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Review

Overweight and Obesity in Adults with Type 1 Diabetes: A Growing Challenge

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Abstract: The prevalence of obesity in adults with type 1 diabetes is increasing and reflects the rates of the general adult population. The coexistence of overweight or obesity and type 1 diabetes poses a major challenge to effective glycemic and weight management. In addition, individuals living with T1D and overweight or obesity are at greater cardiometabolic risk and are more prone to develop chronic complications in comparison to normal weight individuals with type 1 diabetes. Although obesity represents a growing challenge in the type 1 diabetes population, awareness of this issue is still low. This review provides a summary of current data on prevalence trends, causes, current strategies, and challenges in managing obesity in adults with type 1 diabetes.

Keywords: anti-obesity medication; glucagon-like peptide 1 receptor agonist; obesity; type 1 diabetes

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1. Introduction

Obesity is defined as a complex and multifactorial disease, characterized by the excessive accumulation of body fat. It is a significant public health concern worldwide due to its high prevalence and association with various health complications [1,2]. The prevalence of obesity has been steadily increasing over the past few decades [3,4]. This rising trend is observed in developed as well as developing countries. Factors such as changes in eating habits, sedentary lifestyles, and genetic predisposition contribute to this rise. Obesity has far-reaching clinical consequences, affecting various organ systems and increasing the risk of numerous chronic diseases [4,5]. Adiposity, particularly excess visceral fat, contributes to insulin resistance and increases the probability of developing type 2 diabetes (T2D) [6].

The association between obesity and type 1 diabetes (T1D) is complex and not as straightforward as the relationship between obesity and T2D. T1D is an autoimmune disease in which the body's immune system attacks and destroys the insulin-producing cells in the pancreas, resulting in insulin deficiency and a lifelong need for insulin replacement

therapy. It is believed that psychosocial factors, lifestyle, behavior, insulin replacement therapy, and fear of hypoglycemia contribute to the development of obesity, in addition to independent factors such as duration of disease, sex, and age. Regarding all of these factors, it is still not clear if weight control strategies for T2D are also valid for T1D, as people with T1D could experience difficulties such as hypoglycemia during exercise, the restriction of dietary carbohydrates, and fasting [7]. Therefore, it could be challenging to achieve weight management goals in T1D in contrast to T2D, where all strategies are focused on double-digit weight loss as an important step in obesity and T2D and treatment [8]. In 2022, worldwide, there were 8.75 million people living with T1D. Around 17% of them were under 20 years of age. Furthermore, there were 530,000 newly diagnosed cases of T1D among all age groups in 2022 [9]. Annually, the incidence of T1D has increased globally by 2.8% and in Europe by 3.9%. In a national sample of the U.S., researchers found that 62% of adults with T1D were overweight or obese in comparison to 64% of those without diabetes and 86% with T2D [10,11]. Unlike T2D, obesity is not a common risk factor for developing T1D. In fact, T1D is more often associated with lower body weight or normal weight at diagnosis. Historically, people with T1D, compared to the general population, have been thought to have lower rates of obesity. However, obesity is more prevalent in people with T1D than previously thought [12,13].

The coexistence of overweight or obesity and T1D represents a huge challenge for effective weight and glycemic management. Furthermore, individuals living with T1D and overweight or obesity are at greater cardiometabolic risk and more prone to the development of chronic complications compared to normal-weight patients with T1D [14,15]. Also, higher impendence of cancers such as liver, pancreas, stomach, colon, esophagus, lung, thyroid, ovarian, and endometrial cancers was reported in people with T1D. Additionally, a study conducted on 9000 cancers in patients with T1D showed a 17% higher risk in women and a 15% higher risk in men with T1D [16,17]. Although obesity in T1D represents a growing challenge, awareness on this issue is still low.

In the present review, we will summarize current data on prevalence trends, causes, current strategies, and challenges in the management of obesity in individuals with T1D as an important step in establishing an effective and safe evidence-based approach.

2. Epidemiology of Obesity in Adults with Type 1 Diabetes

Several recent studies have shown that rates of obesity in adults with T1D are increasing and reflect rates of the general adult population. Wallace and co-investigators examined data from 4060 people with T1D from the Geisinger Health System in Pennsylvania between 2004 and 2018 and found that 37% of people with T1D had obesity [18]. Moreover, over time, the prevalence of obesity in adults with T1D has increased (from 32.6% in 2004 to 36.8% in 2018).

In Israel, female T1D patients aged 18–25 years, compared with healthy Israeli women in the same age group, were significantly overweight, at 26.3% versus 7.8%, respectively. Among men in all age groups, there was no difference, compared with healthy men in the general population, in the prevalence of overweight and obesity [19]. In a large sample of 20,985 T1D patients (mean age 38.6 years) involved in the Swedish National Diabetes Registry during 1998–2003, the prevalence of overweight and obesity was 35.1% and 8.9%, respectively [20].

Significantly higher rates of obesity were found in a US cohort (age 35–67 years) and an Australian cohort (age 30–75 years), in which 35.9% and 37.1% of adults with T1D had obesity, respectively [21,22]. Data from the Pittsburgh Epidemiology of Diabetes Complications (EDC) study, with 18 years of follow-up, demonstrated that the prevalence of overweight in T1D adults increased by 47%, while the prevalence of obesity increased seven-fold, representing a faster rise than in the general population [23].

Overall, these studies show a worryingly high prevalence of obesity among individuals with T1D.

As the prevalence of global trends in obesity and T1D are rising in many developed and developing countries, the priorities of national policy agendas should be intervention and prevention programs as tools to avoid the continuous increase in obesity and therefore to ensure the health of the global population [24,25].

3. Mechanisms Linking Type 1 Diabetes and Obesity

The interactions between obesity and autoimmune processes are a growing area of research. It has been established that adipose tissue produces a variety of adipokines involved in the regulation of numerous physiological functions, including the immune response. Lately, autoimmune diseases have experienced a significant increase in Western countries, following the same trajectory as obesity. Obesity appears to be an important factor contributing to the onset and progression of autoimmune diseases [26].

More than 75,000 women participated in a large, prospective study with long-term follow-up as part of the Danish National Birth Cohort to assess the risk of developing autoimmune diseases in relation to weight status [27]. The study found that the risk of autoimmune disease was increased by 27% in women with obesity compared with normal-weight women, with the strongest levels of evidence supporting an increased risk of T1D (HR 2.67) and sarcoidosis (HR 3.59).

There are several feasible mechanisms that could explain the connection between obesity and T1D. Two decades ago, the accelerator hypothesis postulated that excess adiposity increases insulin resistance, resulting in glucotoxicity, which accelerates β-cell apoptosis and increases immunogenicity in vulnerable individuals, leading to overt diabetes mellitus [28]. Accordingly, T1D and T2D are both disorders of insulin resistance, representing two extremes of the diabetes spectrum. The overload hypothesis states that in the context of triggered autoimmunity, obesity-associated insulin resistance leads to β-cell overload, accelerating their apoptosis and immune system damage [29,30]. Therefore, both hypotheses identify three processes that variably accelerate the loss of β-cells through apoptosis: obesity, insulin resistance, and autoimmunity. Obesity is believed to be the main driver for the rising incidence not only of T2D but also of T1D. In people with islet autoimmunity, obesity accelerates the development of T1D. In addition, an unhealthy lifestyle, supported an obesogenic environment, obviously contributes to the growing incidence of both types of diabetes. The 21st-century lifestyle promotes the consumption of highly energy-dense foods, larger portions, less physical activity, and more sedentary behavior. As a result, people are gaining weight more easily than ever before, making obesity one of the most common chronic diseases worldwide. Likewise, current dietary guidelines propose a flexible approach to carbohydrate intake in accordance with intensive insulin therapy. Although these guidelines are designed to facilitate greater flexibility around dietary choices, they may lead to the intake of high-calorie foods and potentially unhealthy dietary patterns that are contributing to the high prevalence of obesity and metabolic syndrome in subjects with T1D [31]. Moreover, some animal and human studies have been conducted to investigate the altered gut microbiome in obesity as an important environmental modulator of susceptibility to diabetes [32,33]. These studies have demonstrated an association between the gut microbiome and β-cell autoimmunity. Although an association has been observed, the exact mechanism of how the gut microbiome interacts with host immunity, induces antigen-specific pathogenic T cells, and modulates β-cell autoimmunity in the context of T1D is not yet fully understood.

To add another layer of complexity to the connection between obesity and T1D, insulin itself is known to stimulate lipogenesis, inhibit protein catabolism, and slow basal metabolic rate. Combined with the non-physiologic route of exogenous insulin delivery bypassing the portal vein circulation, this is likely related to weight gain in individuals treated with insulin. Furthermore, insulin therapy itself may exacerbate the state of insulin resistance. Therefore, increasing insulin doses often appears to be necessary to maintain glycemic control, leading to a vicious cycle of insulin resistance and weight gain. It has been shown that patients treated with insulin gain an average of about 5 kg in body weight [34].

There is a growing body of evidence that gastrointestinal hormones play a significant role in energy homeostasis and food intake. In addition to insulin, the secretion of other islet hormones such as amylin and glucagon is also impaired in T1D patients. Consequently, in addition to dysglycemia, this may as well be related to alterations in appetite and satiety regulation, contributing to weight gain [35].

4. Pathophysiology of Obesity in Type 1 Diabetes

Genetic predisposition and environmental factors such as a sedentary lifestyle and unhealthy eating habits can contribute to the development of obesity in patients with type 1 diabetes. High-calorie intake can contribute to obesity in patients with type 1 diabetes, especially if insulin doses are not adjusted appropriately. Different factors such as insulin dosing and fear of hypoglycemia during exercise can contribute to inactive lifestyles. Additionally, some patients with type 1 diabetes have comorbidities or chronic diabetic complications that limit their ability to engage in physical activity [36]. Stress, anxiety, depression, and other mental disorders can also affect eating behaviors and contribute to weight gain in patients with type 1 diabetes. Some patients with type 1 diabetes may develop so-called "double diabetes", a condition where features of both type 1 and type 2 diabetes are present. This can occur due to insulin resistance, which is commonly associated with obesity. It is well known that higher doses or frequent exogenous insulin administration can lead to weight gain. Insulin therapy can promote weight gain through several mechanisms: anabolic effects, inhibition of lipolysis, and appetite stimulation. Insulin is an anabolic hormone that promotes the storage of glucose and fats within cells and inhibits lipolysis, which can promote fat storage and weight gain [37,38]. Finally, some individuals may experience increased hunger and appetite due to insulin therapy. The pathophysiology of obesity in type 1 diabetes is multifactorial, so managing both conditions requires a multifactorial and often multidisciplinary approach that addresses each of these factors through a combination of lifestyle modifications, medical treatment, occasionally surgical treatment, and psychological support [36].

5. The Risk of Diabetic Complications in Individuals with Type 1 Diabetes and Obesity

The adverse effects of obesity in the T1D population are not well studied, although the accumulating evidence suggests that it contributes to adverse health outcomes, just like in the general population and in individuals with T2D [36]. Adding excess adiposity on top of T1D contributes to a higher risk of developing more severe diabetic complications earlier in the course of the disease, as well as the possibility of additional obesity-related complications. With obesity, just like the rest of the population, individuals with T1D may develop insulin resistance, visceral fat, dyslipidemia, fatty liver disease, and other features of metabolic syndrome that put them at a higher risk of cardiovascular disease (CVD) and other chronic non-communicable diseases [39,40].

Besides insulin resistance and CVD, frequent complications in the obese T1D population are microvascular complications, arterial hypertension, dyslipidemia, non-alcoholic fatty liver disease (NAFLD), obstructive sleep apnea, and psychosocial disorders. While type 1 diabetes is primarily characterized by insulin deficiency, obesity can lead to insulin resistance, which can worsen glycemic control and increase the risk of long-term complications such as nephropathy, neuropathy, and retinopathy. NAFLD, associated with insulin resistance and metabolic syndrome, can progress to non-alcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma. Furthermore, obesity is one of the major risk factors for obstructive sleep apnea, which is associated with an increased risk of cardiovascular disease [41].

However, while a lot of emphasis has been placed on CVD in T2D, CVOTs in the T1D population are lacking. The current European Society of Cardiology Guidelines on the management of CVD in patients with diabetes are designed to guide the prevention and management of the manifestations of CVD in patients with diabetes, focusing primarily on T2D population [42].

Moreover, obesity in patients with T1D increases the risk of the development of heart failure (HF) and HF-related death. A 16-year Finnish cohort study has shown that in adults with T1D, central obesity has a stronger association in comparison with general obesity with the risk of hospitalization or death due to HF. In addition, it has been suggested that the waist-to-hip ratio (WHR) as an indicator of central obesity may be considered as a screening tool to identify individuals with T1D at high risk for HF [43]. A nationwide population-based Swedish study of 26,125 patients with T1D followed for a median of 10.9 years found that the risk of major CVD, HF, CVD death, and mortality increased with increasing BMI, with associations being more pronounced in men than in women. Contrary to the effects of glycemic control and other cardiovascular risk factors, the risks caused by obesity appeared modest but higher than in normal-weight subjects [44].

Likewise, it has been shown that obesity is a risk factor for the development of microvascular complications in individuals with T1D. An Australian study in a sample of 501 adults with T1D demonstrated that BMI > 30 kg/m^2 increased the risk of the development of diabetic retinopathy, independently of glycemic control compared to normal weight patients [45]. Several studies have highlighted a strong association between obesity and diabetic kidney disease (DKD) in T1D. UK National Diabetes Audit data, which included a total of 58,791 T1D patients, demonstrated that patients with T1D and DKD were up to twice as likely to have obesity when compared to T1D patients with normal renal function [46].

A recent study including a US cohort of adults with T1D and T2D in a large healthcare system showed that obesity was associated with an increased likelihood of low eGFR in T1D (adjusted odds ratio = 1.52) [18]. Furthermore, after age was accounted for, the burden of DKD in T1D exceeded that of T2D, indicating the need for increased vigilance and the evaluation of renal protective medications in T1D.

It is well documented that psychosocial disorders are more common in obese people and also that obesity has a significant psychosocial impact on patients with type 1 diabetes. Psychosocial factors can negatively affect self-care behaviors, glycemic control, and overall quality of life in obese patients with type 1 diabetes [47].

6. Obesity Management Strategies in Adults with Type 1 Diabetes

6.1. Lifestyle Interventions

Diet, behavioral modifications, and regular physical activity are essential components of all diabetes and obesity management strategies. There is extensive research and expert consensus on how to manage individuals with T2D and obesity through lifestyle interventions. However, the optimal nutritional approach to weight management and metabolic control remains controversial. A variety of dietary patterns are acceptable for the management of diabetes, all of which emphasize the consumption of non-starchy vegetables and whole foods over highly processed foods and encourage patients to minimize their intake of refined grains and added sugars [48]. Current American Diabetes Association (ADA) Standards of Medical Care highlight that in patients with T2D, weight loss can be achieved through a hypocaloric diet with a macronutrient composition and eating pattern based on the individual's medical status, preferences, and food availability [49].

Current guidelines lack evidence to address the most appropriate weight management strategies in adults with T1D. Randomized controlled clinical trials evaluating nutritional approaches to optimize weight management in T1D have not been conducted. Individuals with T1D and obesity may benefit from eating plans that are lower in total carbohydrate and glycemic index and higher in fiber and lean protein content [50].

Even though considered the "gold standard" for dietary patterns, in T1D, there is insufficient evidence of Mediterranean diet intervention. A 6-month trial that randomized patients with T1D and metabolic syndrome to a non-calorie-restricted Mediterranean diet versus a low-fat diet, showed similarly beneficial results on waist circumference, anthropometric and metabolic outcomes, with both dietetic approaches [51]. Likewise, the ACTION Study Group evaluated, in young adults with T1D and overweight or obesity, the

effect of a hypocaloric low carbohydrate, hypocaloric moderate low fat, and Mediterranean diet without calorie restriction on body weight and glycemia. Three months of the diet, irrespective of macronutrient distribution or caloric restriction, resulted in weight loss while improving or maintaining HbA1c levels without increasing the risk of hypoglycemia in adults with T1D [52]. Although low-carbohydrate (<130 g carbohydrate/day) and ketogenic diets (<55 g carbohydrate/day) are very popular for weight loss in the populace with obesity and T2D, there is limited evidence of their use in T1D as some concerns have been expressed mainly regarding the risks of hypoglycemia and DKA [31,53].

For weight loss, individualized dietary plans should support calorie reduction by employing the use of appropriate portion sizes and behavioral interventions as part of a lifestyle program, with appropriate modifications in the medication schedule to minimize associated adverse effects such as weight gain and hypoglycemia. The occurrence of hypoglycemia and its compensatory overeating is one of the main barriers to diet interventions in T1D. Therefore, education is mandatory to properly adjust insulin doses alongside carbohydrate intake to prevent hypoglycemia. Further research on nutrition-based interventions in patients with T1D and obesity is warranted.

The benefits of regular physical activity in obesity and T1D management are well established [54]. Regular physical activity promotes weight loss and has a positive effect on the cardiovascular system, reducing visceral body fat and increasing insulin sensitivity, which in turn helps maintain normal blood glucose levels [55]. In general, adults with obesity are recommended to exercise at least 150 min per week at moderate to vigorous intensity and to do two or three sessions of resistance training per week. For younger and more physically fit individuals, shorter-duration sessions of vigorous intensity or interval training may be sufficient. Although the metabolic benefits of exercise are striking, the effects are short-lived and wear off within 48 to 96 h. Thus, a continuous exercise program is required to maintain the favorable metabolic milieu that exercise can provide.

Physical activity and exercise recommendations in individuals with T1D and obesity should be tailored to meet the specific needs of an individual, including the challenges related to blood glucose management during exercise and the presence of diabetes-related complications. A usual obstacle to weight management in T1D is a reluctance to engage in exercise for fear of hypoglycemia that can take place during, after, or overnight following exercise [56]. Healthcare professionals generally provide limited guidance on insulin dosing and carbohydrate adjustments to maintain stable blood glucose levels during exercise. Thus, it is important to be adequately educated on strategies to reduce the risk of hypoglycemia. Besides frequent glucose monitoring, additional carbohydrate intake and/or reductions in insulin are typically required to prevent hypoglycemia during and after prolonged, predominantly aerobic exercise. For low- to moderate-intensity aerobic activities lasting 30 to 60 min undertaken when circulating insulin levels are low (i.e., fasting conditions), ~10–15 g of carbohydrate is recommended to prevent hypoglycemia. After exercise, the decrease in the long-acting insulin doses by ~20–30%, and 50% of bolus (or in the case of insulin pumps, the reduction in basal rate by ~10–50% and 25–75% of bolus or even its suspension for 1–2 h prior to and during exercise) may limit hypoglycemia [57].

Psychological assessment and cognitive behavioral therapy involving specific, attainable, and relevant goal setting; an approach to problem-solving; stress reduction; self-monitoring of food intake and exercise; stimulus control; social support; and education should be integrated into the routine clinical management of obesity in T1D. In the context of a structured weight intervention program, these behavioral interventions have proven to be beneficial. A retrospective matched cohort study indicated that patients with T1D and obesity who participated in an intensive multidisciplinary weight management program achieved significant weight loss and a significant reduction in daily insulin dose after one year compared with standard treatment [58]. Weight loss was associated with an improvement in glycemic control compared with baseline.

6.2. Pharmacotherapy

Currently, adjunctive antihyperglycemic pharmacotherapy is not indicated for individuals with T1D. However, there is evidence that in select individuals with T1D and excess adiposity, certain drugs that were originally produced to treat patients with T2D, such as metformin and glucagon-like peptide 1 receptor agonists (GLP-1RA), may have beneficial effects on obesity and cardiovascular disease risk factors.

The off-label use of metformin in T1D is quite common in clinical practice. A meta-analysis of seven randomized controlled clinical trials evaluating the addition of metformin to insulin therapy in individuals with T1D demonstrated a sustained reduction in body weight and total daily insulin dose requirement but no consistent effect on HbA1c [59]. However, most of these trials were small and of short duration. Recently published findings from the REMOVAL (REducing with MetfOrmin Vascular Adverse Lesions) trial provided some proof of concept for a beneficial cardiovascular effect of metformin in T1D, including weight loss of 1.2 kg and a reduction in LDL-cholesterol levels and atherosclerosis progression [60]. Of note, the study population consisted of middle-aged individuals with long-duration T1D already treated with antihypertensive agents and statins.

The use of GLP-1RAs in T1D has been shown to have beneficial effects on both weight loss and insulin dose reduction, especially in patients with residual beta cell function (detectable C-peptide) and/or obesity [61,62]. Further studies are needed to investigate the potential impact of these agents on clinical outcomes such as microvascular and macrovascular complications. To date, the largest randomized control trials investigating GLP-1RAs in T1D are the ADJUNCT ONE and ADJUNCT TWO trials, which have reported similar results with respect to significant weight loss [63,64]. ADJUNCT ONE was a 52-week randomized, placebo-controlled, double-blind trial, which randomized 1398 adults with T1D to liraglutide or placebo. Significant, dose-dependent reductions in body weight were shown in the liraglutide treatment groups with mean loss of 4.0 kg with 1.8 mg, 2.7 kg with 1.2 mg, and 1.3 kg with 0.6 mg liraglutide daily. A real-world exploratory study demonstrated that adding semaglutide 1.0 mg once weekly in adults with T1D and overweight/obesity was well tolerated, safe, and resulted in a mean body weight reduction of 8.5 kg after six months with additional promising effects on insulin requirement and glycemic control [65]. Several GLP-1 receptor agonists have shown beneficial effects on weight loss in people without type 1 or type 2 diabetes [66,67]. A new class of drugs is promising for the treatment of type 2 diabetes and obesity—the coagonist of gut hormone receptors. Several classes of coagonists of gut hormone receptors are in development. Tirzepatide was the first coagonist of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptors approved by the US Food and Drug Administration 2022 for treating type 2 diabetes. The results of clinical trials showed a superior reduction of HbA1c compared to GLP-1 receptor agonists or basal insulin. Tirzepatide achieved weight loss of up to 22.5%. According to the results of clinical trials in obese people with and without diabetes, tirzepatide was indicated for the treatment of type 2 diabetes and obesity [68–70]. The triple GIP-GLP-1-glucagon co-agonists designed in 2015 are also a promising therapy for type 2 diabetes and obesity [71,72]. Significant rates of euglycemic ketoacidosis as adverse events have prevented the widespread use of SGLT-2 inhibitors as an adjunct therapy in T1D despite their favorable effect on weight loss [73–77].

According to current guidelines, anti-obesity pharmacotherapy, as an addition to lifestyle changes, is indicated in patients with BMI $\geq$ 30 kg/m^2 or BMI $\geq$ 27 kg/m^2 in the presence of obesity-related complications. Even though these drugs are not contraindicated in T1D, there is a scarcity of evidence about their use in these populations as individuals with T1D have been excluded from randomized clinical trials evaluating anti-obesity medications. However, it seems reasonable to assume that subjects with T1D and obesity, who are unable to accomplish a significant and sustained weight loss with lifestyle interventions, may benefit from pharmacotherapy in real life [78]. Therefore, there is an urgent need for studies that would clarify the efficacy, safety, and tolerability of anti-obesity medications in the T1D population.

6.3. Bariatric Surgery

Bariatric surgery has been shown to be effective in treating patients with T2D and obesity, but its outcomes in populations with T1D and obesity are still not well known [79]. According to a systematic review that included 30 studies with a total of 706 patients with T1D and obesity who underwent bariatric surgery (70.4% Roux-en-Y gastric bypass, 18.6% sleeve gastrectomy), significant weight loss and reduction in insulin requirements were reported [80]. However, no significant changes in HbA1c levels were observed. These advantages outweigh the adverse events observed, such as an increased risk of hypoglycemia and DKA. Nevertheless, in this group of patients, close monitoring provided by a multidisciplinary team is necessary to provide a tailored and, along with diabetes care and education, modifiable insulin regimen during all phases of management. Longer and larger studies are required to establish the role of metabolic surgery in individuals with T1D and obesity [81].

7. Conclusions and Future Directions

Emerging evidence suggests a growing prevalence of obesity among individuals with T1D, placing them at higher risk of developing diabetic complications and posing an immense challenge for effective glycemic and weight management. Action plans on T1D-obesity treatment goals for clinicians should be clarified. To achieve and sustain glycemic equilibrium, multidisciplinary teams are indispensable with complementary holistic interventions as part of structured programs with the goal of sustaining a patient-centered approach that considers individual preference and adherence. Finally, it is important to point out that not everyone has equal access to health care. It is known that developed countries have more available pharmacotherapy as well as technological innovations, which today have a significant role in treatment. Unequal access to treatment resources will result in significant differences in glycemic control and consequently the appearance of obesity-related complications, especially in groups of lower socioeconomic status [82]. Current clinical guidelines lack evidence on the most appropriate weight management strategies in people living with T1D and obesity. The results of ongoing clinical trials for new anti-obesity drugs are promising. New insulin formulations for the treatment of type 1 diabetes will be also available soon. A lower risk of hypoglycemia and lower risk of weight gain from new insulin formulations will help prevent obesity in people with type 1 diabetes as well. Further clinical trials for treating obesity in people with type 1 diabetes are warranted.

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References

1. Frühbeck, G.; Busetto, L.; Dicker, D.; Yumuk, V.; Goossens, G.H.; Hebebrand, J.; Halford, J.G.C.; Farpour-Lambert, N.J.; Blaak, E.E.; Woodward, E.; et al. The ABCD of Obesity: An EASO Position Statement on a Diagnostic Term with Clinical and Scientific Implications. *Obes. Facts* **2019**, *12*, 131–136. [CrossRef]
2. Cooper, A.J.; Gupta, S.R.; Moustafa, A.F.; Chao, A.M. Sex/Gender Differences in Obesity Prevalence, Comorbidities, and Treatment. *Curr. Obes. Rep.* **2021**, *10*, 458–466. [CrossRef] [PubMed]
3. Wen, Y.; Liu, T.; Li, S.; Gong, R.; Li, C. Trends in the prevalence of metabolically healthy and unhealthy obesity in the US adult population: Analysis of eight NHANES cross-sectional survey cycles, 1999–2014. *BMJ Open* **2022**, *12*, e062651. [CrossRef] [PubMed]
4. Pi-Sunyer, F.X. The obesity epidemic: Pathophysiology and consequences of obesity. *Obes. Res.* **2002**, *10* (Suppl. S2), 97S–104S. [CrossRef] [PubMed]
5. Powell-Wiley, T.M.; Poirier, P.; Burke, L.E.; Després, J.P.; Gordon-Larsen, P.; Lavie, C.J.; Lear, S.A.; Ndumele, C.E.; Neeland, I.J.; Sanders, P.; et al. Obesity and Cardiovascular Disease: A Scientific Statement from the American Heart Association. *Circulation* **2021**, *143*, e984–e1010. [CrossRef]
6. Ruze, R.; Liu, T.; Zou, X.; Song, J.; Chen, Y.; Xu, R.; Yin, X.; Xu, Q. Obesity and type 2 diabetes mellitus: Connections in epidemiology, pathogenesis, and treatments. *Front. Endocrinol.* **2023**, *14*, 1161521. [CrossRef] [PubMed]
7. Van der Schueren, B.; Ellis, D.; Faradji, R.N.; Al-Ozairi, E.; Rosen, J.; Mathieu, C. Obesity in People Living with Type 1 Diabetes. *Lancet Diabetes Endocrinol.* **2021**, *9*, 776–785. [CrossRef]
8. Lingvay, I.; Sumithran, P.; Cohen, R.V.; le Roux, C.W. Obesity management as a primary treatment goal for type 2 diabetes: Time to reframe the conversation. *Lancet* **2022**, *399*, 394–405. [CrossRef]
9. International Diabetes Federation. IDF Diabetes Atlas 2022 Reports. Available online: https://www.diabetesatlas.org (accessed on 14 March 2024).
10. Fang, M.; Jeon, Y.; Echouffo-Tcheugui, J.B.; Selvin, E. Prevalence and Management of Obesity in U.S. Adults with Type 1 Diabetes. *Ann. Intern. Med.* **2023**, *176*, 427–429. [CrossRef]
11. Patterson, C.C.; Harjutsalo, V.; Rosenbauer, J.; Neu, A.; Cinek, O.; Skrivarhaug, T.; Rami-Merhar, B.; Soltesz, G.; Svensson, J.; Parslow, R.C.; et al. Trends and cyclical variation in the incidence of childhood type 1 diabetes in 26 European centres in the 25 year period 1989–2013: A multicentre prospective registration study. *Diabetologia* **2019**, *62*, 408–417. [CrossRef] [PubMed]
12. Oboza, P.; Ogarek, N.; Olszanecka-Glinianowicz, M.; Kocelak, P. Can type 1 diabetes be an unexpected complication of obesity? *Front. Endocrinol.* **2023**, *14*, 1121303. [CrossRef]
13. Polsky, S.; Ellis, S.L. Obesity, insulin resistance, and type 1 diabetes mellitus. *Curr. Opin. Endocrinol. Diabetes Obes.* **2015**, *22*, 277–282. [CrossRef]
14. Chobot, A.; Górowska-Kowolik, K.; Sokołowska, M.; Jarosz-Chobot, P. Obesity and diabetes—Not only a simple link between two epidemics. *Diabetes Metab. Res. Rev.* **2018**, *34*, e3042. [CrossRef]
15. Corbin, K.D.; Driscoll, K.A.; Pratley, R.E.; Smith, S.R.; Maahs, D.M.; Mayer-Davis, E.J. Advancing Care for Type 1 Diabetes and Obesity Network (ACT1ON). Obesity in Type 1 Diabetes: Pathophysiology, Clinical Impact, and Mechanisms. *Endocr. Rev.* **2018**, *39*, 629–663. [CrossRef]
16. Harding, J.L.; Shaw, J.E.; Peeters, A.; Cartensen, B.; Magliano, D.J. Cancer risk among people with type 1 and type 2 diabetes: Disentangling true associations, detection bias, and reverse causation. *Diabetes Care* **2015**, *38*, 264–270. [CrossRef]
17. Carstensen, B.; Read, S.H.; Friis, S.; Sund, R.; Keskimäki, I.; Svensson, A.M.; Ljung, R.; Wild, S.H.; Kerssens, J.J.; Harding, J.L.; et al. Cancer incidence in persons with type 1 diabetes: A five-country study of 9000 cancers in type 1 diabetic individuals. *Diabetologia* **2016**, *59*, 980–988. [CrossRef]
18. Wallace, A.S.; Chang, A.R.; Shin, J.I.; Reider, J.; Echouffo-Tcheugui, J.B.; Grams, M.E.; Selvin, E. Obesity and Chronic Kidney Disease in US Adults With Type 1 and Type 2 Diabetes Mellitus. *J. Clin. Endocrinol. Metab.* **2022**, *107*, 1247–1256. [CrossRef]
19. Pinhas-Hamiel, O.; Levek-Motola, N.; Kaidar, K.; Boyko, V.; Tisch, E.; Mazor-Aronovitch, K.; Graf-Barel, C.; Landau, Z.; Lerner-Geva, L.; Ben-David, R.F. Prevalence of overweight, obesity and metabolic syndrome components in children, adolescents and young adults with type 1 diabetes mellitus. *Diabetes Metab. Res. Rev.* **2015**, *31*, 76–84. [CrossRef]

20. Vestberg, D.; Rosengren, A.; Olsson, M.; Gudbjörnsdottir, S.; Svensson, A.M.; Lind, M. Relationship between overweight and obesity with hospitalization for heart failure in 20 985 patients with type 1 diabetes: A population-based study from the Swedish National Diabetes Registry. *Diabetes Care* **2013**, *36*, 2857–2861. [CrossRef]
21. Holt, S.K.; Lopushnyan, N.; Hotaling, J.; Sarma, A.V.; Dunn, R.L.; Cleary, P.A.; Braffett, B.H.; Gatcomb, P.; Martin, C.; Herman, W.H.; et al. Prevalence of low testosterone and predisposing risk factors in men with type 1 diabetes mellitus: Findings from the DCCT/EDIC. *J. Clin. Endocrinol. Metab.* **2014**, *99*, E1655–E1660. [CrossRef]
22. Fourlanos, S.; Elkassaby, S.; Varney, M.D.; Colman, P.G.; Harrison, L.C. Higher body mass index in adults at diagnosis of the slowly progressive formof type 1 diabetes mellitus is associated with lower risk HLA genes. *Diabetes Res. Clin. Pract.* **2014**, *104*, e69–e71. [CrossRef]
23. Conway, B.; Miller, R.G.; Costacou, T.; Fried, L.; Kelsey, S.; Evans, R.W.; Orchard, T.J. Temporal patterns in overweight and obesity in Type 1 diabetes. *Diabet. Med.* **2010**, *27*, 398–404. [CrossRef]
24. González-álvarez, M.A.; Lázaro-Alquézar, A.; Simón-Fernández, M.B. Global trends in child obesity: Are figures converging? *Int. J. Environ. Res. Public Health* **2020**, *17*, 9252. [CrossRef]
25. Malik, V.S.; Willet, W.C.; Hu, F.B. Nearly a decade on—trends, risk factors and policy implications in global obesity. *Nat. Rev. Endocrinol.* **2020**, *16*, 615–616. [CrossRef]
26. Versini, M.; Jeandel, P.-Y.; Rosenthal, E.; Shoenfeld, Y. Obesity in autoimmune diseases: Not a passive bystander. *Autoimmun. Rev.* **2014**, *13*, 981–1000. [CrossRef]
27. Harpsoe, M.C.; Basit, S.; Andersson, M.; Nielsen, N.M.; Frisch, M.; Wohlfahrt, J.; Nohr, E.A.; Linneberg, A.; Jess, T. Body mass index and risk of autoimmune diseases: A study within the Danish National Birth Cohort. *Int. J. Epidemiol.* **2014**, *43*, 843–855. [CrossRef]
28. Wilkin, T.J. The accelerator hypothesis: Weight gain as the missing link between type i and type ii diabetes. *Diabetologia* **2001**, *44*, 914–922. [CrossRef]
29. Islam, S.T.; Srinivasan, S.; Craig, M.E. Environmental determinants of type 1 diabetes: A role for overweight and insulin resistance. *J. Paediatr. Child Health* **2014**, *50*, 874–879. [CrossRef]
30. Dahlquist, G. Can we slow the rising incidence of childhood-onset autoimmune diabetes? The overload hypothesis. *Diabetologia* **2006**, *49*, 20–24. [CrossRef]
31. Scott, S.N.; Anderson, L.; Morton, J.P.; Wagenmakers, A.J.M.; Riddell, M.C. Carbohydrate Restriction in Type 1 Diabetes: A Realistic Therapy for Improved Glycaemic Control and Athletic Performance? *Nutrients* **2019**, *11*, 1022. [CrossRef]
32. Winiarska-Mieczan, A.; Tomaszewska, E.; Donaldson, J.; Jachimowicz, K. The Role of Nutritional Factors in the Modulation of the Composition of the Gut Microbiota in People with Autoimmune Diabetes. *Nutrients* **2022**, *14*, 2498. [CrossRef]
33. Campbell, C.; Kandalgaonkar, M.R.; Golonka, R.M.; Yeoh, B.S.; Vijay-Kumar, M.; Saha, P. Crosstalk between Gut Microbiota and Host Immunity: Impact on Inflammation and Immunotherapy. *Biomedicines* **2023**, *11*, 294. [CrossRef] [PubMed]
34. The Diabetes Control and Complications Trial Research Group. Influence of intensive diabetes treatment on body weight and composition of adults with type 1 diabetes in the Diabetes Control and Complications Trial. *Diabetes Care* **2001**, *24*, 1711–1721. [CrossRef]
35. Boyle, C.N.; Zheng, Y.; Lutz, T.A. Mediators of Amylin Action in Metabolic Control. *J. Clin. Med.* **2022**, *11*, 2207. [CrossRef]
36. Vilarrasa, N.; San Jose, P.; Rubio, M.Á.; Lecube, A. Obesity in Patients with Type 1 Diabetes: Links, Risks and Management Challenges. *Diabetes Metab. Syndr. Obes.* **2021**, *14*, 2807–2827. [CrossRef]
37. Bielka, W.; Przezak, A.; Molęda, P.; Pius-Sadowska, E.; Machaliński, B. Double diabetes-when type 1 diabetes meets type 2 diabetes: Definition, pathogenesis and recognition. *Cardiovasc. Diabetol.* **2024**, *23*, 62. [CrossRef]
38. Kietsiriroje, N.; Pearson, S.; Campbell, M.; Ariëns, R.A.S.; Ajjan, R.A. Double diabetes: A distinct high-risk group? *Diabetes Obes. Metab.* **2019**, *21*, 2609–2618. [CrossRef]
39. Chillarón, J.J.; Flores Le-Roux, J.A.; Benaiges, D.; Pedro-Botet, J. Type 1 diabetes, metabolic syndrome and cardiovascular risk. *Metabolism* **2014**, *63*, 181–187. [CrossRef]
40. Chiesa, S.T.; Marcovecchio, M.L. Preventing cardiovascular complications in type 1 diabetes: The need for a lifetime approach. *Front. Pediatr.* **2021**, *9*, 696499. [CrossRef]
41. Memaj, P.; Jornayvaz, F.R. Non-alcoholic fatty liver disease in type 1 diabetes: Prevalence and pathophysiology. *Front. Endocrinol.* **2022**, *13*, 1031633. [CrossRef]
42. Marx, N.; Federici, M.; Schütt, K.; Müller-Wieland, D.; Ajjan, R.A.; Antunes, M.J.; Christodorescu, R.M.; Crawford, C.; Di Angelantonio, E.; Eliasson, B.; et al. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes: Developed by the task force on the management of cardiovascular disease in patients with diabetes of the European Society of Cardiology (ESC). *Eur. Heart J.* **2023**, *44*, 4043–4140. [CrossRef] [PubMed]
43. Parente, E.B.; Harjutsalo, V.; Forsblom, C.; Groop, P.H.; FinnDiane Study Group. The impact of central obesity on the risk of hospitalization or death due to heart failure in type 1 diabetes: A 16-year cohort study. *Cardiovasc. Diabetol.* **2021**, *20*, 153. [CrossRef] [PubMed]
44. Edqvist, J.; Rawshani, A.; Adiels, M.; Björck, L.; Lind, M.; Svensson, A.M.; Gudbjörnsdottir, S.; Sattar, N.; Rosengren, A. BMI, mortality, and cardiovascular outcomes in type 1 diabetes: Findings against an obesity paradox. *Diabetes Care* **2019**, *42*, 1297–1304. [CrossRef] [PubMed]

45. Price, S.A.; Gorelik, A.; Fourlanos, S.; Colman, P.G.; Wentworth, J.M. Obesity is associated with retinopathy and macrovascular disease in type 1 diabetes. *Obes. Res. Clin. Pract.* **2014**, *8*, e178–e182. [CrossRef] [PubMed]
46. Hill, C.J.; Cardwell, C.R.; Maxwell, A.P.; Young, R.J.; Matthews, B.; O'Donoghue, D.J.; Fogarty, D.G. Obesity and kidney disease in type 1 and 2 diabetes: An analysis of the National Diabetes Audit. *QJM* **2013**, *106*, 933–942. [CrossRef]
47. Kalra, S.; Jena, B.N.; Yeravdekar, R. Emotional and Psychological Needs of People with Diabetes. *Indian J. Endocrinol. Metab.* **2018**, *22*, 696–704. [PubMed]
48. Evert, A.B.; Dennison, M.; Gardner, C.D.; Garvey, W.T.; Lau, K.H.K.; MacLeod, J.; Mitri, J.; Pereira, R.F.; Rawlings, K.; Robinson, S.; et al. Nutrition therapy for adults with diabetes or prediabetes: A consensus report. *Diabetes Care* **2019**, *42*, 731–754. [CrossRef] [PubMed]
49. American Diabetes Association Professional Practice Committee. 5. Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes: Standards of Care in Diabetes-2024. *Diabetes Care* **2024**, *47* (Suppl. S1), S77–S110, Corrected in *Diabetes Care* **2024**, *47*, 761–762.
50. ElSayed, N.A.; Aleppo, G.; Bannuru, R.R.; Bruemmer, D.; Collins, B.S.; Ekhlaspour, L.; Hilliard, M.E.; Johnson, E.L.; Khunti, K.; American Diabetes Association Professional Practice Committee; et al. 8. Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes: Standards of Care in Diabetes-2024. *Diabetes Care* **2024**, *47* (Suppl. S1), S145–S157.
51. Mottalib, A.; Kasetty, M.; Mar, J.Y.; Elseaidy, T.; Ashrafzadeh, S.; Hamdy, O. Weight Management in Patients with Type 1 Diabetes and Obesity. *Curr. Diabetes Rep.* **2017**, *17*, 92. [CrossRef]
52. Fortin, A.; Rabasa-Lhoret, R.; Lemieux, S.; Labonté, M.E.; Gingras, V. Comparison of a Mediterranean to a low-fat diet intervention in adults with type 1 diabetes and metabolic syndrome: A 6-month randomized trial. *Nutr. Metab. Cardiovasc. Dis.* **2018**, *28*, 1275–1284. [CrossRef] [PubMed]
53. Igudesman, D.; Crandell, J.; Corbin, K.D.; Zaharieva, D.P.; Addala, A.; Thomas, J.M.; Casu, A.; Kirkman, M.S.; Pokaprakarn, T.; Riddell, M.C.; et al. Weight management in young adults with type 1 diabetes: The advancing care for type 1 diabetes and obesity network sequential multiple assignment randomized trial pilot results. *Diabetes Obes. Metab.* **2023**, *25*, 688–699. [CrossRef] [PubMed]
54. Feinman, R.D.; Pogozelski, W.K.; Astrup, A.; Bernstein, R.K.; Fine, E.J.; Westman, E.C.; Accurso, A.; Frassetto, L.; Gower, B.A.; McFarlane, S.I.; et al. Dietary carbohydrate restriction as the first approach in diabetes management: Critical review and evidence base. *Nutrition* **2015**, *31*, 1–13. [CrossRef] [PubMed]
55. Absil, H.; Baudet, L.; Robert, A.; Lysy, P.A. Benefits of physical activity in children and adolescents with type 1 diabetes: A systematic review. *Diabetes Res. Clin. Pract.* **2019**, *156*, 107810. [CrossRef]
56. Pomar, M.D.B.; García, N.V.; Herrera, M.Á.R.; Barahona, M.J.; Bueno, M.; Caixàs, A.; Continente, A.C.; Ciudin, A.; Cordido, F.; de Hollanda, A.; et al. The SEEN comprehensive clinical survey of adult obesity: Executive summary. *Endocrinol. Diabetes Nutr.* **2021**, *68*, 130–136.
57. Roberts, A.J.; Taplin, C.E.; Isom, S.; Divers, J.; Saydah, S.; Jensen, E.T.; Mayer-Davis, E.J.; Reid, L.A.; Liese, A.D.; Dolan, L.M.; et al. Association between fear of hypoglycemia and physical activity in youth with type 1 diabetes: The SEARCH for diabetes in youth study. *Pediatr. Diabetes* **2020**, *21*, 1277–1284. [CrossRef] [PubMed]
58. Colberg, S.R.; Sigal, R.J.; Yardley, J.E.; Riddell, M.C.; Dunstan, D.W.; Dempsey, P.C.; Horton, E.S.; Castorino, K.; Tate, D.F. Physical Activity/Exercise and Diabetes: A Position Statement of the American Diabetes Association. *Diabetes Care* **2016**, *39*, 2065–2079. [CrossRef] [PubMed]
59. Mottalib, A.; Tomah, S.; Hafida, S.; Elseaidy, T.; Kasetty, M.; Ashrafzadeh, S.; Hamdy, O. Intensive multidisciplinary weight management in patients with type 1 diabetes and obesity: A one-year retrospective matched cohort study. *Diabetes Obes. Metab.* **2019**, *21*, 37–42. [CrossRef]
60. Vella, S.; Buetow, L.; Royle, P.; Livingstone, S.; Colhoun, H.M.; Petrie, J.R. The use of metformin in type 1 diabetes: A systematic review of efficacy. *Diabetologia* **2010**, *53*, 809–820. [CrossRef]
61. Timmons, J.G.; Greenlaw, N.; Boyle, J.G.; Chaturvedi, N.; Ford, I.; Brouwers, M.C.G.J.; Tillin, T.; Hramiak, I.; Hughes, A.D.; Jenkins, A.J.; et al. Metformin and carotid intima-media thickness in never-smokers with type 1 diabetes: The REMOVAL trial. *Diabetes Obes. Metab.* **2021**, *23*, 1371–1378. [CrossRef]
62. Guyton, J.; Jeon, M.; Brooks, A. Glucagon-like peptide 1 receptor agonists in type 1 diabetes mellitus. *Am. J. Health Syst. Pharm.* **2019**, *76*, 1739–1748. [CrossRef]
63. Wang, W.; Liu, H.; Xiao, S.; Liu, S.; Li, X.; Yu, P. Effects of insulin plus glucagon-like peptide-1 receptor agonists (GLP-1RAs) in treating type 1 diabetes mellitus: A systematic review and meta-analysis. *Diabetes Ther.* **2017**, *8*, 727–738. [CrossRef]
64. Mathieu, C.; Zinman, B.; Hemmingsson, J.U.; Woo, V.; Colman, P.; Christiansen, E.; Linder, M.; Bode, B.; the ADJUNCT ONE Investigators. Efficacy and safety of liraglutide added to insulin treatment in type 1 diabetes: The ADJUNCT ONE treat-to-target randomized trial. *Diabetes Care* **2016**, *39*, 1702–1710. [CrossRef] [PubMed]
65. Ahrén, B.; Hirsch, I.B.; Pieber, T.R.; Mathieu, C.; Gómez-Peralta, F.; Hansen, T.K.; Philotheou, A.; Birch, S.; Christiansen, E.; Jensen, T.J.; et al. Efficacy and safety of liraglutide added to capped insulin treatment in subjects with type 1 diabetes: The ADJUNCT TWO randomized trial. *Diabetes Care* **2016**, *39*, 1693–1701. [CrossRef]
66. Iqbal, J.; Wu, H.X.; Hu, N.; Zhou, Y.H.; Li, L.; Xiao, F.; Wang, T.; Jiang, H.L.; Xu, S.N.; Huang, B.L.; et al. Effect of glucagon-like peptide-1 receptor agonists on body weight in adults with obesity without diabetes mellitus-a systematic review and meta-analysis of randomized control trials. *Obes. Rev.* **2022**, *23*, e13435. [CrossRef] [PubMed]

67. Alkhezi, O.S.; Alahmed, A.A.; Alfayez, O.M.; Alzuman, O.A.; Almutairi, A.R.; Almohammed, O.A. Comparative effectiveness of glucagon-like peptide-1 receptor agonists for the management of obesity in adults without diabetes: A network meta-analysis of randomized clinical trials. *Obes. Rev.* **2023**, *24*, e13543. [CrossRef] [PubMed]
68. Nogueiras, R.; Nauck, M.A.; Tschöp, M.H. Gut hormone co-agonists for the treatment of obesity: From bench to bedside. *Nat. Metab.* **2023**, *5*, 933–944. [CrossRef]
69. Nauck, M.A.; D'Alessio, D.A. Tirzepatide, a dual GIP/GLP-1 receptor co-agonist for the treatment of type 2 diabetes with unmatched effectiveness regrading glycaemic control and body weight reduction. *Cardiovasc. Diabetol.* **2022**, *21*, 169. [CrossRef]
70. Karagiannis, T.; Avgerinos, I.; Liakos, A.; Del Prato, S.; Matthews, D.R.; Tsapas, A.; Bekiari, E. Management of type 2 diabetes with the dual GIP/GLP-1 receptor agonist tirzepatide: A systematic review and meta-analysis. *Diabetologia* **2022**, *65*, 1251–1261. [CrossRef]
71. Müller, T.D.; Blüher, M.; Tschöp, M.H.; DiMarchi, R.D. Anti-obesity drug discovery: Advances and challenges. *Nat. Rev. Drug Discov.* **2022**, *21*, 201–223. [CrossRef]
72. Gutgesell, R.M.; Nogueiras, R.; Tschöp, M.H.; Müller, T.D. Dual and Triple Incretin-Based Co-agonists: Novel Therapeutics for Obesity and Diabetes. *Diabetes Ther.* **2024**, *15*, 1069–1084. [CrossRef] [PubMed]
73. Mertens, J.; De Winter, H.; Mazlom, H.; Peiffer, F.W.; Dirinck, E.I.; Bochanen, N.; Van Gaal, L.F.; De Block, C. 751-P: Effect of Once-Weekly Semaglutide on Weight Change and Metabolic Control in People with Type 1 Diabetes—Six-Months Results from the Real-World STEMT Trial. *Diabetes* **2022**, *71* (Suppl. S1), 751-P. [CrossRef]
74. Henry, R.R.; Thakkar, P.; Tong, C.; Polidori, D.; Alba, M. Efficacy and safety of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to insulin in patients with type 1 diabetes. *Diabetes Care* **2015**, *38*, 2258–2265. [CrossRef] [PubMed]
75. Dandona, P.; Mathieu, C.; Phillip, M.; Hansen, L.; Tschöpe, D.; Thorén, F.; Xu, J.; Langkilde, A.M.; Proietto, J.; Stranks, S.; et al. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes: The DEPICT-1 52-Week Study. *Diabetes Care* **2018**, *41*, 2552–2559. [CrossRef] [PubMed]
76. Mathieu, C.; Dandona, P.; Gillard, P.; Senior, P.; Hasslacher, C.; Araki, E.; Lind, M.; Bain, S.C.; Jabbour, S.; Arya, N.; et al. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (the DEPICT-2 study): 24-week results from a randomized controlled trial. *Diabetes Care* **2018**, *41*, 1938–1946. [CrossRef] [PubMed]
77. Rosenstock, J.; Marquard, J.; Laffel, L.M.; Neubacher, D.; Kaspers, S.; Cherney, D.Z.; Zinman, B.; Skyley, J.S.; George, J.; Soleymanlou, N.; et al. Empagliflozin as adjunctive toinsulin therapy in type 1 diabetes: The EASE trials. *Diabetes Care* **2018**, *41*, 2560–2569. [CrossRef] [PubMed]
78. Buse, J.B.; Garg, S.K.; Rosenstock, J.; Bailey, T.S.; Banks, P.; Bode, B.W.; Danne, T.; Kushner, J.A.; Lane, W.S.; Lapuerta, P.; et al. Sotagliflozin in combination with optimized insulin therapy in adults with type 1 diabetes: The North American in Tandem1 Study. *Diabetes Care* **2018**, *41*, 1970–1980. [CrossRef] [PubMed]
79. Casu, A.; Bilal, A.; Pratley, R.E.; Advancing Care for Type 1 Diabetes, Obesity Network (ACT1ON). Pharmacological therapies to address obesity in type 1 diabetes. *Curr. Opin. Endocrinol. Diabetes Obes.* **2020**, *27*, 194–206. [CrossRef] [PubMed]
80. Vendrame, F.; Calhoun, P.; Bocchino, L.E.; Pratley, R.E.; Casu, A. Impact of bariatric surgery and weight loss medications in adults with type 1 diabetes in the T1D Exchange Clinic Registry. *J. Diabetes Complicat.* **2021**, *35*, 107884. [CrossRef] [PubMed]
81. Parmar, C.; Appel, S.; Lee, L.; Ribeiro, R.; Sakran, N.; Pouwels, S. Choice of Bariatric Surgery in Patients with Obesity and Type 1 Diabetes Mellitus? an Up-to-Date Systematic Review. *Obes. Surg.* **2022**, *32*, 3992–4006. [CrossRef]
82. Kueh, M.T.W.; Chew, N.W.S.; Al-Ozairi, E.; le Roux, C.W. The emergence of obesity in type 1 diabetes. *Int. J. Obes.* **2024**, *48*, 289–301. [CrossRef] [PubMed]