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Treatment of Obesity in Individuals with Type 1 Diabetes

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The prevalence of obesity (OB) is increasing among individuals with type 1 diabetes (T1D), posing unique challenges for managing their blood sugar levels and long-term health. Unlike type 2 diabetes (T2D), which is closely linked to OB and insulin resistance (IR), addressing OB in T1D requires careful consideration, because patients rely on external insulin, which can contribute to weight gain. In this review, we will discuss the causes and complications of OB in individuals with T1D, current approaches to treatment, potential lifestyle, and medical, and surgical interventions to manage weight while effectively maintaining optimal blood sugar control.

Introduction

In the past, type 1 diabetes (T1D) was commonly associated with a lean body type. However, in recent years, there has been a significant increase in the prevalence of overweight (OW) and obesity (OB) among individuals with T1D, with rates approaching those of the general population.[1,2] For instance, a study in the USA found that 34% of adults with T1D were OW, and 28% were affected by OB.[3] In Canada, one registry reported that 34.6% of adults with T1D were OW, and 19.8% were affected by OB.[4] Similar trends have been observed in studies from other parts of the world.[5-8]

Research has shown that a significant number of children and adolescents with T1D also struggle with OW and OB. According to the SEARCH for Diabetes in Youth study, 22.1% of children and adolescents with T1D in the USA (aged 3–19 years) were OW, compared to 16.1% of their peers without T1D. Additionally, 12.6% of them were affected by OB, compared to 16.9% of their peers without T1D.[9] Another study of 5529 adolescents (aged 13–18 years) in the T1D Exchange registry in the USA found similar or slightly higher rates of OW (22.9%) and OB (13.1%).[10] Globally, data from the international SWEET registry, which included 55 pediatric diabetes centres and over 30,000 individuals from all continents, reported that the prevalence of OW and OB among children and adolescents with T1D (aged 2–18 years) was 27.2% for girls and 22.3% for boys.[11]

This evolving situation brings added challenges to T1D management, as OW and OB can worsen insulin resistance (IR) and raise the risk of heart disease, hypertension, and dyslipidemia. Addressing OB in T1D requires special attention to how insulin treatment affects weight gain and blood sugar control.

It is becoming more evident that insulin use in individuals living with T1D can impact body composition and lead to an excess accumulation of fat, posing health risks. Additionally, there is a rising concern that T1D is more likely to occur in individuals with OW and OB. The accelerator hypothesis suggests that the line between T1D and T2D is becoming less

clear, as weight gain is consistently identified as a significant factor for both conditions.[12,13]

This review delves into the unique challenges and strategies for treating OB in individuals with T1D, focusing on the pathophysiology and complications of OB. It also covers a range of interventions, from lifestyle changes to pharmacologic approaches and metabolic surgery, as well as the emerging role of new weight management medications. These strategies are crucial in addressing the complex interplay between OB and T1D.

Pathophysiology of Obesity in T1D

Despite the apparent paradox, OB in individuals with T1D is a complex outcome of multiple factors:

- ***Genetic predisposition:*** Some data suggest that genetic factors play a role in the development of OB in individuals with T1D. A study on a cohort of 1119 children with T1D revealed an association between body mass index (BMI) and known OB susceptibility genes.[14] Fat mass and the OB-associated (*FTO*) gene is associated with higher BMI in individuals with T1D.[14] In the Diabetes Control and Complications Trial (DCCT), it was demonstrated that individuals with T1D on intensive insulin therapy with a family history of T2D gained more weight than those without a family history of T2D.[15]

- ***Intensive insulin therapy:*** Although insulin is essential for controlling glucose and preventing diabetes complications, it can promote increased caloric intake or conserve ingested calories, leading to weight gain.[16-19] Another theory suggests that administering insulin peripherally bypasses the effects on the liver, which can potentially cause hyperinsulinemia and fat accumulation in peripheral tissues.[18,19] Other pathways explaining insulin-induced weight gain have been proposed, including alterations to the growth hormone or insulin-like growth factor 1 (IGF-1) system. This system plays a key role in maintaining body composition by delicately balancing anabolism and catabolism.[20,21]

- ***Age and duration of diabetes:*** In a retrospective observational cohort study of children and adolescents with T1D (aged 0–18 years), weight gain was linked to both age and the duration of T1D. This association could be a result of prolonged and intensive insulin use following diagnosis.[22]

- ***Fear of hypoglycemia:*** In the DCCT, the risk of severe hypoglycemia was increased threefold in individuals treated with intensive insulin therapy compared to those on conventional therapy.[19] Weight gain in individuals with T1D can be attributed to defensive snacking to prevent exercise-related hypoglycemia or consuming extra carbohydrates to counter hypoglycemia. While the use of insulin analogues has reduced the risk of hypoglycemia, it remains the most common acute complication of T1D.[23] Automated insulin delivery (AID) systems could potentially decrease the frequency of hypoglycemia by better-matching insulin delivery with glucose levels. However, the current use of these systems is limited, and it is uncertain whether they will significantly reduce defensive snacking and weight gain.[24] Fear of hypoglycemia during exercise could be a key factor contributing to weight gain in individuals with T1D. Data from accelerometers in adults newly diagnosed with T1D indicated lower moderate-vigorous physical activity levels than those for adults without T1D. Nevertheless, these findings were not comprehensive.[25] Education on adjusting insulin doses with physical activity is essential for individuals with T1D, because without this knowledge some may be discouraged from exercising, potentially contributing to weight management issues.[26–28]

- ***Insulin resistance***: OB in individuals with T1D can lead to IR, resulting in a condition known as "double diabetes," which can complicate the management of T1D.[29,30] IR can also occur independently of weight in individuals with T1D.[31] The cause of this IR could be linked to the external delivery of insulin, and it manifests with a unique phenotype associated with abnormal physiological outcomes, regardless of weight.

Complications of Obesity in Individuals with Type 1 Diabetes:

Long-term data on OB in individuals with T1D is currently limited. However, it is reasonable to assume that OW and OB may have more severe effects on this group of individuals than on the general population. High BMI was associated with an increased risk of major cardiovascular disease, heart failure, cardiovascular death, and mortality in individuals with T1D, especially in men.[6] IR in individuals with T1D has significant implications and has been linked to a higher risk of microvascular complications.[32,33] Additionally, studies suggest a connection between excess adiposity, IR, and

coronary artery calcification, with cardiovascular disease being the leading cause of death in adults with T1D.[34,35]

Treatment Strategies For Managing Obesity in Individuals with T1D

Managing OB in individuals with T1D requires a delicate balance between optimizing glycemic control and achieving sustainable weight loss. Several treatment modalities have been explored, including lifestyle interventions, pharmacologic approaches, and surgical procedures.

1. Lifestyle and behavioural modifications

The treatment of OB is complex and must involve a multidisciplinary approach, including lifestyle and behavioural modifications (e.g., diet and physical activity), which constitute the backbone of OB management in general. Dietary adjustments, physical activity, and behavioural therapy are essential for promoting weight loss while maintaining glycemic control.

Dietary modifications: Lifestyle changes are not just beneficial, but they are also the key to success in managing obesity in individuals with T1D. The most effective strategy is a high-intensity dietary program with frequent contact with individuals, which has the potential to result in an average weight loss of approximately 5–10%.[36] However, maintaining weight loss over time is challenging for most individuals.

Many diets can lead to weight loss in individuals with OW or OB, such as the Mediterranean diet, plant-based or vegetarian diet, or low carbohydrate diet. There is inadequate research in T1D to support one diet over another.[37-40] The specific breakdown of macronutrients in a diet seems to have less effect on weight loss than adherence to the diet. Therefore, any diet plan should be tailored to the individual's clinical characteristics and preferences, emphasizing the importance of personalized care. This approach should be designed to improve long-term adherence, which is crucial for successful weight management. Therefore, the presence of a dietitian in the multidisciplinary team is essential.[38]

The primary focus of any OB dietary program, with or without diabetes, is to decrease overall caloric intake. A reduction of 500–1000 kcal per day or 25–30% of daily caloric intake can result in a weight loss of 0.5 kg to 1 kg per week, equivalent to more than a 5% weight loss over an average period of 6 months. For individuals with T1D, it is essential to promote the consumption of carbohydrates with a low glycemic index and high fibre content sourced from vegetables, legumes, fruits, and whole grains. These high-fibre foods play a crucial role in the diet, providing a sense of fullness and aiding in digestion, empowering individuals to make informed dietary choices. It is also important to avoid added sugar, refined carbohydrates, and highly processed foods.[38-40]

The current ADA guidelines recommend no specific macronutrient composition of meal plans for individuals with T1D but emphasize the importance of balancing the insulin dose with the carbohydrate content.[40] However, special attention should be given to the evidence surrounding low carbohydrate (<130 g carbohydrate/day) and ketogenic diets (<55 g carbohydrate/day) for individuals with T1D. While these diets are popular for weight loss in individuals with OB and T2D, there is limited evidence of their effectiveness for individuals with T1D, and concerns have been raised about the risks of hypoglycemia and diabetic ketoacidosis (DKA).[41] For instance, a low carbohydrate diet may reduce hepatic glycogen stores, thereby impairing the effect of glucagon in the event of hypoglycemia. A study on individuals with insulin pump–treated T1D found that a low carbohydrate diet (<50 g/day) attenuated the glycemic response to a subcutaneous glucagon bolus compared to a high carbohydrate diet.[42]

The effectiveness and safety of intermittent fasting for individuals with T1D have not been proven. Therefore, proper training and adjustments to insulin doses are essential to prevent hypoglycemia.

Physical activity: Regular physical activity has numerous benefits, including weight management, reducing the risk of cardiovascular disease and mortality, improving dyslipidemia, and enhancing mental health outcomes.[43,44] For individuals with T2D, physical activity can improve IR, reduce insulin dose requirements, and limit insulin-associated weight gain. However, individuals with T1D may face an increased risk of hypoglycemia with physical activity, leading to fewer than 5% of adolescents with T1D meeting the pediatric clinical guidelines for physical activity.[45] The development of AID systems may allow for a more individualized approach and make exercising safer by preventing hypoglycemia and providing a better balance between glucose levels and insulin administration.

Behavioural therapy: It is common for individuals with OB and T1D to experience psychosocial challenges that need to be identified and addressed effectively. These challenges include

fear of hypoglycemia, diabetes distress, anxiety, depression, lack of support, low self-esteem, and the stress of managing a chronic illness. Additionally, eating disorders are estimated at approximately 7% among individuals with T1D.[46]

Integrating psychological assessment and behavioural therapy into the standard clinical care for OB in individuals with T1D is essential. This should involve setting achievable goals, self-monitoring food intake and exercise, problem-solving strategies, developing coping skills, controlling environmental triggers, stress management, education, and, most importantly, social support. These behavioural interventions are beneficial when part of a structured weight management program.[36]

2. Pharmacological interventions

The interaction between insulin, appetite control, and weight gain in individuals with T1D is intricate. Using medication alongside lifestyle changes can be helpful in addressing OB in individuals with T1D.

A. Anti-obesity medications:

Patients who do not achieve significant weight loss with lifestyle changes may be considered for anti-OB medications. According to current guidelines, anti-OB medications can be considered for individuals with a BMI of 30 kg/m^2 or higher or a BMI of 27 kg/m^2 or higher with OB-related complications, in addition to lifestyle modifications.[47,48] Food and Drug administration (FDA)-approved long-term anti-OB medications include Orlistat, Naltrexone-Bupropion combination, Pheteramine-Topiramate combination, Liraglutide at a dose of 3 mg, Semaglutide at a dose of 2.4 mg, and Tirzepatide, while Phentermine is approved for short-term use only.[49,50] While there is limited data on the use of these medications in individuals with T1D due to their exclusion from major trials, it is reasonable to assume that individuals with OB and T1D may benefit from these drugs in practical settings. The exclusion of T1D from clinical trials for pharmacological obesity management introduces bias and exacerbates discrimination against these patients due to their OB.

B. Glucose-lowering agents as adjuncts to insulin treatment in T1D:

Amylin analogs (e.g., Pramlintide): Amylin is a hormone that is co-secreted with insulin from pancreatic beta cells. Pramlintide, a synthetic amylin analog, is the only adjuvant therapy for T1D approved by the FDA.[51] It has been shown to improve long-term glycaemic control and induce an average weight loss of 0.4–1.3 kg compared to an average weight gain of 0.8–1.2 kg in the placebo group.[52,53]

Metformin: Metformin has been traditionally used to treat individuals with T2D, but it has also been studied as an adjunct treatment for individuals with T1D, especially those with OB and IR. Metformin works by reducing the production of glucose in the liver, enhancing the body's sensitivity to insulin in the peripheral tissues, and decreasing the absorption of glucose, which can result in a slight reduction in weight and lower insulin requirements.[54] Some clinical trials involving a small number of participants with T1D have looked into the effects of adding metformin to insulin compared to adding a placebo. These trials have shown a decrease in insulin doses (ranging from -5.7 to -8.8 units per day) and a decrease in weight (ranging from -1.74 kg to -3.8 kg) with no impact on hemoglobin A1c (HbA1c) levels.[47,55] The REMOVAL trial involved 428 patients with T1D who were randomly assigned to receive either metformin or a placebo.[48] The trial measured the progression of common carotid artery intima-media-thickness (cIMT) as an indicator of atherosclerosis. The results showed a reduction in body weight by 1.17 kg but no decrease in HbA1c levels, insulin requirements, progression of mean cIMT, or increase in hypoglycemia compared to the placebo.[48]

Dipeptidyl peptidase-4 (DPP-4) inhibitors: The DPP-4 inhibitors work by increasing the levels of endogenous glucagon-like peptide 1 (GLP1) by inhibiting its metabolism by the enzyme DPP-4. This rise in GLP1 levels leads to a reduction in glucagon and an increase in insulin secretion in a glucose-dependent manner. In individuals with T1D, there is a contradictory increase in glucagon levels, which is associated with post-meal glucose levels.[56] Sitagliptin is the sole DPP-4 inhibitor examined in individuals with T1D, and it has not led to any significant weight loss.[57,58]

GLP-1 Receptor Agonists: GLP-1 receptor agonists are frequently used to treat individuals with T2D and have been shown to effectively reduce weight by decreasing appetite, increasing a feeling of fullness, and slowing down the emptying of the stomach.[59] These medications may also be beneficial for individuals with OB and T1D, leading to weight loss and reduced insulin requirements without increasing the risk of severe hypoglycemia.

Liraglutide and exenatide were the only GLP-1 agonists studied extensively in individuals with

T1D.[60] Lixisinetide and albiglutide were each studied in a single study.[60] A recent meta-analysis included 24 studies using 4 different GLP-1 analogues with 3377 patients.[60] Liraglutide had the most substantial evidence, with an estimated weight loss of −4.89 kg for the 1.8 mg dose, −3.77 kg for the 1.2 mg dose, and −2.27 kg for the 0.6–0.9 mg dose. The estimated weight loss was −4.06 kg for exenatide. As expected, GLP-1 agonist treatment was associated with more gastrointestinal side effects, but it did not significantly increase the risk of DKA, or symptomatic or severe hypoglycemia.[60]

Semaglutide has been evaluated in some observational trials involving individuals with T1D. It resulted in an average weight loss of 7.23–8.8 kg (7.6–10.6%), and improved HbA1c and time in range (TIR) without increasing the risk of hypoglycemia or DKA.[61-64]

Tirzepatide is a dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist that has been shown to reduce weight in individuals with T2D and OB.[49,50,59] It has been studied in individuals with T1D in 2 observational studies. The first study included 26 patients and revealed a significant reduction in body weight by 3.4%, 10.5%, and 10.1% at 3, 6, and 8 months after starting tirzepatide, respectively, that was accompanied by improved HbA1c and TIR.[65] The other study included 62 patients with T1D and OW or OB matched with 37 control participants.[66] Tirzepatide resulted in an average weight loss of 21 kg (18.5%) at one year, with a significant improvement in HbA1c and TIR.[66]

SGLT2 inhibitors: SGLT2 inhibitors increase urinary glucose excretion, which helps improve glycemic control and results in modest weight loss.[59] However, only a few studies have evaluated their use in individuals with T1D.

Dapagliflozin: In the DEPICT-1 and DEPICT-2 trials, patients who were given dapagliflozin 5 mg or dapagliflozin 10 mg experienced a significant reduction in body weight (ranging from -2.95% to -4.54% compared to placebo), as well as a decrease in HbA1c levels (-0.33% to -0.37% with dapagliflozin 5 mg and -0.36% to -0.42% with dapagliflozin 10 mg) and insulin dosage. The rates of hypoglycemia did not differ, but the incidence of DKA was higher in the treatment groups (2.6% to 4% with dapagliflozin 5 mg, 2.2% to 3.4% with dapagliflozin 10 mg, and 0% to 1.9% with placebo).[67,68]

Empagliflozin: In the EASE-1 trial, patients were randomly assigned to receive empagliflozin at a dose of 10 mg, 25 mg, or a placebo. In the EASE-2 and EASE-3 trials, patients were randomized to receive empagliflozin at doses of 2.5 mg, 10 mg, 25 mg, or a placebo.[69,70] Across all trials, empagliflozin was associated with a significant reduction in weight (-1.5 kg to -3.6 kg) and HbA1c levels compared to the placebo. Additionally, the insulin dose was also decreased. However, higher rates of DKA were observed in patients receiving higher doses of empagliflozin (10 mg and 25 mg). Specifically, the rates of DKA were 0.8% with empagliflozin 5 mg, 4.3% with empagliflozin 10 mg, 3.3% with empagliflozin 25 mg, and 1.2% with placebo.[70]

Sotagliflozin (combined SGLT1 and SGLT2 inhibitor): The inTandem program assessed the effectiveness and safety of using sotagliflozin in individuals with T1D.[71-73] The 3 trials demonstrated a decrease in weight (-1.98 kg to -4.34 kg), HbA1c levels (-0.21% to -0.46%), and insulin dosage. The incidence of documented hypoglycemia was lower, but there were more gastrointestinal adverse events in the sotagliflozin group. The DKA rate was higher in patients treated with sotagliflozin (3.4% with sotagliflozin 200 mg, 4.2% with sotagliflozin 400 mg, and 0.4% with placebo).

When considering SGLT2 inhibitors for those with T1D, it is crucial to carefully select patients and closely monitor them. In randomized controlled trials, the increased risk of DKA has limited the approval of SGLT-2 inhibitors for individuals with T1D. Dapagliflozin was approved by the European Drug Agency (EDA). However, in October 2021, the manufacturing company voluntarily removed the T1D indication for dapagliflozin after recommendations from UK and EU medicines regulators to add an inverted black triangle to the label to indicate the need for additional monitoring when prescribing this drug.[74]

3. Metabolic surgery

Most studies evaluating the effect of metabolic surgery in individuals with T1D are limited by the small sample size and inclusion of different types of surgeries. They mainly focused on weight loss and insulin use. Additionally, long-term follow-up is lacking, and side effects have not been systematically reported.

The most extensive study evaluating metabolic surgery in patients with T1D is a register-based nationwide cohort study from Sweden.[75] Individuals with T1D and obesity who underwent Roux-en-Y gastric bypass (RYGB) surgery were compared with patients with T1D and OB who were matched for age, sex, BMI, and calendar time who did not undergo surgery. A total of 387 individuals who had

undergone RYGB and 387 control patients were identified and followed for 9 years. The participants' weight was reduced by 25% at 1 year and 29% at 2 years after surgery compared to 5% at 1 and 2 years in the control group. HbA1c decreased by 1% at 1 year and 0.8% at 2 years after surgery compared to no change in the control group. The analysis also showed a lower risk for cardiovascular disease, cardiovascular death, hospitalization for heart failure, and stroke for the RYGB group. There was a higher risk for serious hyperglycemic events and substance abuse after surgery.

A systematic review that included 30 studies with 706 patients revealed a mean excess weight loss of 74.57% at ≥6 follow-up months.[76] The most common procedure performed was RYGB (n = 497, 70.4%), followed by SG (n = 131, 18.6%). The insulin dose was reduced from a mean of 92.3 IU/day preoperatively to a mean of 35.8 IU/day post-operatively. No significant trends were found for changes in HbA1c levels. Reductions in comorbidities such as hypertension and cardiovascular disease were recorded in multiple studies. The main side effects were episodes of hypoglycemia and DKA, and there was no mortality.

In summary, the use of metabolic surgery in T1D patients with severe OB has been shown to effectively reduce weight and insulin dosage while improving OB-related conditions such as hypertension, dyslipidemia, and obstructive sleep apnea. Recent studies indicate a significant decrease in cardiovascular disease and mortality. Despite the observed adverse events, such as an elevated risk of hypoglycemia and DKA, the benefits of this approach outweigh the drawbacks. However, it is crucial for these patients to receive close monitoring from a multidisciplinary team to ensure a personalized and adjustable insulin regimen throughout all stages of treatment, in addition to diabetes care and education. New diabetes technologies, including real-time continuous glucose monitoring and AID systems, may offer valuable support in this scenario.

Conclusion and Future Directions

Obesity in individuals with T1D is a challenging and rapidly growing health issue. It significantly affects glycemic control and increases the risk of long-term complications. A comprehensive approach to treatment, including lifestyle changes, medication, and, in some cases, metabolic surgery, is crucial for achieving weight loss and improving metabolic outcomes in these patients. Providing extensive education and support to help individuals match insulin doses to food intake and exercise is fundamental in managing both weight and sugar levels in these individuals.

While existing evidence highlights the concern of undesired weight gain in treating individuals with T1D, high-quality data on this topic is limited. Further research is needed to understand the full impact of OB on the overall health of individuals with T1D. Future treatments and technologies should not only focus on enhancing glucose control but also on facilitating weight management. It is equally important to explore adjunct therapies that can improve glycemic control through insulin-independent pathways, as these could offer new avenues for treatment.

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