REVIEW

Obesity in Patients with Type 1 Diabetes: Links, Risks and Management Challenges

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Abstract: Obesity affects large numbers of patients with type 1 diabetes (T1D) across their lifetime, with rates ranging between 2.8% and 37.1%. Patients with T1D and obesity are characterized by the presence of insulin resistance, of high insulin requirements, have a greater cardiometabolic risk and an enhanced risk of developing chronic complications when compared to normal-weight persons with T1D. Dual treatment of obesity and T1D is challenging and no specific guidelines for improving outcomes of both glycemic control and weight management have been established for this population. Nevertheless, although evidence is scarce, a comprehensive approach based on a balanced hypocaloric diet, physical activity and cognitive behavioral therapy by a multidisciplinary team, expert in both obesity and diabetes, remains as the best clinical practice. However, weight loss responses with lifestyle changes alone are limited, so in the "roadmap" of the treatment of obesity in T1D, it will be helpful to include anti-obesity pharmacotherapy despite at present there is a lack of evidence since T1D patients have been excluded from anti-obesity drug clinical trials. In case of severe obesity, bariatric surgery has proven to be of benefit in obtaining a substantial and long-term weight loss and reduction in cardiovascular risk. The near future looks promising with the development of new and more effective anti-obesity treatments and strategies to improve insulin resistance and oxidative stress. Advances in precision medicine may help individualize and optimize the medical management and care of these patients. This review, by gathering current evidence, highlights the need of solid knowledge in all facets of the treatment of patients with obesity and T1D that can only be obtained through high quality well-designed studies.

Keywords: obesity, type 1 diabetes, dual diabetes, insulin resistance, metabolic syndrome, bariatric surgery

Introduction

The prevalence of overweight and obesity in adults and children is continuously increasing worldwide and has doubled in more than 73 countries since 1980.[1] Using the Global Burden of Disease study data, the estimated prevalence of obesity around the world in 2015 was 5.0% in children and 12.0% in adults, with high BMI accounting for 4 million deaths mainly due to cardiovascular disease.[1] This dramatic increase in the prevalence of overweight and obesity affects patients with T1D which are especially vulnerable to excess weight. In this regard, increased BMI in T1D is associated with a greater cardiometabolic risk and enhanced development of chronic complications compared to lean patients with T1D.[2] On the other hand, insulin resistance leads to high insulin requirements and hinders glycemic control and weight management. In the present review, we will

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summarize existing data on prevalence, trends, links and causes of obesity in patients with T1D.

Dual treatment of obesity and T1D is full of barriers and challenges as the equilibrium between intensified insulin therapy and optimal weight is difficult. Nowadays, no specific evidence-based guidelines for improving both glycemic control and weight management have been established for this population. In this paper, we will review the outcomes of specific nutritional, exercise and psychological strategies used in this clinical situation that may be useful to improve their care. For those patients unable to achieve a significant and sustained weight loss with lifestyle interventions, we will describe the evidence of adjunctive pharmacological treatments added to insulin, the potential benefits of approved anti-obesity drugs and the indications, outcomes and risks of bariatric surgery (BS). Also, in the near future new and more potent anti-obesity drugs under development promise to facilitate the management of these patients. Our review highlights that although it is a growing problem, the knowledge in obesity approach in T1D is still very scarce, and therefore there is an urgent need for high quality designed studies from which evidence-based guidelines can be derived.

Epidemiology of Obesity in Type 1 Diabetes
How Often Does Obesity Appear in Type 1 Diabetes?

When dealing with a patient with obesity and diabetes, it is essential to make a proper classification into T1D or type 2 diabetes (T2D) as they are heterogeneous diseases with variable clinical presentation and disease progression. T1D is caused by autoimmune β-cell destruction, which leads to an absolute insulin deficiency, and insulin treatment is needed from the onset of the disease. On the other hand, T2D is due to peripheral insulin resistance and a progressive loss of adequate insulin secretion.[3]

Obesity affects large amounts of patients with T1D across their lifetime, with a prevalence that has increased during recent decades, and with rates ranging between 2.8% and 37.1%.[4] However, differences appear according to the definition of obesity, the age of the examined population, and the country. When obesity is defined as a body mass index (BMI) ≥95th percentile, its prevalence ranges from 5.2% in Israel for the age cohort 5 to 30 years[5] to 13.5% in adolescents (mean age 15.4 years) from the T1D Exchange Registry (T1DX) study, with higher prevalence

in those of black/African American descent (17.9%) and Hispanic/Latino descent (15.9%).[6] When a more conservative criteria is used (BMI > 97th percentile), data from the large multicenter German and Austrian database (Diabetes Patienten Verlaufsdokumentation) showed a lower prevalence of obesity of as low as 2.8% among patients aged <20 years old.[7] In the T1DX and the Prospective Diabetes Follow-up Registry, the BMI z scores in patients aged 2 to 18 years diagnosed with T1D for at least 1 year from Germany, Austria and the United States were greater than the respective country-specific national data.[8] However, in the USA population aged 3 to 19 years from the SEARCH for Diabetes in Youth Study, youths with T1D had a higher prevalence of being overweight (22.1% vs 16.1%), but not of obesity (12.6%), than non-diabetic youths.[9]

When obesity is defined by a BMI ≥ 30 kg/m^2, its prevalence was 8.9% in patients from Sweden aged ≥18 years old[10] which increased to 35.9% in American men between 35 and 67 years[11] and 37.1% in one cohort of newly diagnosed T1D between 30 and 75 years from Australia.[12]

What Has Happened in the Previous Decades Regarding the Relationship Between Obesity and Type 1 Diabetes?

Overall, obesity rates seem to have stabilized among younger people but have increased over time in adults with T1D. In Australia, a retrospective study that included 1975 children aged <16 years at diagnosis of T1D, showed that the prevalence of obesity remained steady (34–35%) between 1995 and 2009.[13] Similarly, a US study that examined trends in obesity over 10 years among 507 youths (aged 8–16 years) with T1D found a consistent prevalence rate across time, suggesting a plateau of obesity incidence.[14] However, when adults with T1D from the Pittsburgh Epidemiology of Diabetes Complications Study were evaluated, the prevalence of obesity increased over time, from 3.4% at baseline (1986 to 1988) to 22.7% during the final reported time point (2004 to 2007).[15] Notably, the rise in obesity's prevalence was not due to aging of the cohort and occurred faster than the increase in the general population.[15] Similarly, in the Epidemiology of Diabetes Interventions and Complications trial, the obesity prevalence in T1D increased from 1% at baseline (1983 to 1989) to 31% at year 12 (2005), a rate change that was much higher than observed in the general population.[16]

Is Obesity a Risk Factor for Developing Diabetes?

It has been suggested that there is a likely association between higher birthweight, childhood obesity and higher BMI, and subsequent increased risk of childhood-onset T1D.[17,18] However, it is unclear at what age obesity shows the greatest impact nor the underlying mechanism. A British study in 168 young people presenting with T1D between 1980 and 2002 showed that both pre-onset and post-diagnosis BMI were inversely correlated with age at onset, suggesting that heavier children developed T1D earlier.[19] Similarly, a systematic review and meta-analysis that included 4 studies that measured BMI prior to the diagnosis of T1D, supported the temporal association between exposure to obesity and the development of T1D.[17,20–23] Although the studies varied in the definition of obesity, the age at measurement and in sample size, with odds ratios (OR) that ranged from 1.73 to 3.77, the metanalysis obtained a pooled OR of 2.03 (95% CI 1.46–2.80). On the other hand, the reversed trend in the incidence of childhood T1D in Sweden, starting in 2000, has been partially attributed to changes in non-genetic risk factors such as the good control of childhood obesity.[24] Finally, in 91 children with clinical onset of type-1 diabetes at 4–15 years of age, there was increased weight (BMI) gain in the first year of life compared with their 125 healthy siblings.[25] Remarkably, this early growth was associated at diagnosis with the presence of autoantibodies toward the IA-2 and the tyrosine phosphatase pancreatic-cell-like protein, but not with antibodies to glutamic acid decarboxylase. Similarly, in the Finnish population, the risk of type 1 diabetes onset increased 1.19-fold per a 1 kg/m^2 rise in the infancy maximum BMI.[26]

As the combined prevalence of overweight and obesity in the childhood population has accelerated in many developing and developed countries, effective prevention and intervention programs should be a priority of national policy agendas to avoid the continuing increase of T1D in childhood for decades to come.[27]

Mechanisms Underlying the Relation Between Obesity and Type 1 Diabetes

Among several possible mechanisms highlighted to explain the association between obesity and subsequent onset of T1D, there appears the classical "accelerator hypothesis".[28] In this theory, increased body weight boosts the demand for peripheral insulin, imposing more stress on β cells and rendering them more antigenic and more vulnerable to autoimmune attack. At the same time, the ectopic lipid deposition in islets acts as an additional trigger of β cell apoptosis and the subsequent onset of T1D. Thus, a link between beta cell lipotoxicity and islet inflammation related to cytokine toxicity associated with obesity has been shown in experimental models.[29] Insulin resistance in T1D may also implicate the transient receptor potential vanilloid-1 (TRPV1+) sensory neurons to promote the local islet inflammation.[30] In fact, TRPV1 may contribute to obesity and T2D, where sensory innervation of fat may play an analogous role to sensory neurons in pancreatic β cells. In addition, adipose tissue is characterized by the production of adipokines which stimulate the generation of reactive oxygen species and pro-inflammatory molecules, collaborating in the development of a dysfunctional antioxidant system and insulin-resistance.[31] In this context, the increased oxidative stress that is associated with obesity might make the achievement of correct metabolic control in patients with T1D difficult.

The gut microbiome is altered in obesity and should be considered as an important environmental modulator of the susceptibility to diabetes in subjects with obesity.[32] In fact, both animal and human studies have demonstrated a link between gut microbiota and β cell autoimmunity.[33] However, the underlying mechanisms of how the gut microbiota interacts with host immunity, induce antigen-specific pathogenic T cells, and modulate β cell autoimmunity in the initiation of T1D are not yet fully elucidated.

Given that a genetic component is well known to exist in T1D, genomics offers an opportunity to discover new targets for this disease. In this way, the transcription factor 7 like-2 (*TCF7L2*) loci on chromosome 10, that has often been related with T2D in genome-wide association studies (GWAS), has also been associated with both latent autoimmune diabetes in adults and various presentations of T1D.[34] However, this genetic overlap between T1D and T2D is still controversial, as Field et al failed to find any evidence for association between *TCF7L2* and type 1 diabetes in 6199 white UK type 1 diabetic subjects and 7596 geographically matched white control subjects.[35] On the other hand, in 830 newly diagnosed autoimmune T1D, *TCF7L2* variants were associated with single autoantibodies at diagnosis, higher C-peptides, and lower glucose levels during an oral glucose tolerance test.[36]

Obesity, Type 1 Diabetes Mellitus, and Diabetes Complications

Some studies have assessed the impact of obesity in the development of chronic complications in patients with T1D, suggesting that individuals with obesity are at an increased risk for macrovascular and some microvascular complications, such as retinopathy.[2,4] Excess weight gain in patients with T1D is associated with the development of central adiposity, insulin resistance, inflammation and dyslipidemia; all of which are key elements of the metabolic syndrome and T2D and are established risk factors for cardiovascular disease (CVD).[37,38] In patients with T1D and obesity, the coexistence of these clinical characteristics of T2D, such as insulin resistance and cardiometabolic

complications, has been referred to as "double diabetes".[39,40] (see Figure 1). Regarding this, when the components of the metabolic syndrome were evaluated in 326 individuals with T1D aged between 5 and 34 years, the prevalence of low levels of high-density lipoprotein-cholesterol was three times higher and hypertension was four times higher among obese individuals compared with normal-weight individuals.[5] In a similar way, the prevalence of the metabolic syndrome increased from 4.9% among patients with normal weight to 35.3% among obese patients.[5] Moreover, in an observational study in adults with T1D, obesity was associated with the presence and progression of coronary artery calcium, a marker of subclinical atherosclerosis.[41] Similarly, data from the
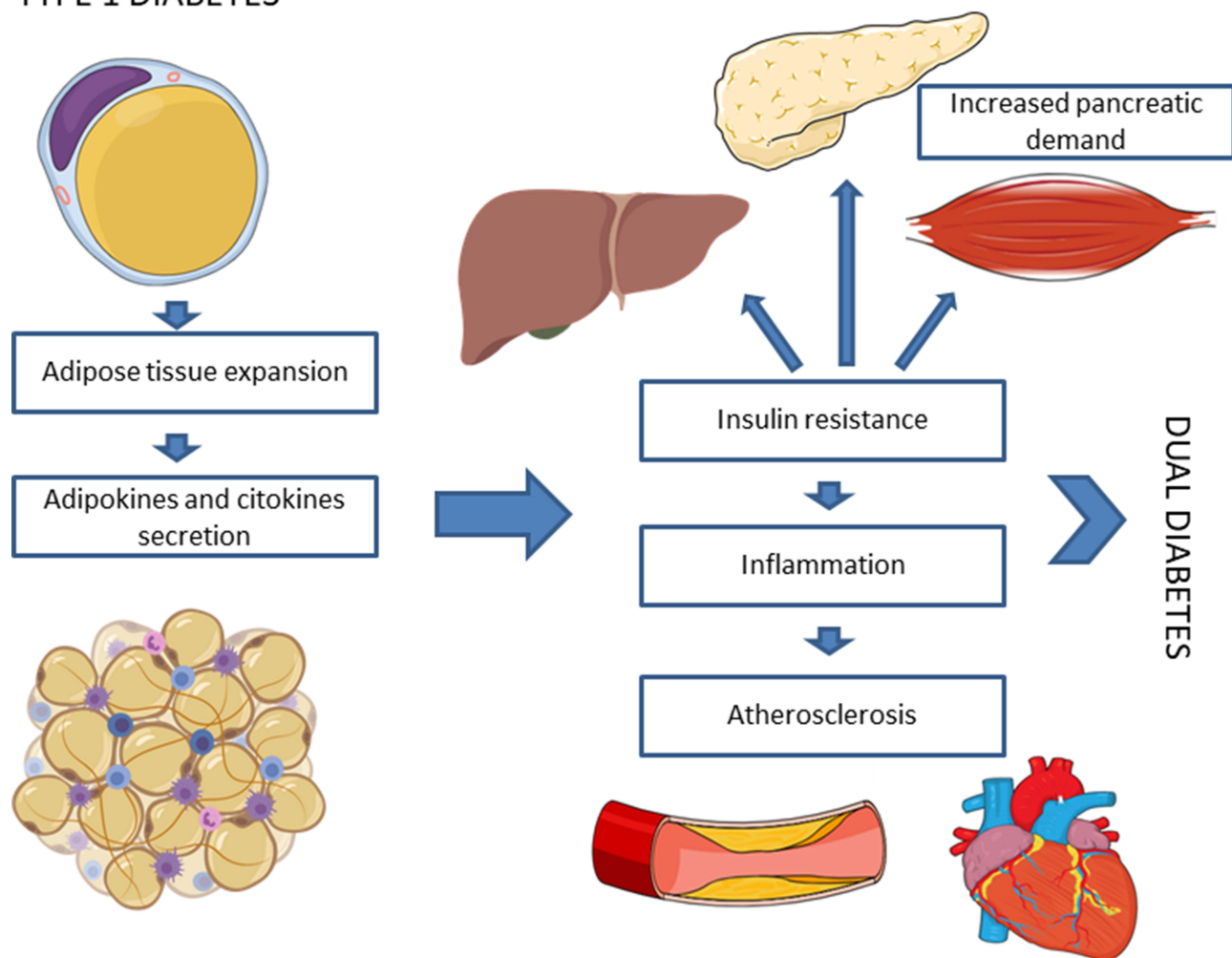
Figure 1 In patients with type 1 diabetes adipose tissue deposits produce adipokines and inflammatory cytokines that induce insulin-resistance contributing to the development of cardiometabolic complications. The coexistence of these clinical characteristics of type 2 diabetes in patients with type 1 diabetes has been referred to as double diabetes.

DCCT showed that in those patients with T1D with the most excessive weight gain, there were increases in both cardiometabolic risk factors (lipids, blood pressure) and more extensive atherosclerosis.[37,38] In addition, after year 14, the cardiovascular events in the intensive insulin therapy group with the most weight gain were significantly higher than the minimal weight gain group (P = 0.024; unadjusted hazard ratio 1.99; 95% CI, 1.12 to 3.63), with the event rate becoming indistinguishable from the conventional group.[37,41]

Data from 20,985 adults with T1D included in the Swedish National Diabetes Registry showed that obesity was significantly associated with an increased risk for a heart failure hospitalization, with an adjusted Hazard Ratio (HR) of 1.55 and 2.90 for BMI 30–34.9 kg/m^2 and (95% CI, 1.20 to 1.99) and BMI $\geq$ 35 kg/m^2, respectively.[10] In a prospective study of 501 Australian adults with T1D, obesity defined as a BMI > 30 kg/m^2 was the main risk factor for cardiovascular disease and retinopathy, although with a similar HbA1c and disease duration compared to non-obese patients.[42] In the same study, obesity was also associated with albuminuria in women. Similarly, in a cross-sectional study with 176 adults with T1D, BMI appeared to be significantly correlated with retinopathy only in those without previous nephropathy.[43]

Patients with T1D and obesity therefore receive more drugs than their normal-weight counterparts in order to treat the associated cardiometabolic risk factors. This can lead to polypharmacy which is a problematic issue as it exposes patients to adverse drug reactions, drug-drug or drug–disease interactions and is associated with morbidity.[44]

Causes of Increasing Prevalence of Obesity in Type 1 DM

Exogenous insulin use and intensive insulin treatment has been considered a key factor promoting weight gain in patients with T1D.[2] Since the Diabetes Control and Complications Trial (DCCT), multiple daily injections or insulin pump therapy coupled with frequent blood glucose monitoring has become the standard of care of T1D.[45] Despite the beneficial outcomes in the DCCT, adults receiving intensive insulin therapy gained an average of 5 kg more than those receiving conventional therapy.[46] However, studies that have followed cohorts of patients with T1D in the long term have observed that despite doubling the use of intensive insulin therapy after DCCT,

z-BMI and prevalence of overweight and obesity remained stable during a 10-year interval, similar to the general pediatric population. These findings go against intensive insulin therapy being the main reason for the rising prevalence of obesity in patients with T1D.[14]

It is the availability of high-energy density diets and increased portion size, along with a sedentary lifestyle which are the main drivers of obesity development worldwide.[47,48] The trigger therefore of the increasing prevalence of obesity in T1D is the obesogenic environment. Nevertheless, obesity is a complex multifactorial chronic disease; besides unhealthy habits, other exogenous factors such as the presence of altered eating behavior, eating disorders, short sleep duration, chronic stress and other psychosocial factors are implicated in its etiology. Moreover, current scientific knowledge has shown that other non-modifiable endogenous biological factors such as gut hormone profile, genetic predisposition, epigenetics or intestinal microbiota may also play a role in obesity development.[49] Different causes of obesity in T1D are illustrated in Figure 2.

Regarding biological factors, gastrointestinal hormones including ghrelin, cholecystokinin, gastric inhibitory peptide (GIP), glucagon-like peptide-1 (GLP-1), oxyntomodulin, amylin, insulin, leptin, pancreatic peptide and pancreatic polypeptide Y (PPY) among others, are key regulators in food intake. However, in T1D, the secretion of insulin, amylin (which favors delaying gastric emptying and inhibits intake) and glucagon are markedly dysregulated.[50] Apart from the expected loss of secretion of amylin and insulin by β cells, α cells are also dysfunctional resulting in a deficient secretion of glucagon in
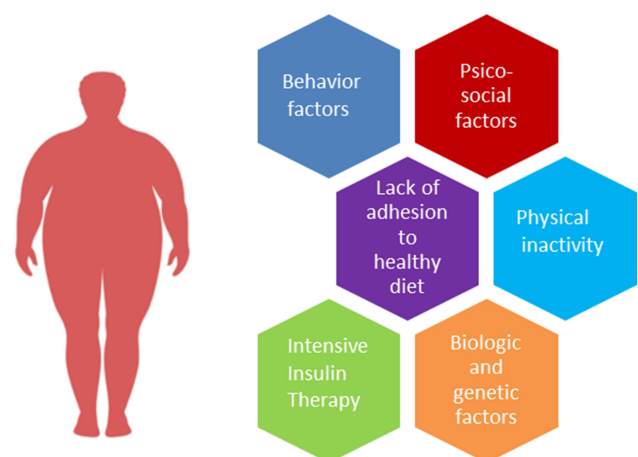
Figure 2 Illustration of the main modifiable and endogenous biological factors implicated in obesity etiology.

hypoglycemia and lack of glucagon suppression in the postprandial state.[51] All this inherent hormonal disbalance can potentially contribute to alterations in food intake, thus promoting weight gain.

From what has been explained previously, when treating a patient with obesity and T1D we have to take into account the coexistence of two chronic diseases in which all the above aspects are interrelated and should be carefully addressed.[52]

Treatment of Obesity in T1D: Challenges and Opportunities

The pillars of obesity treatment include a healthy eating plan, scheduled physical activity, and behavioral interventions that should be adapted in case of T1D. Structured lifestyle intervention programs have shown to be more effective in weight loss than a standard course of action in patients with obesity.[49] Although evidence is scarcer, these structured programs have proven equally beneficial when T1D coexists.[53] These programs should be executed by a multidisciplinary team that includes endocrinologists, dietitians/nutritionists, nurses, educators, physical activity professionals as well as clinical psychologists.[54] The participation of a diabetes educator and a close follow-up by an expert team in diabetes is mandatory to adjust carbohydrate intake and to carefully titrate insulin dose to prevent hypoglycemia. Indeed, one of the main barriers to diet interventions in T1D is the occurrence of hypoglycemia and its compensatory overeating.[55]

The administration of short-acting insulin immediately after meals or within 20 minutes from the start of the meal can be useful in some cases to avoid low glucose values.[53] On the other hand, it is important to assess changes in insulin type to those with a more favorable profile in terms of weight. Multiple trials have shown that patients with diabetes who used insulin detemir as the basal component of intensive insulin therapy, maintained weight neutrality or even had small weight reductions over 1 year in comparison to NPH insulin.[56] In a recent meta-analysis including patients with T1D and T2D, those receiving insulin detemir gained less body weight than those given degludec or Glar-100.[57] Another systematic review concluded there was less weight gain with basal insulin analogues detemir and Glar-300 compared to Glar-100 and degludec but with a low quality of evidence.[58] Therefore, in the case of obesity and T1D, switching long-acting insulin to either

detemir or Glar-300 could be somewhat useful to prevent weight gain.

The incorporation of the new technology of continuous subcutaneous insulin infusion (CSII) in T1D treatment has shown no clinical benefit over multiple daily injections, in terms of weight outcomes in newly diagnosed children and in young patients with T1D, either during the first year of insulinization[59] or over a 10-year follow-up.[60]

Diet

For the management of obesity in T1D lifestyle changes are essential, which must necessarily begin with a dietary modification towards a healthy eating pattern. A high intensity face-to-face dietary intervention program (with more than 14 sessions in 6 months) in the context of a comprehensive lifestyle intervention is the most effective strategy, obtaining average weight losses of 5–10%.[53] A variety of diets can lead to weight loss in overweight or obese adults with and without T2D (the Mediterranean-diet, low-carbohydrate, vegetarian or plant-based)[54,61,62] but to date, there is inadequate research in T1D to support one over another.[63] Taking into account that the macronutrient composition of a diet has less impact on weight loss than the adherence to it, the proposed diet plan must be adapted to the clinical characteristics and preferences of each patient, and must be planned to facilitate long-term adherence. The presence of a dietitian in the multidisciplinary team is therefore essential.[61]

The main component of any dietary intervention in obesity, independent of the presence of diabetes, is reducing total caloric intake. An energy reduction in the diet of 500–1000 kcal per day or 25–30% of the daily caloric intake can lead to a weight loss of 0.5 and 1 kg/week, equivalent to more than 5% weight loss in an average period of 6 months. The reduction of the size of the consumed portions and/or the energy density of the diet are effective strategies to reduce weight in patients with obesity. Focus should be made in T1D in encouraging consumption of carbohydrates with low glycemic index and high fiber content from vegetables, legumes, fruits, and whole grain and avoid refined carbohydrates, added sugars and highly processed foods.[61–63.]

In our environment, the hypocaloric Mediterranean diet is the one that best represents this balanced and healthy approach that is desired for T1D. The Mediterranean diet is characterized by a high content of vegetables, fruits, legumes, complex starches and food rich in omega-3 fatty acid (fatty fish), omega-6 fatty acid

(nuts) and monounsaturated fatty acids (olive oil) and promotes low intakes of saturated, trans fatty acids and added sugars.[64] Moreover, it is associated with a reduction in the risk of numerous diseases including cardiovascular disease, cancer, type 2 diabetes and neurodegenerative diseases.[65] Even though hypothetically optimal, there is little evidence of Mediterranean diet intervention in T1D. In a trial that randomized patients with T1D and metabolic syndrome to a 6-month non-calorie restricted Mediterranean diet versus a low-fat diet, the effects on waist circumference, anthropometric and metabolic outcomes were similarly favorable with both dietetic approaches.[66]

Current ADA guidelines suggest a flexible approach to carbohydrate intake matched with intensive insulin therapy because there is no ideal macronutrient composition for meal plans.[63] However, the evidence of low carbohydrate (<130g carbohydrate/day) and ketogenic diets (<55g carbohydrate/day) in T1D deserves special attention. Although it is very popular to lose weight in populations with obesity and T2D, there is limited evidence of their use in T1D as some concerns have been raised mainly regarding the risks of hypoglycemia and DKA.[67] In this respect, a low carbohydrate diet (LCD) can impair the effect of glucagon in the presence of hypoglycemia due to a reduction in hepatic glycogen stores. In a study performed on individuals with insulin pump–treated T1D, an LCD (<50 g/day) attenuated the glycemic response to a subcutaneous glucagon bolus compared to a high carbohydrate diet.[68]

Only a handful of studies, limited by small sample sizes and mostly non-RCT, have been published comparing the effects of LCD versus higher carbohydrate diets.[68–72] A systematic review based on them concluded that due to their heterogeneity it was unclear which diet was superior regarding HbA1c improvement, total daily insulin, incidence of hypoglycemia, or BMI.[73]

Recently, other popular forms of diet plans for weight loss are intermittent fasting, understood as the severe restriction of intake >60% for 2–3 days a week or alternate days, or as a limitation of the intake period to 8–10 hours a day or less during most days (time-restricted feeding). In review studies and meta-analysis of the few trials carried out to date, it has not been possible to verify a significantly greater weight loss with these diets compared to conventional low-calorie diets.[74,75] Additionally, their effectiveness and safety in people with T1D have not yet been conclusively proven and would therefore clearly require

adequate training and an adjustment in medication in order to avoid hypoglycemia.

From previously revised data we can conclude that further studies centered on nutrition-based interventions in patients with T1D and obesity are needed. Nevertheless, our recommended dietetic approach to lose weight in T1D would be a hypocaloric diet based on the Mediterranean diet pattern, with 40–50% of the energy coming from carbohydrates with low glycemic index and high fiber content (>25–30 g/1000 kcal), 15–25% from proteins (or 1.2 g/kg ideal body weight), and 30–35% from fat (ensuring a high content in monounsaturated fats and low in trans and saturated fats).

Physical Activity

The benefits of physical activity on cardiovascular and psychological health are multiple and its promotion is pivotal in obesity and T1D management.[76] However, patients with T1D engage in less physical activity than those without diabetes and have a tendency to live a sedentary lifestyle that promotes obesity development.[77] The practice of physical activity in isolation as a treatment for obesity has a modest effect on weight loss. However, when associated with a hypocaloric diet, exercise has been shown to decrease fat mass and visceral adiposity, decrease the loss of lean body mass, and increase insulin sensitivity. In addition, maintaining physical exercise has been shown to be useful in reducing the risk of weight regain.[62]

The goal for children and adolescents with T1D according to ADA recommendations is 60 min of moderate to vigorous intensity aerobic activity daily (walking, jogging, dancing, pedaling, etc.), with vigorous muscle-strengthening and bone-strengthening activities at least 3 days per week.[63] For adults, it is recommended 150 min or more of moderate to vigorous intensity aerobic activity per week, spread over at least 3 days/week and 2–3 sessions/week of resistance exercise. Shorter durations (minimum 75 min/week) of vigorous intensity or interval training may be sufficient for younger and more physically fit individuals. The same recommendations are given for people with obesity.[62]

The prescription of physical exercise must be individualized and the participation of physical activity professionals should be considered for a better adaptation to the characteristics and functional capacity of the patient, with the aim of improving adherence. The main barrier to do exercise in T1D is the fear of severe hypoglycemia[78] that may occur during or up to 24 h after exercise due to increased insulin sensitivity and delayed replenishment of liver and muscle glycogen following exercise. On the other hand, an

excessive and/or frequent intake of carbohydrates is not advisable in people with obesity because it promotes weight gain. Therefore, it is important to be educated on strategies to reduce hypoglycemia that can take place during, after and overnight following exercise. After exercise, the decrease of the long-acting insulin doses by ~20–30%, and 50% of bolus (or in case of insulin pumps the reduction of basal rate by ~10–50% and 25–75% of bolus or even its suspension for 1–2 h during exercise), may lower the risk of hypoglycemia.[79] Along with frequent blood glucose monitoring, accessible rapid-acting carbohydrates before, during, and after exercise is advisable. For low-to-moderate intensity aerobic activities (30–60 min), and if the patient is fasting, the recommendation is 10–15 g of carbohydrate and after insulin boluses it can reach 0.5–1.0 g of carbohydrates/kg per hour of exercise.[63,80]

The use of new technologies such as accelerometers, smart-watches, and mobile phone applications can contribute to assess and improve the adherence of patients to exercise programs.[81]

Psychological and Behavioral Therapy

Patients with overweight or obesity are vulnerable to stigma and discrimination in the workplace, at school, in healthcare settings and in society in general leading to negative psychological consequences. Health care providers should avoid stigmatization and weight bias and employ a motivational interview with the patient.[82]

Psychosocial disturbances in obesity and in T1D are frequent and they should be identified and treated appropriately.[83,84] Some are characteristics of diabetes such as fear of hypoglycemia and diabetes distress, and others are shared by both diseases such as anxiety, depression, lack of support, low self-esteem and the distress of coping with a chronic disease. Eating disorders are also frequent in both entities, with estimated prevalence of 7% in patients with T1D[85] and reaching 16–50% in cases of obesity alone according to different studies.[86,87] In patients with T1D suffering from eating disorders, insulin omission is frequent and is associated with a worse metabolic control, risk of ketoacidosis events and higher rates of diabetes complications.[88] On clinical suspicion raised by a poor glycemic control and recurrence of hypoglycemic episodes, several questionnaires can be useful to identify eating disorders in T1D such as the Diabetes Eating Problem Survey, Eating Disorder Inventory-3, and modified SCOFF.[89,90] In a preliminary study, initiation of pump therapy improved disordered eating behaviors probably due to greater flexibility in eating patterns and increased regulation of hunger and satiety. However, evidence is still scarce and further studies are needed to evaluate the impact of CSII insulin pumps on eating problems.[91]

Derived from the above knowledge, psychological assessment and behavioral therapy should be incorporated into the routine clinical management of obesity in T1D and involve clear and reasonable goal setting, self-monitoring of food intake and exercise, an approach to problem solving, development of skills for managing difficulties, stimulus control, stress reduction, education and social support. These behavioral interventions have proven to be beneficial in the context of a structured weight intervention program.[53]

Pharmacological Treatment of Obesity in T1D

Those patients who have insufficient weight loss with diet and exercise are candidates for drug treatment. Current guidelines indicate that pharmacological obesity treatment can be used in patients with BMI ≥ 30 kg/m^2 or BMI ≥ 27 kg/m^2 in the presence of complications, as an addition to lifestyle changes.[49,54,62] Anti-obesity medications approved for long-term use by both the EMA (European Medicines Agency) and FDA (U.S Food and Drug Administration) are Orlistat, Naltrexone-Bupropion and Liraglutide 3.0 mg. The Phentermine–Topiramate combination is only FDA approved.[49,54,62] These treatments have shown that along with weight loss there is an improvement in insulin resistance and metabolic control in T2D (Table 1) but no data are available on their effects on diabetic complications. Although these drugs are not contraindicated in T1D, data about their use in these patients are nonexistent as they have been excluded from the main trials. Despite these limitations, it seems reasonable to assume that obese people with T1D may benefit from these drugs in real life. Not including T1D in pharmacological obesity management clinical trials introduces a bias that leads to a further increase in a discrimination due to the obesity of these patients. Table 1 shows the main results of these studies in patients with T2D as well as in their adverse events and contraindications.

Anti-Obesity Medications
Orlistat
Orlistat is a reversible inhibitor of lipases. At the recommended therapeutic dose of 120 mg three times a day, orlistat inhibits dietary fat absorption by approximately 30%. In a meta-analysis of 14 studies, orlistat reduced weight 2.9% more than placebo.[92]

Table 1 Anti-Obesity Pharmacological Therapy in Randomised Clinical Trials (>1 Year of Duration), Including Subjects with Type 2 Diabetes

	Duration (Years)	Participants (n)	Weight Loss		≥5% Weight Loss		Dropouts	Side Effects	Contraindications
			Drug	Placebo	Drug	Placebo			
Orlistat[92] Meta-analysis	1–4	6196	−6.4%	−3.5%	54%	33%	≈ 30%	Oily spotting, flatus with discharge, diarrhea, fecal urgency	Chronic malabsorption syndrome, cholestasis and oxalate nephrolithiasis
Naltrexone-Buppropion COR-1[93] COR-2[94] COR-BMOD[95] COR-DIABETES[96]	1 1 1 1	1742 1496 793 505	−6.1% −6.4% −9.3% −5.0%	−1.3% −1.2% −5.1% −1.8%	48.0% 50.5% 66.4% 44.1%	16.0% 17.1% 42.5% 26.3%	50% 46% 48% 48%	Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, and diarrhea	Uncontrolled hypertension, seizures, eating disorders, chronic opioid use, concurrent use with monoamine oxidase inhibitors within 14 days
Phentermine/ topiramate CONQUER[97] 4(7.5/46 mg) (15/92 mg) **SEQUEL**[99] (7.5/46 mg) (15/92 mg) **EQUIP**[98] (15/92 mg) **OB-202/DM-230 Study**[100] **Plus CONQUER**	1 2 1 1	2487 498 995 676 227 295 1026 451	−7.8% -9.8% -9.3% -10.5% 10.9% -9.6%	−1.2% -1.2% -1.8% -1.8% -1.6% -2.6%	62% 70% 75.2% 79.3% 66.7% 65%	21% 21% 30% 30% 17.3% 24%	30.9% 36.0% 17.6% 16.9% 41.2% 19.7%	Paraesthesia, dizziness, dysgeusia, insomnia, constipation, and dry mouth	Glaucoma, hyperthyroidism, concurrent use with monoamine oxidase inhibitors within 14 days
Liraglutide 3.0 mg (SCALE studies)[101] **Obesity/ prediabetes**[102] **Maintenance diabetes**[104]	1 3 1 1	3731 2254 422 846	−8.0% -6.1% -6.2% -6.0%	−2.0% -1.9% -0.2% -2.0%	63.2% 49.6% 50.5% 69.2%	27.1% 23.7% 21.2% 27.2%	18% 47.4% 25% 26.7%	Nausea, vomiting, constipation or diarrhea	Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2

Notes: Subjects with diabetes were included in specific clinical trials (COR-DIABETES, SCALE Diabetes). For phentermine-topiramate, sub-studies were used that included patients with T2D, such as OB-202/DM-230 and a sample from the CONQUER study.
Abbreviations: COR, Contrave Obesity Research; BMOD, behaviour modification; SCALE, Satiety and Clinical Adiposity — Liraglutide Evidence.

Naltrexone-Bupropion (NB)

Bupropion is an inhibitor of the reuptake of dopamine and norepinephrine and is involved in the regulation of appetite (anorectic action) and in the hedonic reward circuits. Naltrexone is a μ-opioid inhibitor. In the COR (Contrave Obesity Research) studies,[93–96] Naltrexone-Bupropion sustained-release (SR) at a dose of 32/360 mg reduced weight 4.5% more than placebo (Table 1).

Phentermine-Topiramate

Phentermine has been used for the treatment of obesity since 1955, and together with the antiepileptic topiramate, this drug combination exerts an anorexigenic action by acting on the GABA and glutamate receptors. In the different randomized double-blind studies (EQUIP, CONQUER and SEQUEL),[97–100] the percentages of total weight loss have been, on average: low doses −5.1%, medium dose −7.1% and high doses −10.9% (Table 1).

Liraglutide 3.0 mg

Liraglutide is an analog of the incretin GLP-1 (Glucagon Like Peptide-1) and is well known for its efficacy and safety in the treatment of T2D at doses of 1.2–1.8 mg/day. However, the higher dose of 3.0 mg/day is used for obesity treatment.

Among the four pivotal SCALE studies (Satiety and Clinical Adiposity – Liraglutide Evidence),[101–104] the study concerning obesity with/without prediabetes, which included 3731 patients, showed a total weight loss after 56 weeks of treatment of −8% compared to −2.6% with placebo. A lower decrease was observed in the SCALE-diabetes study of −6.0%. Liraglutide's safety and efficacy have been verified for the treatment of adolescents with obesity[105] (pending approval by regulatory agencies) and it is the anti-obesity drug of choice according to some societies.[62]

Other GLP1 Agonists (Semaglutide, Dulaglutide)

These are long-acting GLP1 analogs approved for use in T2D to improve glycemic control which also exert an additional action on body weight. In a head-to-head study, weekly administered semaglutide 1 mg achieved a weight reduction of −6.5 kg compared to 3.0 kg with dulaglutide 1.5 mg.[106] However, neither treatment was intended to treat obesity.

We have preliminary data that show that obese patients with T2D treated with high-dose Semaglutide 2.4 mg can achieve a reduction of approximately –9·6% and −15% of starting weight in patients with and without diabetes, respectively.[107,108] Of note, one-third of participants in this last study achieved 20% of weight loss similar to that obtained with sleeve gastrectomy (SG). The development of new drugs in the future for weight and glycemic control will be based on the combination of drugs like tirzepatide (dulaglutide plus a GIP analog), and combinations of GLP1, GIP, Glucagon coagonists/triagonists, combinations of Semaglutide and Pramlintide analog (Cagrilintide) and the YY peptide agonists.[109]

The authors believe that for those patients unable to achieve a significant and sustained weight loss with lifestyle interventions, the addition of approved anti-obesity drugs and the use of novel molecules derived from gastrointestinal peptides in the near future, will be very useful for weight management in T1D patients, as some approach bariatric surgery (BS) results. As a growing problem worldwide, T1D with obesity should be included in weight loss clinical trials.

Oral Glucose-Lowering Drugs as Adjuncts to Insulin Treatment in T1D

A number of oral glucose-lowering drugs used in T2D treatment have been explored as adjuncts to insulin treatment in T1D in the search of improving metabolic control and body weight. Results of the most relevant trials are listed in Table 2.

Metformin

Metformin is the first-line treatment for T2D. It decreases hepatic glucose production, increases insulin sensitivity and decreases glucose absorption.[110] Some clinical trials with limited number of participants with T1D have evaluated the effects of metformin added to insulin compared to placebo and have demonstrated a decrease with respect to placebo in insulin dose (−5.7 to −8.8 UI/d) and in weight (−1.74 to −3.8 kg), but no effect on HbA_{1c}.[111,112] The REMOVAL trial randomized 428 patients with T1D to metformin or placebo and measured the progression of common carotid artery intima-media-thickness (cIMT) as a marker of atherosclerosis.[115] Body weight was reduced (−1.17 kg, 95% CI 1.66 to −0.9) but there was no reduction in HbA_{1c}, insulin requirements, progression of mean cIMT and no increase in hypoglycemia compared to placebo.

Dipeptidyl Peptidase IV Inhibitors (DPP-IV Inhibitors)

The DPP-IV inhibitors enhance levels of endogenous glucagon-like peptide 1 (GLP1) by blocking its metabolism by the enzyme DPP-IV. This increase of GLP1 levels, leads to a decrease in glucagon and an increase in insulin secretion. T1D patients experience a paradoxical increase in glucagon, which correlates with postprandial glucose levels.[114] Sitagliptin has been evaluated and compared to placebo in a limited number of studies in patients with T1D,[115,116] none observing significant effects on weight.

Glucagon Like Peptide 1 Analogs (GLP1a)

Of the six available GLP1a only two have been evaluated in patients with T1D: Exenatide and Liraglutide.

Exenatide: There are few studies evaluating exenatide in patients with T1D, all methodologically heterogeneous and with a limited number of patients. The studies demonstrate a decrease in insulin requirements,[117–119] but only a small number of them show a significant decrease in HbA_{1c}[117,118] and in weight loss.[117,119]

Liraglutide: The Lira-1 trial showed no differences in HbA_{1c}, but there were significant differences in weight

Table 2 Studies Analysing the Effects of Oral Glucose-Lowering Drugs as Adjuncts to Insulin Treatment in T1D

		n	Duration (Weeks)	Change in HbA_{1c} (%)	Change in Weight (kg)	Change in Insulin Dose
Biguanides						
REMOVAL[113]	Metformin 1000 mg	428	156	−0.13**	−1.17**	−0.05 IU/kg/d
GLP1a						
Lira-1[120]	Liraglutide 1.8 mg	100	24	−0.2	−6.80*	−0.1 IU/kg/d
ADJUNCT ONE[121]	Liraglutide 1.8 mg Liraglutide 1.2 mg Liraglutide 0.6 mg	1398	52	−0.2 ** −0.15* −0.09*	−4.90 ** −3.55** −2.19**	−5%* (ΔBL) −2% (ΔBL) +4% (ΔBL)
ADJUNCT TWO[122]	Liraglutide 1.8 mg Liraglutide 1.2 mg Liraglutide 0.6 mg	853	26	−0.35 ** −0.23** −0.24**	−5.10** −4.00** −2.50**	Ratio 0.90** Ratio 0.93** Ratio 0.95**
iSGLT2						
DEPICT-1[124]	Dapagliflozin 10 mg Dapagliflozin 5 mg	833	52	−0.36** (ΔBL) −0.33** (ΔBL)	−3.90** −2.56**	NR NR
DEPICT-2[125]	Dapagliflozin 10 mg Dapagliflozin 5 mg	815	24	−0.42** −0.37**	−3.74%† −3.21%†	−16.71% −11.19%
EASE-1[126]	Empagliflozin 25 mg Empagliflozin 10 mg Empagliflozin 2.5 mg	75	4	−0.53* −0.38** −0.49**	−1.90** −1.80** −1.50**	−0.07 IU/kg/d* −0.09 IU/kg/d * −0.08 IU/kg/d *
EASE-2[127]	Empagliflozin 25 mg Empagliflozin 10 mg	730	52	−0.45*** −0.39***	−3.60*** −3.20***	−12.9%*** −12.0%***
EASE-3[127]	Empagliflozin 25 mg Empagliflozin 10 mg Empagliflozin 2.5 mg	977	26	−0.52*** −0.45*** −0.28***	−3.40*** −3.00*** −1.80***	−12.6%*** −9.5%*** −6.4%***
InTandem1[128]	Sotagliflozin 400 mg Sotagliflozin 200 mg	793	52	−0.31** −0.25**	−4.34** −3.14**	−12.64%** −8.02**
InTandem1[129]	Sotagliflozin 400 mg Sotagliflozin 200 mg	782	52	−0.32%* −0.21%*	−2.18** −1.98**	−8.17%** −6.26%*
InTandem1[130]	Sotagliflozin 400 mg	1402	24	−0.46**	−2.98**	−5.3 UI/d **
Amylin mimetics						
Whitehouse et al[133]	Pramlintide 30μg or 60μg	480	52	−0.39**	NR	+2.3%* (ΔBL)
Edelman et al[134]	Pramlintide 30μg or 60μg	296	29	−0.19	−1.3***(ΔBL)	−12% (ΔBL)
Ratner et al[135]	Pramlintide 60μg or 90μg	651	52	−0.29**	NR	NR

Notes: †Mean percent change. *p<0.05. **p<0.001. ***p<0.0001.
Abbreviations: ΔBL, change from baseline; NR, not reported.

loss (−6.8 kg) and in insulin dose (5.8 UI of bolus/day) in the group of patients with T1D treated with liraglutide 1.8 mg/d with respect to the placebo group. In the liraglutide group, the perceived frequency of hypoglycemia was lower and the most frequent adverse events were gastrointestinal effects.[120]

The two trials with the largest number of patients at present (ADJUNCT ONE and ADJUNT TWO) have reported similar results with respect to a significant weight loss (from −4.1 to −5.1 kg) and a reduction in insulin dose in the liraglutide group, but also a decrease in HbA_{1c} (from 0.2% to 0.35%).[121,122] The gastrointestinal disorders,

symptomatic hypoglycemia and hyperglycemia with ketosis, were more frequent in the liraglutide groups.

Sodium-Glucose Cotransporter Inhibitors

SGLT2 is located in the renal proximal tubule and favors glucose reabsorption and SGLT1 promotes glucose absorption in the small intestine. Inhibition of these transporters by SGLT2 and SGLT1 inhibitors leads to a decrease in glucose reabsorption in the kidney and the small intestine, respectively. Moreover, patients with diabetes mellitus present an overexpression of SGLT2.[123] SGLT2 inhibitors and dual (SGLT2 and SGLT1) inhibitors have been evaluated in patients with T1D.

Dapagliflozin: The DEPICT-1 and DEPICT-2 trials randomized to receive dapagliflozin 5 mg, dapagliflozin 10 mg or placebo.[124,125] In both trials, patients in the groups of dapagliflozin presented a significant decrease in HbA_{1c} compared to placebo (from -0.33% to -0.37% with dapagliflozin 5 mg and from -0.36% to -0.42% with dapagliflozin 10 mg), in insulin dose and in body weight (the mean percentage change vs placebo ranged from -2.95% to -4.54%). There were no differences in the rates of hypoglycemia, but 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).

Empagliflozin: The EASE-1 trial[126] randomized patients to receive empagliflozin 10 mg, empagliflozin 25 mg and placebo and the EASE-2 and EASE-3 trials[127] randomized patients to empagliflozin 2.5 mg, 10 mg, 25 mg or placebo. All trials showed a significant decrease in HbA_{1c} with all doses of empagliflozin vs placebo (from -0.28% to -0.53). Patients in the treatment groups also experienced a higher reduction in weight (from -1.5 kg to -3.6 kg) and in insulin dose. While in the EASE-1 there were no differences in the rate of DKA, in the EASE-2 and 3[127] trials there were higher rates of DKA in the groups of patients with the higher doses of empagliflozin (10 mg and 25 mg): 0.8% with empagliflozin 5 mg, 4.3% with empagliflozin 10 mg, 3.3% with empagliflozin 25 mg and 1.2% with placebo.

Sotagliflozin: The program inTandem has evaluated the efficacy and safety of the dual blockade of SGLT1 and SGLT2 by sotagliflozin in T1D.[128–130] The three trials showed a reduction in HbA_{1c} in the groups of patients treated with sotagliflozin (from -0.21% to -0.46%), in weight (from -1.98 to -4.34 kg) and in insulin dose. The frequency of documented hypoglycemia was lower and gastrointestinal events and DKA were more frequent in patients treated with sotagliflozin. With respect to DKA, 3.4% of patients with sotagliflozin 200 mg presented DKA, 4.2% with sotagliflozin 400 mg and 0.4% with placebo.

Amylin Mimetics

Pramlintide: Pramlintide is a hormone co-secreted with insulin in the postprandial period by β cells in response to nutrient stimuli. It modulates glucose absorption, delays gastric emptying and suppresses glucagon secretion.[131] It is deficient in patients with T1D.[132] Pramlintide is an amylin analogue, administered subcutaneously in addition to prandial insulin, approved in the USA for the clinical use in T1D and T2D. Pramlintide has been evaluated adjunct to intensive insulin therapy in T1D and trials have shown significant reductions in HbA_{1c} (from -0.19% to -0.39% compared to placebo), in weight and in insulin doses.[133–135] Hypoglycemia and gastrointestinal adverse events were more frequent in patients treated with Pramlintide.

Of all these evaluated treatments, in addition to pramlintide, which has been approved in the USA for T1D since 2005, dapagliflozin 5 mg was approved in Europe in 2019 for the use in patients with T1D and BMI ≥ 27 kg/m^2 when insulin alone does not provide an adequate glycemic control despite optimal insulin treatment.

Natural Product Supplementation

Numerous plants, their extracts and isolated components are under investigation for their possible beneficial effects on body weight. Phytochemicals are plant organic compounds without nutritional effect but with bioactivity, such as carotenoids, polyphenols, flavonoids, alkaloids, tannins, steroids, etc., with a large number of phytoconstituents such as genistein, capsaicin, catechins, ephedrine or caffeine. They are potential sources of new drugs due to their biological activity on metabolic pathways involved in the regulation of intake and energy balance. In human studies, the effect of most of them on body weight is supported by low-quality evidence and only some (green tea, white kidney bean, caffeine, bitter orange, diacylglycerol, resveratrol, grapefruit, chromium) have moderate-quality evidence. However, none is capable of inducing a clinically relevant weight loss, with the most effective ones (green tea) leading to a 2 kg reduction.[136,137] Therefore, for the time being, these natural products lack adequate clinical

investigations and scientific validation to be recommended for obesity therapy.

Bariatric Surgery in T1D with Severe Obesity

In patients with T1D and BMI above or equal to 35 kg/m^2 with associated comorbidities or BMI above or equal to 40 kg/m^2, BS can be a treatment option as supported by IFSO since 2016.[138] However, contrary to firm benefits of BS in T2D, little is known of its outcomes and risks in populations with T1D.[139] Therefore, ADA guidelines state that larger and longer studies will be required in order to establish the role of metabolic surgery in such patients.[61]

Pathophysiology

Patients with T1D have a reduced endogenous insulin secretion, but body weight loss can decrease insulin resistance in hepatic and peripheral tissues and may improve hepatic insulin sensitivity leading to a reduction in insulin requirements. A role of gastrointestinal hormones in metabolic improvement has also been suggested in animal studies.[140] In this regard, a preliminary study in which one woman with T1D who underwent RYGB reported an increase in the incretin hormones GLP-1, PYY, and GIP after a mixed meal test.[141] However, other authors were not able to correlate GLP-1 nor glucagon concentrations to changes in glycemic control and insulin requirements.[142]

Outcomes of BS in Patients with T1D

The results of obesity surgery in patients with T1D have only been described until recently in case reports and small series,[141–163] most with a short follow-up that have given place to several systematic reviews.[164–168] The main results are summarized in Table 3. Overall, they have shown a significant reduction in body weight and weight-adjusted insulin requirements and an improvement in other cardiovascular risk factors (mainly hypertension, dyslipidemia and obstructive sleep apnea). However, only modest and transient benefits on glycemic control have been found, mainly occurring within the first year after bariatric surgery (see Table 3). Our group published the results of a cohort of 32 patients with T1D undergoing BS with a mean follow up of 4.6 years and observed that HbA$_{1c}$ was reduced 0.6% during the first year, but in the long term, it returned to baseline values.[163] Nonetheless, a sustained reduction of 51% in total daily insulin dose, and a decrease in about 50% of patients with hypertension, dyslipidemia and obstructive sleep apnea was observed.

Safety of BS in Patients with T1D

Besides the improvement of insulin sensitivity after weight loss that requires an appropriate reduction in exogenous insulin dose, the change in glucose kinetics and nutrient intake and absorption may favor hypoglycemic events. Regarding this, food intolerance and vomiting after bariatric surgery and the mismatch between insulin peak after subcutaneous administration, and the higher and earlier postprandial glucose excursion caused by the rapid delivery of carbohydrates to the jejunum promotes hypoglycemia. Thus, this risk would be expected to be greater after mixed and malabsorptive techniques.[169] However, it is still unknown if the type of surgical technique has a real impact on hypoglycemic events and which one would be the appropriate choice in this context. In our retrospective non-randomized series, 9.3% of patients had a serious hypoglycemic event, but their frequency did not differ between those surgeries bypassing the duodenum (Roux-en-Y gastric bypass (RYGB) and duodenal switch) and with restrictive ones (SG).[163] Recently, Höskuldsdóttir et al have published data from a register-based nationwide Swedish cohort including 387 individuals with T1D who had undergone RYGB that were compared to 387 age/BMI/sex and diabetes duration matched control patients.[170] In this large bariatric population, there was a numeric but not statistically significant difference in hypoglycemic events leading to coma (HR 1.57; P = 0.205).

DKA is a life-threatening complication that ranges from 6.2 up to 25% in a series of patients with T1D undergoing BS.[163,171] In the nationwide Swedish cohort, a higher risk for serious hyperglycemic events (HR 1.99) was found after RYGB surgery compared to controls.[170] Poor peri-operative glycemic control along with omission or non-compliance with prescribed insulin doses was associated with DKA.

Of note, in the Swedish study a significantly increased risk for alcohol and substance abuse was found after surgery (HR 3.71), as has also been reported in other bariatric series.[172]

Effects of BS on Diabetic Complications

In preliminary case reports, anecdotical microalbuminuria regression to normoalbuminuria[153,163] and inconsistent results regarding retinopathy have been described.[153] In the Swedish cohort study, no difference was found regarding the risk of kidney disease or leg amputation after RYGB compared to controls.[170] A lower risk for cardiovascular disease

Table 3 Studies Analyzing the Effects of Bariatric Surgery in Patients with T1D

Study	n	Type of Surgery	Follow-Up	Mean Decrease in BMI	Mean Reduction in Insulin UI/kg	Mean Changes in HbA$_{1c}$ (%)	Improvement in CVRF
Czupryniak et al[144] 2010	3	RYGB (n=3)	6.3 years	8.7	0.23	↓3	BP, dyslipidemia
Mendez et al[145] 2010	3	RYGB (n=3)	1year	16.5	0.20	↑0.07	
Garcia-Caballero et al 2013[157]	5	SAGB (n=5)	19m	7	47 UI/d	↓1.6	BP, dyslipidemia
Raab et al 2013[148]	6	RYGB (n= 2); SG (n=1) BPD (n=3)	1 year	13.8	0.57	↓1.2	
Chuang et al 2013[147]	2	RYGB (n=1); SG (n=1)	20m	18.1	↑0.05	↑1.95	BP, dyslipidemia
Fuertes-Zamorano et al 2013[146]	2	SADI-S (n=2)	4.5 years	23.0	0.26	↓0.85	Dyslipidemia
Reyes Garcia et al, 2013[158]	1	RYGB (n=1)	10 m	14.6	88UI	↓1.3	
Blanco et al 2014[142]	7	RYGB (n=7)	2 years	12.1	↑0.01	↓0.1 NS	–
Brethauer et al 2014[150]	10	RYGB (n=7); SG (n=1), GB (n=2)	3years	11.1	0.34	↓1.1	BP, dyslipidemia
Tang et al 2014[151]	6	RYGB (n=1), SG (n=2), GB (n=3)	16 m	11.4	NR	↑0.1 NS	–
Lanno et al 2014[152]	22	RYGB (n=16); SG (n=6)	37 m	8.7	0.3	↓0.2 NS	–
Middelbeek et al 2015[153]	10	RYGB (10)	5years	9.7	0.05	↑1.7	Increase in HDL
Maraka et al 2015[154]	10	RYGB (n=9), SG (n=1)	2 years	13.1	NR	↓0.4 NS	Dyslipidemia
Robert et al 2015[155]	10	BPD (n=7), SG (n=3)	4.5years	16.5	0.7	↓0.4 NS	BP, dyslipidemia
Rottenstreich et al 2015[160]	13	RYGB (n=) SG (n=10)	2years	9.8	0.19	↓0.8 NS	BP
Vilarrasa et al 2017[163]	32	RYGB (n=11); SG (n=15), DS (n=6)	4.6 years	9.0	0.3	↑0.2NS	BP, dyslipidemia, OSA
Faucher et al 2016[161]	13	RYGB (n=6); SG (7)	1year	11.5	0.33	↓0.7	
Moreno-Fdez et al 2016[159]	6	RYGB (n=3), SG (n=3)	4.5 years	14.2	0.10	↓0.6 NS	Triglycerides
Al Sabah et al 2017[162]	10	SG (n=10)	4 years	10.5	0.46	↓0.3 NS	
Landau et al 2019[156]	26	RYGB (n=10); SG (n=5); GB (n=8)	3.5 years	9.3	NR	↑0.04 NS	BP, increase HDL
Hoskuldsdóttir et al 2020[170]	387	RYGB (n=387)	9 years	12	NR	↓0.8	CV disease and CV mortality

Abbreviations: BP, blood pressure; OSA, obstructive sleep apnea; CV, cardiovascular; RYGB, Roux- en-Y gastric bypass; SAGB, single anastomosis gastric bypass; SG, sleeve gastrectomy; GB, gastric banding; SADI-S, single anastomosis duodeno-ileal bypass with sleeve gastrectomy; DS, duodenal switch.

(hazard ratio [HR] 0.43) and cardiovascular death (HR 0.15) was observed in the RYGB group. The differences were most marked with regards to stroke (HR 0.18) and heart failure (HR 0.32).

In summary, bariatric surgery in T1D patients with severe obesity has proved efficient in reducing weight and insulin dose and in improving associated comorbidities, with recent studies showing a significant reduction in cardiovascular disease and mortality. These benefits outweigh the adverse events observed, such as an increased risk of hypoglycemia and DKA. Nevertheless, a close monitoring of these patients by a multidisciplinary team is fundamental to provide a tailored, modifiable insulin regimen during all phases of management along

with diabetes care and education. New diabetes technologies such as real-time monitorization may be especially helpful in this situation.

Endoscopic procedures

Endoscopic procedures are emerging as obesity treatment options but no studies have been published so far in T1D. These procedures are minimally invasive, most are reversible, safer and less costly compared to surgical treatment. However, they are characterized by the transience of their effects and the lack of long-term studies, so that for the time being their recommendation as primary treatments of obesity is not well established.[54,62]

Future Perspectives

Non-traditional therapies for patients with T1D and obesity need to be evaluated in the near future.[173] In this way, pegylated fibroblast growth factor-21 appears as a novel metabolic regulator with the potential to become a powerful therapy to treat diabetes mellitus.[174] Similarly, adiponectin ameliorates non-alcoholic fatty liver disease in streptozotocin-induced T1D.[175] Finally, it still needs to be established whether immunotherapy may find a place in the prevention of progression to overt T1D and improve clinical outcomes in established diabetes in patients with obesity.[176] On the other hand, there is an area of research in the development of strategies based on reducing oxidative stress in patients with T1D and obesity with some evidence coming from supplementation with probiotic/symbiotic and a low dietary intake of advanced glycation end products.[177,178]

An extensive pipeline of obesity medications is currently in Phase II and III development in adults, suggesting that more effective treatments will be available in the coming years. Some examples are the future combinations of drugs such as GLP1 agonists with GIP, Glucagon, or oxynomodulin (dual agonists or triagonists), the combination of Semaglutide with an amylin analog (Cagrilintide)[179] or the novel Bimagrumab which is a monoclonal antibody that binds to the type II activin receptor that regulates skeletal muscle growth, but also decreases adipose tissue improving insulin resistance.[180]

Undoubtedly, the big step ahead in the treatment of T1D and obesity will be provided by advances in precision medicine. Regarding this, the integration of major technological advances achieved in recent years (including high-resolution omic assays, wearable devices that monitor behavior and exposure, and digital imaging technologies) integrated with genetic information will help individualize the efficacy of specific dietary approaches and select medication and surgical techniques for each patient.[181] The introduction of this tailored treatment will definitively enhance the outcomes.

Conclusions

The coexistence of obesity and T1D is a growing problem and poses a challenge for effective glycemic and weight management. All patients should be offered a lifestyle intervention by a multidisciplinary team including a balanced hypocaloric diet, physical activity and cognitive behavioral therapy. In the "roadmap" of the treatment of obesity in T1D, it will be helpful to include approved anti-obesity pharmacotherapy, and in case of morbid obesity, bariatric surgery stands out as an effective procedure to reduce weight and comorbid conditions. In the near future, the development of new and more effective anti-obesity treatments, coupled with strategies to improve insulin resistance and oxidative stress and advances in precision medicine, will provide very useful tools to improve both the weight and metabolic management of these patients.

Disclosure

The authors report no conflicts of interest in this work.

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