Clinical Brief: Should Diabetes Management be More Adipose-centric?

Introduction

Obesity and type 2 diabetes are closely related; more than 90% of people with type 2 diabetes also have overweight or obesity and more than 20% of people with obesity also have type 2 diabetes [1]. Obesity is one of the main modifiable risk factors for diabetes and adverse cardiovascular events, the latter being the leading cause of mortality in patients with type 2 diabetes [2]. In fact, the rise in the prevalence of both diabetes and obesity is a global health challenge and it has been estimated that ~60% to 80% of people with diabetes have a BMI≥30 kg/m2 [3]. The co-occurrence of diabetes and obesity is now commonly termed "diabesity"- a new worldwide epidemic.

Several studies have corroborated the fact that weight loss can be an effective strategy to mitigate the risk of obesity-related comorbidities, including risk of type 2 diabetes and cardiovascular mortality, leading to improvements in lipid profile, blood pressure, severity of obstructive apnea, and health-related quality of life [4]. In fact, weight loss of as little as 5% in people with diabetes can improve cardiometabolic risk factors, and a weight loss of >10% can reduce cardiovascular morbidity and mortality, as demonstrated in the LOOKAHEAD study [5]. This leads to a very pertinent and widely discussed question -- whether the management of diabetes should be more adipose-centric, or whether obesity management should be a primary treatment target for patient with type 2 diabetes [6].

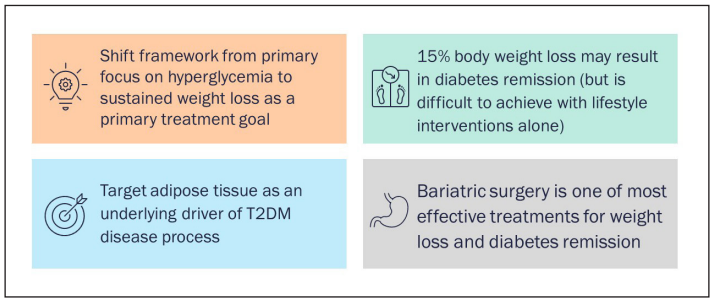

Figure 1: Should diabetes management be more adipose-centric? [6]

Inertia and Challenges in Obesity Management

In the last decade, several studies have shown that many clinicians perceive obesity as a social and behavioral issue brought on by poor lifestyle choices [7-9], and most reported feeling unprepared for their medical training when it comes to treating overweight patients, with some believing that treating obesity is "futile" [8, 9]. As such, it is not surprising that providers still incorrectly document or screen for obesity, recognition of obesity as a disease remains low, including in patients with type 2 diabetes, and consequently, although obesity prevalence is increasing, diagnostic rates remain low [10-13].

Establishing obesity as a disease is often the first step to improving outcomes, however, clinicians often do not know how to approach and initiate the conversation about obesity management with their patients [14, 15]. Surveys have demonstrated that often in obesity-related consultations; clinicians often think that being overweight was not a serious issue or even worse, they tend to judge their patients and fail to motivate them to adhere to weight-loss strategies [14, 15]. Patients reported that clinicians offered banal advice assuming that the patients were unhealthy or were not trying to address their weight, and assumed that other health symptoms were due to obesity without a proper medical history or examination [14]. Much of the inertia can be attributed to clinicians being busy treating other chronic diseases, lack of comfort with prescribing weight-loss interventions, as well as misconceptions about the efficacy and safety of pharmacological treatments and other intensive approaches for treating obesity.

Many studies have underscored the advantages and the impact of lifestyle modifications on weight loss. Improving diet and physical activity can lead to a typical reduction of weight by 5% - 10%, which as mentioned above can have significant benefits on outcomes; however, these changes are difficult to maintain and weight regain is common [16, 17]. According to our expert faculty, Jennifer Green, MD, Professor of Medicine at Duke University School of Medicine,

> "While losing weight, our brain has kind of a weight-happy place and when we move away from that, our brain is unhappy and alters hormone levels to counteract it, so our body makes it more difficult to continue to lose weight once we've started losing and unfortunately, it tends to make us regain the weight back".

This is supported by studies showing that ghrelin, --the hunger hormone -- increases with weight loss, and leptin—which helps prevent hunger and regulate energy balance—decreases with weight loss [18].

Meta-analyses have shown that approximately 50% to 80% of the lost weight is generally regained within 3-5 years and it is harder, especially for people with T2DM, to lose weight only with lifestyle changes. As such, it is pertinent to consider or add anti-obesity medications as adjunct to lifestyle therapy in people with weight-related complications (including uncontrolled diabetes), those who have difficulties losing weight with lifestyle therapy, or who have experienced weight regain following initial success on lifestyle therapy alone [19].

Current Guidelines for T2DM Therapy When Weight is a Primary Concern

The treatment guidelines for type 2 diabetes from the American Diabetes Association (ADA) have undergone significant paradigm changes in recent years, and have prioritized the individualization of therapy according to patients' needs and comorbidities [20]. These guidelines advise that when choosing glycemic-lowering medications for patients with type 2 diabetes and overweight or obesity, the effect of medications on weight should be considered, and advise to minimize or avoid medications that are associated with weight gain whenever possible [20]. The 2022 ADA guidelines also have a section dedicated to the treatment algorithm for type 2 diabetes when there is a compelling need to minimize weight gain or weight loss; suggesting that a glucagon-like peptide-1 receptor agonist (GLP-1 RA) with good efficacy for weight loss or a sodium-glucose contransporter-2 (SGLT-2) inhibitor be considered if first-line therapy with metformin and lifestyle modifications still does not lead to adequate glycemic control in these patients [20].

In T2DM patients who need their treatment regimen intensified to include injectable therapy, the guidelines now recommend considering a GLP-1 RA in most patients prior to insulin [20].

Available Anti-Obesity Medications: Overview and Considerations

Several drugs are currently approved for the treatment of obesity, including phentermine, orlistat, phentermine/topiramate, naltrexone/bupropion, and two GLP-1 RAs -- liraglutide 3.0mg and semaglutide 2.4mg [21, 22]. They are all indicated for individuals with a body mass index (BMI) of ≥30 kg/m2 or BMI ≥27 kg/m2 with at least one adiposity-related disease. Of these, phentermine is only approved for short-term use (12 weeks) [21]. Of note, lorcaserin, which was previously approved for long-term obesity management, was withdrawn from the market in 2020 for a safety issue related to increased cancer incidence [22]. Throughout clinical trials, these drugs have demonstrated efficacy for weight loss, as well as additional benefits in certain cases, including lowering the risk of diabetes, improving glycemic outcomes, and cardiovascular risk [21, 22].

Most of these drugs essentially exert central effects to help reduce the stimuli to eat and facilitate weight loss. In addition, GLP-1RAs have some extra non-central mechanisms for weight loss, as well as potentially metformin [22].

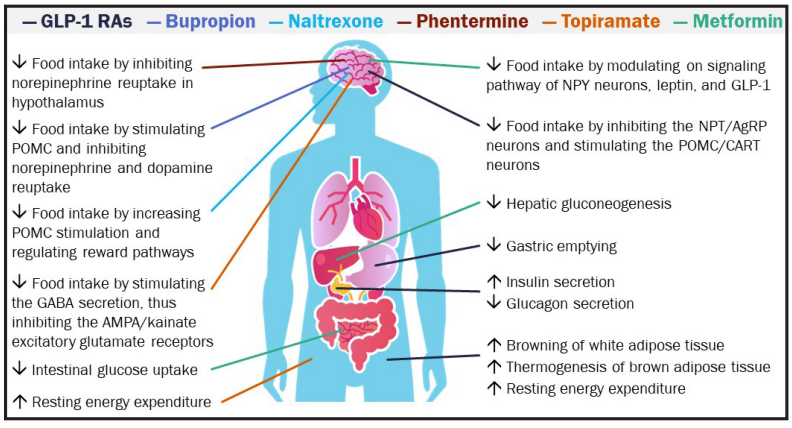

Figure 2. Mechanisms of action of antiobesity medications.

AMPA= α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; AgRP= agouti-related peptide; CART= cocaine and amphetamine-regulated transcript; GABA= γ-Aminobutyric acid; GLP-1= Glucagon-like peptide-1; NPY= neuropeptide Y; POMC = pro-opiomelanocortin

In 2021, a new GLP-1 RA, semaglutide 2.4mg, was FDA ap-

proved for the management of chronic obesity, the first drug approved for this indication since 2014, and one that has been deemed "practice changing", since it showed a reduction in body weight of approximately 15-18% across 4 phase III trials [23]. This approval was based on the positive results from a series of clinical trials – the STEP (Semaglutide Treatment Effect in People with obesity) trials – for weight management in people with obesity. STEP 1 trial showed that there was a striking weight loss compared to placebo with more than half of the participants losing 15% of their body weight from baseline during 68 weeks of treatment with semaglutide 2.4mg coupled with lifestyle intervention when compared to placebo with intervention groups. STEP 2 showed that when semaglutide in combination with lifestyle intervention was administered, there was a statistically significant greater weight loss of 9.6% achieved at 68 weeks with s.c. semaglutide 2.4 mg compared to placebo (3.4% weight loss) and 1.0 mg semaglutide (7.0% weight loss). STEP-3, which monitored the effect of once-weekly sc semaglutide 2.4 mg compared to placebo in 611 adults with obesity or overweight with comorbidities in combination with intensive behavioral therapy (IBT), also met the primary endpoint; showing a statistically significantly higher weight loss of 16.0% achieved with s.c. semaglutide 2.4 mg as an adjunct to IBT, compared to a 5.7% weight loss with placebo plus IBT after the 68-week treatment period [24]. STEP-4 had a unique study designed to show the positive effect of continued treatment with this approach. In this trial, the impact of semaglutide 2.4mg was monitored following a 20-week run-in period, after which the patients were randomly assigned to receive either semaglutide or placebo for the remaining 48 weeks. People who were switched to placebo after initial 20-week run-in period regained 6.9% of the body weight and who continued to take semaglutide lost a total of 17.4% of their total weight from the start over the whole trial [25]. Additionally, trials with this agent are currently ongoing, including the phase 3 SELECT trial, which will look at the effect of this therapy in reducing the risk of cardiovascular events in patients with overweight or obesity with existing cardiovascular disease (ClinicalTrials.gov, NCT03574597).

Given the range of available treatments for obesity, including metabolic surgery, as well as their efficacy and safety, it is important to individualize therapy and select optimal treatment regimens for an individual patient [19, 21]. These include considerations in patients with cardiovascular disease, type 2 diabetes, chronic kidney disease, depression, seizure disorder, psychiatric disorders and more. For patients with type 2 diabetes, liraglutide, semaglutide, or other GLP-1 RAs or SGLT-2 inhibitors should be considered; and in patients that use insulin, adding metformin, pramlintide, or a GLP-1 RA may be considered to mitigate against weight gain [26]. An overview of the efficacy and safety of treatment options for obesity is shown in Table 1 [27].

Drug	Weight Loss (placebo/drug)	Side effects
Orlistat	-6.1% / -10.2%	Liver injury, gastrointestinal symptoms
Phentermine	-1.7% / -6.6% to -7.4% (dose-dependent)	Palpitations, elevated blood pressure
Phentermine/topiramate ER	-1.2% / -7.8 to 9.3% (dose- dependent)	Depression, suicidal ideation, cardiovascular events, memory loss, birth defects
Naltrexone/bupropion SR	-1.3 / -5.0 to -6.1% (dose-dependent)	Seizures, palpitations, transient blood pressure elevations
Liraglutide 3.0 mg	-2.6% / -8%	Nausea/vomiting, diarrhea, constipation, pancreatitis, gallstones
Semaglutide 2.4mg	-2.4% / -14.9%	Nausea/vomiting, diarrhea, constipation

Table 1. Summary of efficacy and safety of currently-available obesity pharmacotherapy

Tirzepatide, and Emerging Approach: Rationale and Overview

Besides the approval of semaglutide 2.4mg, much of the excitement in the field of obesity management also has to do with the approval of a dual GLP-1/GIP RA, tirzepatide, which is currently approved for the management of type 2 diabetes, but has shown promising results in the treatment of obesity in patients with and without T2DM [28]. The rationale for exploring the role of this dual agonist comes from several preclinical and early-stage clinical studies, which seem to suggest that peptide multiagonists such as tirzepatide will enhance the metabolic effects seen with GLP-1 RAs [29]. It is postulated that glucagon, GLP-1, and GIP (glucose-dependent insulinotropic polypeptide) elicit different effects in a variety of tissues, with most actions being complementary and potentially synergistic, and as such targeting them simultaneously can convey certain advantages compared to targeting one peptide alone (Figure 3 [30]).

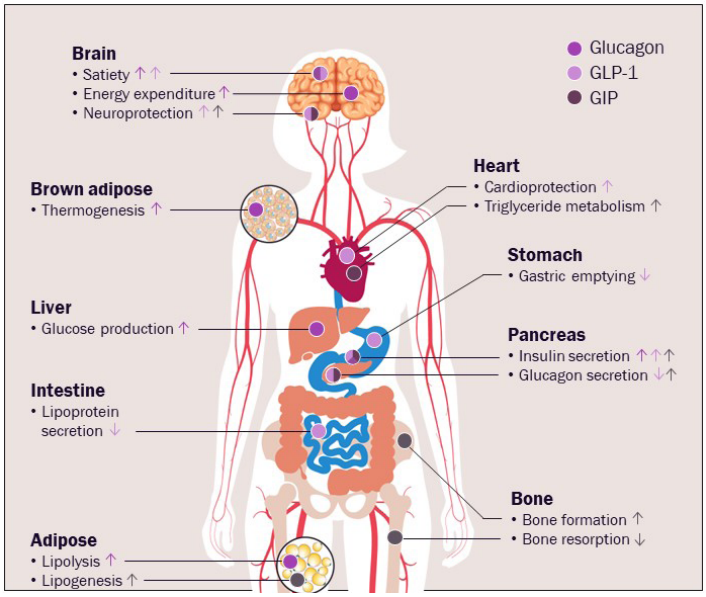

Figure 3. The different effects of glucagon, GLP-1, and GIP (Figure adapted from [30])

In light of this theoretical and early-stage framework, the phase 3 SURPASS clinical trials program is exploring the efficacy and safety of tirzepatide in patients with T2DM (Figure 4), and results from some of these trials have been recently published.

SURPASS: Trials of Tirzepatide in T2DM

Monotherapy	SURPASS-1 vs placebo Drug-naïve or washout from any OAM
2-Drug Combination	SURPASS-2 vs semaglutide Add-on to metformin
2-3 Drug Combination	SURPASS-3 vs insulin degludec Add-on to metformin with or without SGLT-2 inhibitor
2-4 Drug Combination	SURPASS-4 vs insulin glargine Add-on to ≥1 and ≤3 OAMs (metformin, SGLT-2 inhibitor, or SU)
Combination With Insulin	SURPASS-5 vs placebo Both with insulin glargine with or without metformin SURPASS-6 vs insulin lispro(TID) Both with insulin glargine with or without metformin (ongoing)

SURPASS-CVOT

Head-to-head trial comparing tirzepatide vs dulaglutide

>12,000 participants (ongoing)

Figure 4. Overview of SURPASS trials with tirzepatide in T2DM [31-36]. OAM = oral antihyperglycemic medication; SU = sulfonylurea; TID = 3 times daily

Across SURPASS trials 1-5, significant and dose-dependent reductions were seen with tirzepatide in both HbA1c and body weight (Figures 5 and 6). Due to the evidence from these trials, in May 2022, tirzepatide received FDA approval to improve glycemic control in patients with T2DM as an adjunct to diet and exercise [37].

Several trials with tirzepatide are also ongoing, including SURPASS-6, SURPASS-J, SURPASS-AP, and SURPASS-CVOT, all of which will look at the effects of this agent compared to other agents (insulin lispro, dulaglutide, insulin glargine) on weight, HbA1c, and the occurrence of major adverse cardiovascular events (MACE), respectively [38]. In addition, the SURMOUNT phase 3 program, will look specifically at the efficacy and safety of tirzepatide for the management of obesity [38]. Recently, data from the SURMOUNT-1 trial showed that tirzepatide treatment resulted in up to 22.5% weight loss in adults with obesity or overweight, who did not have diabetes at baseline [39]. The study met both co-primary endpoints showing greater reduction with tirzepatide in %body weight and the % of participants achieving at least 5% weight loss compared to placebo [39]. According to these data from SURMOUNT-1 trial, tirzepatide appears to have greater efficacy in inducing weight loss compared to semaglutide 2.4mg, however, additional head-to-head studies are needed to solidify this claim.

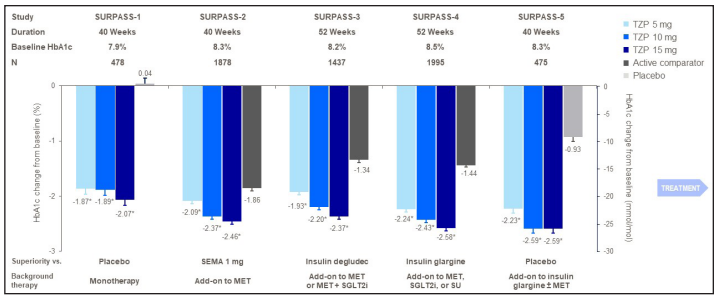

Figure 5. HbA1c change from baseline to primary endpoint (efficacy estimated) [31-36]. HbA1c = glycated hemoglobin; MET = metformin; SEMA = semaglutide; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SU = sulfonylurea; TZP = tirzepatide

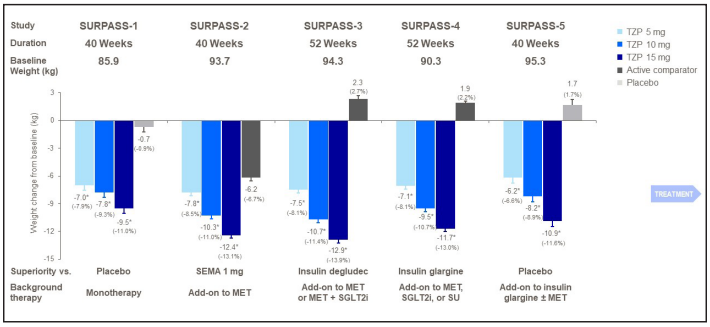

Figure 6. Body weight change from baseline to primary endpoint (efficacy estimated) [31-36]. MET = metformin; SEMA = semaglutide; SGLT2i = sodium-glucose co-transporter-2 inhibitor; SU = sulfonylurea; TZP = tirzepatide

Conclusions

The increasing prevalence and impacts of overweight and obesity in patients with type 2 diabetes renders weight loss and weight loss maintenance an important part of treatment goals. Nonetheless, clinicians that treat patients with type 2 diabetes often do not adequately address obesity, both in the suboptimal selection of antiglycemic therapies that minimize weight gain or induce weight loss, but also in recommending comprehensive treatment strategies for the long-term management of obesity that include the utilization of the full spectrum of available therapies.

The benefits of weight loss in patients with T2DM are substantial, and are apparent with as little as 5% weight loss, and as such, having a goal of at least 5% weight loss for patients with obesity and T2DM should be standard as it can lead to clinically significant improvement. However, therapeutic inertia should be avoided: if patients on anti-obesity medications are not achieving 5% weight loss after 12 weeks, treatment plans should be adjusted adequately. Now, multiple anti-obesity drugs and interventions are available, including for long-term use, and are proved to help sustain weight loss better than lifestyle changes alone. Additionally, clinicians should focus on dedicating time to addressing obesity as any other chronic disease and discuss it in a non-judgmental manner using patient-centered language.

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