/phenetermine combination therapy, and we worry about phentermine in patients with diabetes.

Anti-obesity drugs can be valuable as co-treatment in patients receiving GLP-1 agonist and/or SGLT-2 inhibitor therapy, or for pre-operative weight reduction in bariatric procedures to reduce surgery-associated risks, and may, in fact, obviate the need for bariatric procedures. The Endocrine Society Clinical Practice Guidelines recommend the use of new anti-obesity agents in patients with diabetes who require additional weight loss [125]. Although other diabetes guidelines have not incorporated these agents into their published recommendations, an “evidence-based practice” approach logically argues for their use in patients with diabetes to achieve weight loss over and above what is attained with diet, exercise, GLP-1 agonists and SGLT-2 inhibitors.

Data regarding combination therapy with two or more novel anti-obesity regimens is notably lacking at present, and such therapy should therefore be avoided. However, combining liraglutide and/or an SGLT-2 inhibitor with one of the more novel anti-obesity agents is quite reasonable. Evaluation at regular intervals for weight loss targets is prudent, as is provision of appropriate patient education and tools for lifestyle changes.

Summary

Strong evidence exists to support treatment of both diabetes and obesity, despite the fact that overweight and obesity within the diabetes population is not being effectively controlled. Interventions now exist that better manage weight in patients not at a healthy BMI despite lifestyle modification. To preserve β-cell function in patients with prediabetes for whom a “no concentrated sweet” diet has been unsuccessful in lowering HbA1c within 3 months [161], we recommend combination therapy with up to three agents — four if necessary, tolerable, safe and affordable. Clinicians should preferentially use “weight friendly” anti-diabetes therapies; GLP-1 agonists, SGLT-2 inhibitors and metformin are noteworthy for their ability to induce weight loss. In all cases, sulfonylureas and glinides should be avoided, based on their attendant weight gain, as well as the risk of hypoglycemia, and the limited duration of effectiveness of sulfonylureas due to their contribution to β-cell destruction. We advocate reducing reliance on insulins, both in terms of timing of initiation of basal insulin, and use of bolus insulin.

Declaration of interest

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