Obesity in people living with type 1 diabetes

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Although type 1 diabetes is traditionally considered a disease of lean people, overweight and obesity are becoming increasingly more common in individuals with type 1 diabetes. Non-physiological insulin replacement that causes peripheral hyperinsulinaemia, insulin profiles that do not match basal and mealtime insulin needs, defensive snacking to avoid hypoglycaemia, or a combination of these, are believed to affect body composition and drive excessive accumulation of body fat in people with type 1 diabetes. The consequences of overweight or obesity in people with type 1 diabetes are of particular concern, as they increase the risk of both diabetes-related and obesity-related complications, including cardiovascular disease, stroke, and various types of cancer. In this Review, we summarise the current understanding of the aetiology and consequences of excessive bodyweight in people with type 1 diabetes and highlight the need to optimise future prevention and treatment strategies in this population.

Introduction

Since the discovery of insulin 100 years ago, pharmacological and technological progress has greatly improved the daily clinical care for people with type 1 diabetes. Nonetheless, achieving glycaemic control remains challenging, and requires thorough food literacy and daily efforts to match food intake with insulin requirements. Therefore, how the ongoing global obesity pandemic affects people with type 1 diabetes requires extensive research, because overweight and obesity are known to have deleterious effects on numerous health outcomes.[1] The causes of weight gain in people with type 1 diabetes are thought to be primarily related to exogenous insulin replacement therapy, which (despite continuous progress) remains unphysiological. Therefore, weight management strategies in people living with type 1 diabetes involve specific challenges and require additional counselling and education, yet can still be an effective way to avoid excessive weight gain in people with type 1 diabetes. GLP-1 receptor agonists and SGLT inhibitors have clear benefits for weight management in people with type 2 diabetes and have also proved to be helpful in people with type 1 diabetes, yet remain underused. In the following section, we summarise current knowledge about weight management in people with type 1 diabetes.

A global trend

The increase in prevalence of overweight and obesity in the general population is well documented, and clear patterns have emerged about which subpopulations (in terms of age, sex, social class, race or ethnic background, and lifestyle) are worst affected.[2] These patterns are much less studied for people with type 1 diabetes, because the (fortunately now rare) catabolic state of poorly controlled type 1 diabetes tended to lead to weight loss rather than weight gain.

In established type 1 diabetes, there are large disparities globally in the prevalence of overweight (BMI 25–29·9 kg/m²) and obesity (BMI ≥30 kg/m²). In addition, relevant studies have not used an adequate control group of general population members matched for age, sex, smoking habits, social status, use of concomitant medication, and presence of comorbidities. In Austria, the prevalence of overweight and obesity in a small cohort of adults (n=186) with type 1 diabetes was similar to that of the overall population, but among participants aged 30–49 years, BMI was significantly higher in people with type 1 diabetes than in those without (mean BMI 26·7 kg/m² [SD 4·4] *vs* 24·8 kg/m² [4·3]; corrected p<0·001).[3] In Belgium, a study published in 2021 reported that prevalence of overweight and obesity in a large cohort of 89 834 people with type 1 diabetes (aged 1–80 years) was similar to that of the general population and had remained stable during the past decade.[4] By contrast with Europe, data from RENACED-DT1, a national type 1 diabetes registry initiative in Mexico, showed that, among people with type 1 diabetes, 34·3% had overweight and 8·1% had obesity.[5] The prevalences of overweight and obesity in people with type 1 diabetes were markedly lower than for the general population, because Mexico has one of the highest rates of overweight and obesity of all Organisation for Economic Co-operation and Development countries.[6] In the USA, where obesity is also a major public health concern, its prevalence remains markedly lower in people with type 1 diabetes compared with the general population.[7] In the T1D Exchange Registry US study,[7] among adults with type 1 diabetes, 29% had overweight and 20% had obesity. The reasons for disparities in global prevalence of overweight and obesity in people with type 1 diabetes remain elusive, but could be related to challenges of cost and accessibility in obtaining appropriate diabetes care in some countries. The existence of these disparities should not justify complacency, because there is clear evidence that the increasing rates of overweight and obesity will not spare people with type 1 diabetes, as detailed in the following section.

First, there is a reported high prevalence of overweight and obesity among children and adolescents with type 1 diabetes. The SEARCH for Diabetes in Youth study[8] found that, of children and adolescents (aged 3–19 years) in the USA with type 1 diabetes, 22·1% had overweight, compared with only 16·1% of their peers without type 1 diabetes, and 12·6% had obesity compared with 16·9%. A study of 5529 adolescents[9] (aged 13–18 years) within the T1D Exchange registry of people with type 1 diabetes

in the USA revealed a similar or slightly higher incidence of overweight (22·9%) and obesity (13·1%), compared with SEARCH. Within the type 1 diabetes subgroup, female sex, older age, annual household income below US$35 000 (*vs* ≥$200 000), and highest parental educational attainment being high school (*vs* graduate degree or higher), was associated with an increased prevalence of overweight and obesity, which suggests similar risk factors to those seen in the general population. Another study assessed BMI Z-scores (BMIz) of children and adolescents (aged 2–18 years) from the T1D Exchange registry (USA) and from the Diabetes Prospective Follow-up registry (Germany and Austria), and found that recorded median BMIz values were higher for people in both registries than for people in the general population using either international rates of obesity developed by WHO or the country's national frequency.[10] Global data from the international SWEET registry (55 paediatric diabetes centres from all continents and more than 30 000 people) reported overweight and obesity prevalence in children and adolescents (aged 2–18 years) with type 1 diabetes to be 27·2% for girls and 22·3% for boys.[9–11]

Second, drastic weight gain after diagnosis of type 1 diabetes in childhood has also been reported. For example, the Pittsburgh Epidemiology of Diabetes Complications study[12] revealed that the prevalence of overweight increased from 29% to 42%, and the prevalence of obesity increased from 3% to 23%, in people older than 18 years with type 1 diabetes. The study authors suggested that weight gain in this group could not be explained by ageing or lifestyle alone, and instead proposed that it was a result of insulin replacement therapy.

Although the prevalence of overweight and obesity in people living with type 1 diabetes shows remarkable differences between regions globally, further studies should compare the evolution of fat disposition between people with type 1 diabetes and matched peers across their entire lifespans. The absence of such studies is regrettable, because they might hold the key to a better understanding of the drivers and consequences of the combination of those two chronic diseases, and thus prevent, treat, or even cure them.

A bidirectional relationship

Not only is it becoming increasingly clear that insulin treatment in people living with type 1 diabetes affects body composition and can have a role in excessive fat disposition, which then presents a risk to health, there is also growing concern that type 1 diabetes is increasingly likely to develop in people with overweight and obesity. The accelerator hypothesis proposes that the distinction between type 1 and type 2 diabetes is blurred, with weight gain being a consistent key trigger for both diseases.[13,14] Some data suggest that a family history of type 2 diabetes is increased in people with type 1 diabetes, in particular in people who are not White.[15] This would suggest that the predisposition for type 1 and type 2 diabetes becomes overt when weight increases. However, because data on BMI at onset of type 1 diabetes appear to differ between global regions, it is hard to reach final conclusions on the validity of this hypothesis.[16,17]

Wilkin[18] based his accelerator hypothesis primarily on a small cohort of 168 young people (aged 1·1–15·7 years) presenting with type 1 diabetes between 1980 and 2002. At diagnosis, the mean height, weight, and standardised BMI (BMI SDS) were all close to the population mean. There was an inverse relationship between age at type 1 diabetes diagnosis and BMI SDS 6 months after diagnosis ($r=-0·30$; $p<0·0010$), suggesting that children with higher BMI developed diabetes earlier or were diagnosed earlier than children with lower BMI. This inverse relationship was confirmed in a cohort of German and Austrian children and young adults (aged 0–20 years),[16] whereas a positive relationship between BMI SDS and age at diagnosis of type 1 diabetes was found in Catalan children (aged <16 years, n=3534).[17] However, after diagnosis of type 1 diabetes, increased bodyweight and increased insulin demand were associated with more rapid disease progression.[18] Mechanistically, there are arguments to support a negative influence of overweight or obesity on the pathophysiology of type 1 diabetes, owing to the negative influence of high fatty acid and high glucose concentrations on the health of β cells, making these cells increasingly susceptible to attack by the immune system.[19,20]

Drivers of weight gain in type 1 diabetes

Figure 1 shows drivers of overweight and obesity in people living with type 1 diabetes. Although there is no debate about the benefit of tight glucose control for the prevention of complications in this population, the intensification of insulin therapy required to achieve stringent glucose control often comes at the cost of weight gain.[21–24] Ample evidence suggests that weight gain in all forms of diabetes is largely a result of intensive insulin therapy itself, with numerous studies supporting an association between weight gain and intensification of insulin therapy in people with both types of diabetes.[21–24] In the Diabetes Control and Complications Trial (DCCT),[24] in which individuals were randomly assigned to intensive (HbA_{1c} 6·7–7·2%) or conventional therapy (HbA_{1c} 8·7–9·2%), during the first year, people in the intensive group gained significantly more weight than in the conventional group (5·1 kg [SD 4·6] *vs* 2·4 kg [3·7]; $p<0·0001$). Higher baseline HbA_{1c} concentrations and greater decrements in HbA_{1c} during intensive therapy were both associated with a greater increase in BMI.[24] Intensively treated individuals with at least one severe hypoglycaemic episode also gained more weight than the intensively treated people with no severe hypoglycaemic episodes. Interestingly, there was no relationship between reported caloric

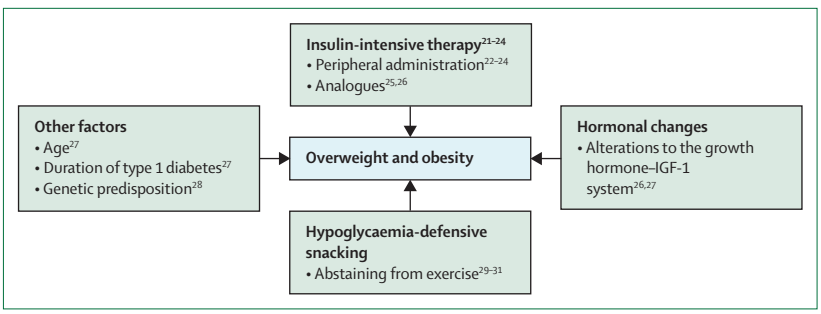

Figure 1: **Drivers of overweight and obesity in people living with type 1 diabetes**
The drivers of weight gain in people with type 1 diabetes are numerous and complex. Although insulin replacement therapy is believed to be the biggest contributor to weight gain, various other influences are also believed to contribute, including genetic predisposition, age, duration of type 1 diabetes, and risk of hypoglycaemia, which might influence defensive snacking and exercise absenteeism. Finally, alterations to the growth hormone–IGF-1 system is also believed to have a role.

intake or amount of exercise and weight change.[24] A retrospective observational cohort study of children and adolescents (aged 0–18 years) with type 1 diabetes found that weight gain was associated with age and time from diagnosis of type 1 diabetes, which could be directly associated with protracted and intensive insulin use.[27]

Although the mechanisms responsible for insulin-associated weight gain are not yet fully understood, several hypotheses have been put forward. One explanation is that, as people achieve an improved state of glycaemic control, blood glucose concentrations fall below the renal threshold, thereby increasing the conservation of ingested calories. In people with type 1 diabetes, being switched to an intensive insulin regime resulted in significantly reduced HbA_{1c} compared with conventional treatment (9·6 % [SD 0·6] *vs* 12·9% [0·9]; p<0·0100) and an almost complete elimination of glycosuria.[23] Consistent with findings from other studies,[21–24] participants also showed a mean bodyweight increase of 2·6 kg (SD 0·8), which the authors proposed was largely accounted for by the increased conservation of ingested calories and, in part, a decrease in daily energy expenditure.[23] However, caution is warranted in the interpretation of these results, given that poor glycaemic control was recorded among participants at baseline.

An alternative (if not mutually exclusive) explanation for insulin-induced weight gain is that people with type 1 diabetes administer insulin peripherally, thereby bypassing effects on the liver and potentially causing hyperinsulinaemia and fat accumulation in peripheral tissues.[32–34] Development of increasingly liver-specific insulins should alleviate the imbalance between peripheral and hepatic insulin, and has benefits in weight management.[25] Some trials and real-world studies report on less weight gain with insulin detemir than with isophane insulin or insulin glargine.[25,26] Because insulin detemir binds to albumin, extending the insulin's half-life, it also creates a larger species that more easily crosses the fenestrated capillaries of the liver, which improves the skewed ratio of hepatic-to-peripheral insulin distribution.[26] However, some hepatic-specific insulins seem to induce liver steatosis, which has hampered their further clinical development. Although basal insulin polyethylene glycol lispro (peglispro) preferentially targeted the liver and was found to be more effective in reducing HbA_{1c} concentrations than insulin glargine, development of basal insulin peglispro was suspended owing to concerns that it could induce liver steatosis.[35] Research in hepatic-preferential insulins is ongoing, and these insulins remain a promising approach for controlling type 1 diabetes and for weight management.

Other pathways explaining insulin-induced weight gain have been proposed, including alterations to the growth hormone or IGF-1 system, which has a key role in maintaining body composition by balancing anabolism and catabolism.[32,33] Controversy exists about the optimal route of administration of insulin replacement therapy. Although it has been proposed that continuous subcutaneous insulin infusion can promote increased weight gain in people with type 1 diabetes, there are no high-quality, prospective, randomised, controlled trials (RCTs) on this. However, one retrospective study that compared continuous subcutaneous insulin infusion versus multiple daily insulin injections during a 10-year study period found no difference in weight gain between the two groups, although people in the continuous subcutaneous insulin infusion group showed more substantial improvements in glycaemic control and a reduction in daily insulin dose requirements by the end of the study.[36] Furthermore, in the DCCT,[24] the intensively treated group had weight gain irrespective of the method of insulin replacement therapy.

Another obvious reason why insulin therapy targeting tight glycaemic control is associated with weight gain is the increased risk of hypoglycaemia. In DCCT,[24] individuals treated with intensive insulin therapy not only had reduced HbA_{1c} concentrations and weight gain, they were 3 times more likely to have a severe hypoglycaemic event than people on conventional therapy. Obvious reasons for weight gain in people with type 1 diabetes are defensive snacking to avoid hypoglycaemia when exercising, or compensatory carbohydrate intake when hypoglycaemia events occur. Although the risk of hypoglycaemia has been lowered by the availability of insulin analogues, it remains the most frequent acute complication in people with type 1 diabetes.[37] Hybrid, closed-loop, artificial pancreas systems might further reduce hypoglycaemia frequency by better matching insulin administration to the glycaemic concentration, but their use is currently low and no firm conclusions can be drawn on whether they will substantially reduce defensive snacking and weight gain.[38] Fear of hypoglycaemia during exercise can be an important factor contributing to weight gain in people with type 1 diabetes. Physical activity data obtained

through accelerometers[39] in newly diagnosed adults with type 1 diabetes showed lower amounts of moderate–vigorous physical activity per day in people with type 1 diabetes than in adults without type 1 diabetes, but these data were far from comprehensive. Nonetheless, hypoglycaemic risk from physical activity means that people with type 1 diabetes should either modulate their insulin doses before exercise (which requires additional planning) or maintain their blood glucose at higher concentrations by increasing carbohydrate intake before and during exercise (which can imbalance energy expenditure and lead to weight gain). Thus, in people with type 1 diabetes, better education about how to adapt insulin doses to physical activity is needed because, otherwise, some of this population might be deterred from exercising, which could contribute to weight management issues.[29–31]

Genetic and phenotypical factors are also likely to contribute to weight gain in people with type 1 diabetes. There is an increased likelihood of a family history of type 2 diabetes among people with type 1 diabetes and obesity, and age and duration of time since diagnosis are factors in the development of overweight or obesity this population.[28] Nonetheless, it is clear that the glucocentric approach that governs diabetes care, although beneficial in avoiding long-term complications, seems to put people with type 1 diabetes at risk of weight gain and trigger the same metabolic disturbances, such as increased insulin resistance, as seen in people with type 2 diabetes.

Consequences of weight gain in people living with type 1 diabetes

Although intensive insulin therapy has been shown to reduce the prevalence of many long-term complications of type 1 diabetes,[21–23] the consequential side-effect of increased bodyweight is almost guaranteed to bring about additional health problems. Long-term research in people without diabetes has clearly shown that overweight and obesity are important risk factors for type 2 diabetes, cardiovascular diseases, some types of cancer, and premature death.[40] Obesity is also highly associated with poorer mental health outcomes, such as anxiety, depression, and self-harming behaviours.[41] Although comprehensive longitudinal data in people with type 1 diabetes are currently non-existent to the best of our knowledge, it is reasonable to assume the effects of overweight and obesity will also affect this population and might even be more detrimental than in the general population. In the study by Edqvist and colleagues,[42] 26 125 people with type 1 diabetes (mean age 33·3 years, 45% women) who were registered in the Swedish National Diabetes Registry were followed up from 1998 to 2012, to assess the risk of death from cardiovascular disease, major cardiovascular disease events, hospitalisations for heart failure, and total deaths. The study authors concluded that risk of major cardiovascular disease, heart failure, cardiovascular death, and mortality increased with increasing BMI, with associations more apparent in men than in women.[42]

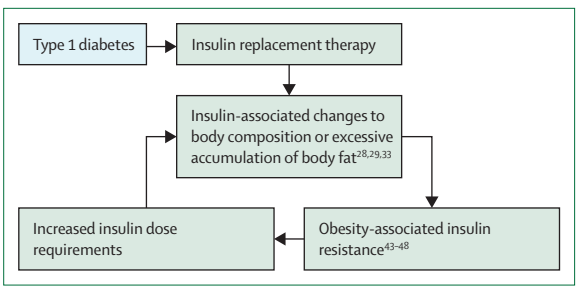

Figure 2: **The vicious cycle of insulin-associated weight gain**
Although the drivers of weight gain in people living with type 1 diabetes are numerous and complex, insulin replacement therapy is believed to be one of the biggest contributors. Development of type 1 diabetes leads to insulin replacement therapy as standard of care. Weight gain associated with intensive insulin therapy increases insulin resistance, leading to increased insulin dose requirements, which in turn promotes further insulin-associated weight gain.

Insulin resistance is common among individuals with overweight or obesity without diabetes, and current evidence suggests that it also effects people with type 1 diabetes and overweight or obesity (figure 2).[43] However, there is sparse evidence in the clinical setting, mainly because it is difficult to measure insulin resistance in people with type 1 diabetes. In the few studies available, insulin resistance was found to be higher in a cohort of adolescents of a healthy weight with type 1 diabetes compared with weight-matched controls.[44] It is not clear whether clinical factors that are more readily obtainable can identify people with type 1 diabetes who are likely to have insulin resistance.[45] Using euglycaemic-hyperinsulinaemic clamps is invasive and costly and thus not easily done in large cohorts. A large-scale meta-analysis of 38 studies that all used euglycaemic-hyperinsulinaemic clamps to measure insulin resistance in people with type 1 diabetes concluded that insulin resistance was higher in people with type 1 diabetes than in healthy, weight-matched controls.[46] The meta-analysis[46] suggested that the insulin resistance that develops in people with type 1 diabetes is because of the exogenous delivery of insulin, and presents with a unique phenotype that correlates with aberrant physiological endpoints, regardless of weight. However, obesity can also increase insulin resistance in people with type 1 diabetes.[47] Thus, the state of insulin resistance that develops in such people differs from insulin resistance in people with obesity, but its consequences are clearly deleterious. For instance, a study found that people with type 1 diabetes with the lowest estimated glucose disposal rate (an indication of insulin resistance) were more likely to have microvascular complications than were people with type 1 diabetes with higher glucose disposal rates.[49] This finding was confirmed by a study that investigated the development of nephropathy in people with type 1 diabetes.[48] There is scarce direct evidence linking excess adiposity and insulin resistance in people with type 1 diabetes to an

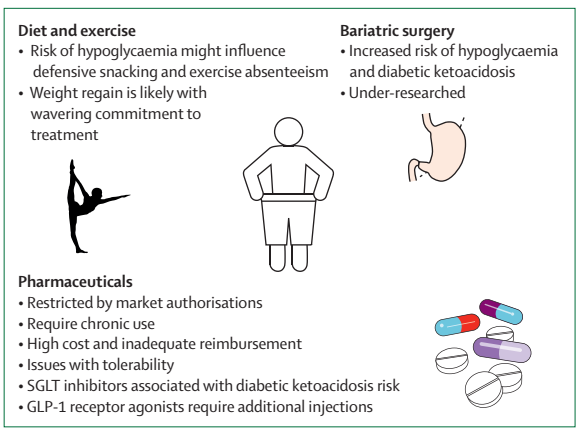

Figure 3: **Schematic overview of issues associated with various approaches to weight management in people with type 1 diabetes**

increased incidence of myocardial infarction and stroke. Weak evidence was provided by a study of a cohort of 40 people with type 1 diabetes (mean age 45·2 [SD 9·2] years; mean duration of diabetes 22·6 [7·8] years), in which a positive correlation between insulin resistance and coronary artery calcification was seen.[47] In any case, cardiovascular disease remains the primary cause of mortality in adults living with type 1 diabetes, which might be related to insulin resistance.[50] Diet and exercise can improve insulin resistance, and although this is better studied in people with type 2 diabetes—in whom only a small change in weight, or increase in exercise, or both, is beneficial—it is possible that a similar effect also exists in people with type 1 diabetes, which is emphasised in position statements that clearly emphasise the benefit of exercise and weight loss in people with type 1 diabetes.[51,52] In addition, metformin as an adjunct therapy also positively affects insulin resistance in type 1 diabetes, which is further elaborated in the treatments section that follows.

Finally, weight gain can also negatively affect compliance with insulin treatment and thereby glycaemic control. Some people living with type 1 diabetes underdose insulin to achieve weight loss, increasing the risk of acute diabetic ketoacidosis events, and long-term complications of diabetes. Based on the available evidence, rates of insulin non-adherence in people living with type 1 diabetes range from 44% to 77% globally, and are typically higher in low-income and middle-income countries.[53] There are numerous reasons for an individual to waiver in their commitment to an insulin regimen (eg, burdensome and onerous insulin replacement therapy regimens, or inadequate education), but one of the main reasons for omitting insulin therapy is to avoid weight gain. A US study of 341 girls and women (aged 13–60 years) with type 1 diabetes found that 31% intentionally omitted insulin treatment, with 9% reporting that this was a frequent occurrence, and half of the omitters stating it was for weight management purposes.[54]

Preventing and treating excessive weight gain in people living with type 1 diabetes

As type 2 diabetes encompasses the majority of diabetes cases, and the incidence of overweight or obesity is higher in the type 2 than type 1 diabetes population, many weight management strategies for people living with diabetes have mostly been trialled and implemented in people living with this condition (figure 3).[55] Whether or not these same treatment strategies are effective, or even safe, for people living with type 1 diabetes is unknown, and all approaches to weight loss present specific difficulties (eg, hypoglycaemia when fasting, cutting carbohydrates, or during exercise) for people living with type 1 diabetes.[56]

Lifestyle and behavioural modifications

The treatment of obesity involves a multidisciplinary approach that also includes lifestyle and behavioural modifications (ie, diet and physical activity). Physical activity can help not only with weight management, but can also reduce cardiovascular disease risk and mortality, improve the lipid profile, and improve mental health outcomes.[57,58] Physical activity also improves insulin sensitivity in people living with type 2 diabetes, thereby reducing insulin dose requirements and limiting insulin-associated weight gain. However, physical activity in the type 1 diabetes population is associated with an increased risk of hypoglycaemia, which probably contributes to fewer than 5% of adolescents with type 1 diabetes achieving the paediatric clinical guidelines for physical activity.[59] A multicentre pilot RCT is investigating the efficacy and cost-effectiveness of an education programme provided to people with type 1 diabetes to facilitate safe and effective exercise (registered as ISRCTN61403534 and ongoing).[60] Advances in hybrid, closed-loop, artificial pancreas systems might enable safer exercise by avoiding hypoglycaemia through providing a better match between glucose concentrations and insulin administration.

Other lifestyle interventions include dietary modifications.[61] In the DiRECT trial,[62] almost half of the participants with type 2 diabetes achieved remission to a non-diabetic state without antidiabetic drugs after a low calory diet consisting of a total diet replacement phase of up to 5 months (825–853 kcal/day formula diet), followed by a structured food-reintroduction phase.[62] Even in people with type 2 diabetes, such diets are not widely used and complying with them is difficult. However, owing to a paucity of good-quality RCTs in type 1 diabetes, it is unclear whether ketogenic diets are a safe option for people with this condition.[63] An observational study on a cohort of 11 people with type 1 diabetes on continuous glucose monitoring suggested that a high-fat ketogenic diet might reduce glycaemic variability, albeit at the expense of an increased risk of hypoglycaemia.[63]

One of the most effective strategies for preventing weight gain in people with type 1 diabetes is likely to be

	ADJUNCT-ONE[73] (n=1398; 52 week follow-up; randomisation 3:1)			ADJUNCT-TWO[74] (n=835; 26 week follow-up; randomisation 3:1)			
	Liraglutide 1·8 mg	Liraglutide 1·2 mg	Liraglutide 0·6 mg	Liraglutide 1·8 mg	Liraglutide 1·2 mg	Liraglutide 0·6 mg	Placebo
Mean effect on body weight, kg	–4·90 (–5·70 to –4·20)	–3·60 (–4·30 to –2·80)	–2·20 (–2·90 to –1·50)	–5·10 *vs* baseline*	–4·00 *vs* baseline*	–2·50 *vs* baseline*	–0·20 *vs* baseline*
Mean effect on HbA_{1c}	–0·20% (–0·32 to –0·07)	–0·15% (–0·27 to –0·03)	–0·09% (–0·21 to 0·03)	–0·35% (–0·50 to –0·20)	–0·23% (–0·38 to –0·08)	–0·24% (–0·39 to –0·10)	NA
Estimated treatment ratio for effect on insulin dosage	0·92 (0·88 to 0·96)	0·95 (0·91 to 0·99)	1·00 (0·96 to 1·04)	0·90% (0·86 to 0·93)	0·93% (0·90 to 0·96)	0·95% (0·92 to 0·99)	NA
Estimated treatment ratio for symptomatic hypoglycaemic events	1·31 (1·07 to 1·59)	1·27 (1·03 to 1·55)	1·17 (0·97 to 1·43)	NS	1·33 (1·07 to 1·67)	NS	NA

Data are mean (95% CI) or estimated treatment ratio (95% CI) for comparison against placebo, unless otherwise stated. NA=not applicable. NS=not significant versus placebo (actual p value not reported). Symptomatic hypoglycaemic events are typical symptoms of hypoglycaemia plus a measured plasma glucose concentration ≤70 mg/dL. *p<0·0001.

Table 1: **GLP-1 receptor agonist liraglutide as adjunct therapy in people living with type 1 diabetes**

	Pooled analysis of DEPICT-1 and DEPICT-2 studies[78]			Phase 3 trial[79] (n=175)	Pooled analysis of Tandem1[80] and Tandem2[81] (n=1575)		
	Dapagliflozin 5 mg/day (n=548)*	Dapagliflozin 10 mg/day (n=566)	Placebo	Ipragliflozin 50 mg/day	Sotagliflozin 200 mg/day	Sotagliflozin 400 mg/day	Placebo
Effect on bodyweight	–3·11% (–3·61 to –2·62)	–3·71% (–4·20 to –3·22)	NA	–2·87 kg (–3·58 to –2·16)	–2·17% (–2·54 to –1·80)	–3·02% (–3·39 to –2·65)	NA
Effect on HbA_{1c}	–0·41% (–0·48 to –0·31)	–0·43% (–0·52 to 0·34)	NA	–0·36% (–0·57 to –0·14)	–0·36% (–0·44 to –0·29)	–0·38% (–0·45 to –0·31)	NA
Effect on insulin dosage	–9·57% (–12·01 to –7·07)	–11·75% (–14·13 to –9·30)	NA	–7·35 IU (–9·09 to –5·61)	7·10 % (SE 1·30); p<0·001 *vs* placebo at 52 weeks	–10·33 % (SE 1·30); p<0·001 *vs* placebo at 52 weeks	NA
Adverse events: diabetic ketoacidosis†	2·00%	1·90%	0·60%	No diabetic ketoacidosis reported in either group	2·90 %	3·80 %	0·20 %

Data are mean (95% CI) for comparison with placebo at 24 weeks, unless otherwise stated. Dapagliflozin is an SGLT2 inhibitor approved for use in Europe and Japan. Ipragliflozin is an SGLT2 inhibitor approved for use in Japan. Sotagliflozin is a dual SGLT1/2 inhibitor approved by the European Medicines Agency. NA=not applicable. IU=international units. *p<0·0001. †Other adverse events were not reported consistently between studies.

Table 2: **Approved SGLT inhibitors as adjunct therapy in people living with type 1 diabetes**

the provision of additional education regarding nutrition, which allows for increasingly accurate tailoring of insulin doses to concentrations that mimic physiological concentrations, enabling insulin to be administered with maximum efficiency. For example, despite that the fact that intensive insulin therapy can promote weight gain in people living with either type 1 diabetes or type 2 diabetes, in one small study (n=16), participants on intensive insulin treatment improved glycaemic control and reduced daily insulin dose requirements while avoiding weight gain.[64] This outcome was made possible by providing additional education to participants, enabling them to increasingly accurately count carbohydrates and fine-tune their basal and prandial insulin concentrations. This study[64] suggested that improved carbohydrate-counting in combination with intensive insulin therapy might be an effective strategy for improving glycaemic control and managing weight gain in type 1 diabetes. However, this approach probably varies between individuals and the financial resources needed to adequately educate patients on the basis of their lifestyle are not currently available. Although this study[64] was small and resource availability is an impediment to wider applicability, it did suggest that optimising insulin management should focus on redistribution of insulin to the recommended 50% basal–50% prandial ratio, with careful attention to accurate insulin dosing for carbohydrate intake, rather than just on increasing the total insulin dose.

Pharmacological agents as adjunct therapies

A promising means of weight management in people with type 1 diabetes is the use of adjunct therapies to reduce the insulin dose needed for maintaining tight glycaemic control, through the improvement of insulin sensitivity (metformin), delay of gastric emptying (pramlintide), suppression of glucagon and appetite (pramlintide), incretin-based effects (GLP-1 receptor agonists), or glucosuria (SGLT inhibitors). Although these therapies have been designed with the goal of improving glycaemic control, they have also shown weight management benefits.[65,66]

Metformin has been the most widely studied adjunct therapy in clinical trials for insulin. The REMOVAL study[67] in people with type 1 diabetes studied the effect of metformin on carotid intima media thickness, a surrogate for cardiovascular disease, and confirmed a statistically significant effect on weight change (–1·17 kg; 95% CI –1·66 to –0·69; p<0·0001), although it did not reach its

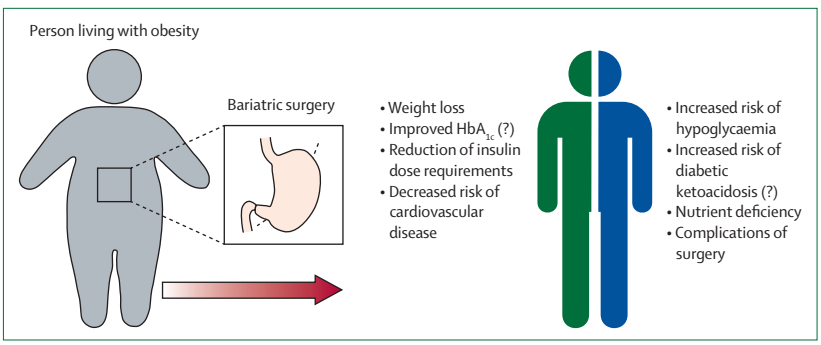

Figure 4: **Advantages and disadvantages of bariatric surgery in people living with type 1 diabetes**
Schematic overview of key benefits (green) and disadvantages (blue) of bariatric surgery.

primary endpoint for carotid intima media thickness. Although real-world evidence suggests that the observed effect on weight loss is transient,[66–69] metformin is still used as an adjunct therapy in adolescents with overweight and type 1 diabetes, on the basis that it is of use in girls (aged 8–18 years) with polycystic ovary syndrome, for whom it promotes insulin sensitisation and weight loss, stimulates ovulation, and regulates menstruation.[70,71]

Promising effects on weight were reported for GLP-1 receptor agonists in people with type 1 diabetes. In particular, liraglutide was studied as adjunct therapy in type 1 diabetes, with the ADJUNCT studies[72–74] reporting a dose-dependent weight loss in people with type 1 diabetes (table 1). Importantly, weight loss associated with liraglutide use in people with overweight or obesity and type 1 diabetes was caused by a reduction in fat mass, with no change in lean mass.[75] Nonetheless, there was a small increase in symptomatic hypoglycaemia, but rates of severe hypoglycaemia were not increased, although the number of events was too low to draw firm conclusions.

The only regulatory approved adjunct therapy for glucose control in people with type 1 diabetes in the USA is pramlintide, a synthetic analogue of human amylin, a hormone co-secreted with insulin by the pancreatic β cells, which delays gastric emptying, suppresses glucagon secretion, and reduces food intake. If taken with insulin, pramlintide reduces HbA_{1c}, daily insulin doses, and postprandial glucose concentrations.[76] In a 1-year RCT that tested the safety and efficacy of pramlintide in people with type 1 diabetes, it was also found to have a modest effect on weight, with people using pramlintide averaging a 0·4 kg reduction in bodyweight, a significant difference compared with an average 0·8 kg increase in the placebo group.[76] In addition to some issues of tolerability (nausea and vomiting), use of pramlintide was associated with 4 times the increased risk of severe hypoglycaemia.[76] However, frequency of injections and cost are the biggest factors limiting its widespread use in people living with type 1 diabetes.[76,77]

SGLT inhibitors control weight gain in people with type 1 diabetes without compromising glycaemic control, and have been approved in Europe and Japan for treating people with type 1 diabetes and overweight or obesity (table 2).[77,78,80,82,83] Despite regulatory approval, safety concerns and inadequate reimbursement have meant that SGLT inhibitors remain underused in clinical practice. It is important to design strategies to mitigate the risk of diabetic ketoacidosis associated with SGLT inhibitor use in people with type 1 diabetes.[84,85] Further research on drug approaches to improve weight management in people with type 1 diabetes is crucial, but this population is frequently overlooked by industry and policy makers, because it represents only a small subset of the people living with obesity.

Bariatric surgery

For many people with type 1 diabetes, reversing obesity through diet, exercise, or adjunct therapies has proven to be an impossible task, and bariatric surgery has been proposed as a solution (figure 4). A small retrospective study of 22 people in Belgium with type 1 diabetes who previously had bariatric surgery revealed a consistent decrease in BMI and insulin dose requirements, but no improvement in glycaemic control.[86] A retrospective study of 61 people with type 1 diabetes in Abu Dhabi, found a median reduction in BMI of 9·2 kg/m² (95% CI 5·8–10·8) at 6 months and 11·4 kg/m² (9·2–13·1) at 12 months, accompanied by a reduction in HbA_{1c} from 8·6% (7·8–9·2) to 7·8% (7·2–8·5), with only three reported cases of diabetic ketoacidosis.[87] A Swedish observational study in people with type 1 diabetes compared 387 people who had Roux-en-Y Gastric Bypass versus a control group of 387 people with obesity, matched for age, sex, BMI, and calendar year of surgery.[88] The authors saw a lower risk of cardiovascular disease (hazard ratio [HR] 0·43 [0·20–0·9]), cardiovascular death (0·15 [0·03–0·68]), and stroke (0·18 [0·04–0·82]) for the bypass group, but no improvement in glycaemic control and a higher risk for hyperglycaemic events (1·99 [1·07–3·72]) and substance misuse (3·71 [1·03–3·29]), compared with the control group.[88] Other studies[87,89] yielded similar results, but all studies emphasised that although short-term results of bariatric surgery in people with type 1 diabetes are encouraging, larger and longer-term studies are needed.[89] However, large-scale prospective trials are difficult to do in this patient group, because bariatric surgery is not often done in people with type 1 diabetes so, for studies to include sufficient numbers, international collaboration is needed.

Conclusion and next steps

The rates of overweight or obesity in the type 1 diabetes population are higher than previously thought and increasing. One of the challenges for people living with type 1 diabetes is to simultaneously achieve glycaemic and weight control, which is difficult because intensification of insulin therapy is believed to be the biggest driver of weight gain. Overall, the drivers and the burden of overweight or obesity in people living with

Search strategy and selection criteria

We searched PubMed for articles published between Jan 1, 1985, and Aug 24, 2021, using the search terms "overweight", "obesity", "weight gain", "weight loss", "weight management", "body weight", "body mass index", "BMI", "insulin-associated weight gain", "adjunct therapies", and "bariatric surgery", in combination with the term "type 1 diabetes". We found 3298 articles and excluded papers not in English or Spanish. We reviewed the remainder for the most relevant articles, and included 87 articles.

type 1 diabetes remain largely understudied. As a starting point, an effort should be made to better grasp the exact prevalence in people living with type 1 diabetes of atypical or excessive accumulation of body fat that eventually leads to overweight and obesity. First, further studies should be done to compare the evolution of fat disposition between people with type 1 diabetes and matched peers across their entire lifespans. This would enable assessment of whether the nature and health effects of atypical fat accumulation differ between people living with type 1 diabetes versus their peers. Second, new treatments and technologies should focus not only on improving glucose control, but also on easing weight management in people living with type 1 diabetes. The development of hepatic-preferential insulins holds some promise, but better education and support for people with regard to matching insulin doses to food intake and exercise could already go a long way to help people with type 1 diabetes to manage their weight. Adjunct therapies that can improve glycaemic control through insulin-independent pathways should also be further explored. In terms of consequences, additional research is warranted to assess the exact magnitude of the deleterious effects on the overall health of people suffering from both overweight or obesity and type 1 diabetes. The existing evidence already indicates that undesired weight gain is a reason for concern in treating people living with type 1 diabetes, but there is a paucity of good-quality data.

This Review is part of a larger effort to draw attention to the topic of weight management in people living with type 1 diabetes. We hope it will foster further research, because only knowledge will enable to us to improve clinical care for people with type 1 diabetes. Increased knowledge will also help in the development of evidence-based consensus guidelines to help clinicians in their daily practice.

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Contributors

BVdS and CM were responsible for the conceptualisation, funding acquisition, methods, and original draft of this Review, and supervised the process. BVdS, CM, and DE wrote the manuscript. DE created the figures. All authors did the literature search and reviewed and edited the manuscript.

Declaration of interests

CM reports consulting fees from Novo Nordisk, Sanofi, Merck Sharp & Dohme, Eli Lilly, AstraZeneca, Boehringer Ingelheim, Roche, Medtronic, ActoBio Therapeutics, Pfizer, Insulet, and Zealand Pharma; and serves or has served on the speaker bureau for Novo Nordisk, Sanofi, Eli Lilly, Boehringer Ingelheim, AstraZeneca, and Novartis. RNF reports personal fees from Novo Nordisk, Sanofi, Abbott, and Medtronic; participation on an advisory board for Novo Nordisk, Sanofi, and Abbott; holds a fiduciary role in international relations for Sociedad Mexicana de Nutricion y Endocrinologa (SMNE); and has received product from Novo Nordisk, Sanofi, Abbott, Medtronic, Eli Lilly, AstraZeneca, Merck Sharp & Dohme, and Pfizer. All other authors declare no competing interests.

References

1 Corbin KD, Driscoll KA, Pratley RE, et al. Obesity in type 1 diabetes: pathophysiology, clinical impact, and mechanisms. *Endocr Rev* 2018; **39:** 629–63.
2 Malik VS, Willet WC, Hu FB. Nearly a decade on—trends, risk factors and policy implications in global obesity. *Nat Rev Endocrinol* 2020; **16:** 615–16.
3 Fellinger P, Fuchs D, Wolf P, et al. Overweight and obesity in type 1 diabetes equal those of the general population. *Wien Klin Wochenschr* 2019; **131:** 55–60.
4 Lavens A, Nobels F, De Block C, et al. Effect of an integrated, multidisciplinary nationwide approach to type 1 diabetes care on metabolic outcomes: an observational real-world study. *Diabetes Technol Ther* 2021; **23:** 565–76.
5 Faradji-Hazán RN, Valenzuela-Lara M, Díaz-Barriga Menchaca AP, et al. Type 1 diabetes care in Mexico: an analysis of the RENACED-DT1 National Registry. *Rev Invest Clin* 2021; **73:** 222–30.
6 Organisation for Economic Co-operation and Development. OECD Health Policy Studies. The heavy burden of obesity: the economics of prevention. Oct 10, 2019. https://www.oecd.org/health/the-heavy-burden-of-obesity-67450d67-en.htm (accessed Aug 24, 2021).
7 Foster NC, Beck RW, Miller KM, et al. State of type 1 diabetes management and outcomes from the T1D Exchange in 2016–2018. *Diabetes Technol Ther* 2019; **21:** 66–72.
8 Liu LL, Lawrence JM, Davis C, et al. Prevalence of overweight and obesity in youth with diabetes in USA: the SEARCH for Diabetes in Youth study. *Pediatr Diabetes* 2010; **11:** 4–11.
9 Minges KE, Whittemore R, Weinzimer SA, Irwin ML, Redeker NS, Grey M. Correlates of overweight and obesity in 5529 adolescents with type 1 diabetes: the T1D Exchange Clinic Registry. *Diabetes Res Clin Pract* 2017; **126:** 68–78.
10 Redondo MJ, Foster NC, Libman IM, et al. Prevalence of cardiovascular risk factors in youth with type 1 diabetes and elevated body mass index. *Acta Diabetol* 2016; **53:** 271–77.
11 Maffeis C, Birkebaek NH, Konstantinova M, et al. Prevalence of underweight, overweight, and obesity in children and adolescents with type 1 diabetes: data from the international SWEET registry. *Pediatr Diabetes* 2018; **19:** 1211–20.
12 Conway B, Miller RG, Costacou T, et al. Temporal patterns in overweight and obesity in type 1 diabetes. *Diabet Med* 2010; **27:** 398–404.
13 Wilkin TJ. The accelerator hypothesis: a review of the evidence for insulin resistance as the basis for type I as well as type II diabetes. *Int J Obes* 2009; **33:** 716–26.
14 Wilkin TJ. The accelerator hypothesis: weight gain as the missing link between type I and type II diabetes. *Diabetologia* 2001; **44:** 914–22.
15 Barone B, Rodacki M, Zajdenverg L, et al. Family history of type 2 diabetes is increased in patients with type 1 diabetes. *Diabetes Res Clin Pract* 2008; **82:** e1–4.
16 Knerr I, Wolf J, Reinehr T, et al. The 'accelerator hypothesis': relationship between weight, height, body mass index and age at diagnosis in a large cohort of 9248 German and Austrian children with type 1 diabetes mellitus. *Diabetologia* 2005; **48:** 2501–04.

17 Giménez M, Aguilera E, Castell C, de Lara N, Nicolau J, Conget I. Relationship between BMI and age at diagnosis of type 1 diabetes in a Mediterranean area in the period of 1990–2004. *Diabetes Care* 2007; **30:** 1593–95.

18 Betts P, Mulligan J, Ward P, Smith B, Wilkin T. Increasing body weight predicts the earlier onset of insulin-dependant diabetes in childhood: testing the 'accelerator hypothesis' (2). *Diabet Med* 2005; **22:** 144–51.

19 Lauria A, Barker A, Schloot N, et al. BMI is an important driver of β-cell loss in type 1 diabetes upon diagnosis in 10 to 18-year-old children. *Eur J Endocrinol* 2015; **172:** 107–13.

20 Eizirik DL, Pasquali L, Cnop M. Pancreatic β-cells in type 1 and type 2 diabetes mellitus: different pathways to failure. *Nat Rev Endocrinol* 2020; **16:** 349–62.

21 Nathan DM, Genuth S, Lachin J, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; **329:** 977–86.

22 Russell-Jones D, Khan R. Insulin-associated weight gain in diabetes—causes, effects and coping strategies. *Diabetes Obes Metab* 2007; **9:** 799–812.

23 Carlson MG, Campbell PJ. Intensive insulin therapy and weight gain in IDDM. *Diabetes* 1993; **42:** 1700–07.

24 The DCCT Research Group. Weight gain associated with intensive therapy in the diabetes control and complications trial. *Diabetes Care* 1988; **11:** 567–73.

25 Russell-Jones D, Simpson R, Hylleberg B, Draeger E, Bolinder J. Effects of QD insulin detemir or neutral protamine Hagedorn on blood glucose control in patients with type I diabetes mellitus using a basal-bolus regimen. *Clin Ther* 2004; **26:** 724–36.

26 Russell-Jones D. Insulin detemir: improving the predictability of glycaemic control. *Int J Obes* 2004; **28** (suppl 2): S29–34.

27 De Keukelaere M, Fieuws S, Reynaert N, et al. Evolution of body mass index in children with type 1 diabetes mellitus. *Eur J Pediatr* 2018; **177:** 1661–66.

28 Purnell JQ, Dev RK, Steffes MW, et al. Relationship of family history of type 2 diabetes, hypoglycemia, and autoantibodies to weight gain and lipids with intensive and conventional therapy in the Diabetes Control and Complications Trial. *Diabetes* 2003; **52:** 2623–29.

29 Colberg SR, Laan R, Dassau E, Kerr D. Physical activity and type 1 diabetes: time for a rewire? *J Diabetes Sci Technol* 2015; **9:** 609–18.

30 Francescato MP, Stel G, Stenner E, Geat M. Prolonged exercise in type 1 diabetes: performance of a customizable algorithm to estimate the carbohydrate supplements to minimize glycemic imbalances. *PLoS One* 2015; **10:** e0125220.

31 Tielemans SM, Soedamah-Muthu SS, De Neve M, et al. Association of physical activity with all-cause mortality and incident and prevalent cardiovascular disease among patients with type 1 diabetes: the EURODIAB Prospective Complications Study. *Diabetologia* 2013; **56:** 82–91.

32 Russell-Jones DL, Rattray M, Wilson VJ, Jones RH, Sönksen PH, Thomas CR. Intraperitoneal insulin is more potent than subcutaneous insulin at restoring hepatic insulin-like growth factor-I mRNA levels in the diabetic rat: a functional role for the portal vascular link. *J Mol Endocrinol* 1992; **9:** 257–63.

33 Sönksen PH, Russell-Jones D, Jones RH. Growth hormone and diabetes mellitus. A review of sixty-three years of medical research and a glimpse into the future? *Horm Res* 1993; **40:** 68–79.

34 Laville M, Andreelli F. Mechanisms for weight gain during blood glucose normalization. *Diabetes Metab* 2000; **26** (suppl 3): 42–45 (in French).

35 Hirose T. Development of new basal insulin peglispro (LY2605541) ends in a disappointing result. *Diabetol Int* 2016; **7:** 16–17.

36 Alderisio A, Bozzetto L, Franco L, Riccardi G, Rivellese AA, Annuzzi G. Long-term body weight trajectories and metabolic control in type 1 diabetes patients on insulin pump or multiple daily injections: a 10-year retrospective controlled study. *Nutr Metab Cardiovasc Dis* 2019; **29:** 1110–17.

37 Burr JF, Shephard RJ, Riddell MC. Physical activity in type 1 diabetes mellitus: assessing risks for physical activity clearance and prescription. *Can Fam Physician* 2012; **58:** 533–35.

38 Taleb N, Haidar A, Messier V, Gingras V, Legault L, Rabasa-Lhoret R. Glucagon in artificial pancreas systems: potential benefits and safety profile of future chronic use. *Diabetes Obes Metab* 2017; **19:** 13–23.

39 Matson RIB, Leary SD, Cooper AR, Thompson C, Narendran P, Andrews RC. Objective measurement of physical activity in adults with newly diagnosed type 1 diabetes and healthy individuals. *Front Public Health* 2018; **6:** 360.

40 Hruby A, Manson JE, Qi L, et al. Determinants and consequences of obesity. *Am J Public Health* 2016; **106:** 1656–62.

41 Mechanick JI, Youdim A, Jones DB, et al. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient—2013 update: cosponsored by American Association of Clinical Endocrinologists, the Obesity Society, and American Society for Metabolic & Bariatric Surgery. *Obesity (Silver Spring)* 2013; **21** (suppl 1): S1–27.

42 Edqvist J, Rawshani A, Adiels M, et al. BMI, mortality, and cardiovascular outcomes in type 1 diabetes: findings against an obesity paradox. *Diabetes Care* 2019; **42:** 1297–304.

43 Cleland SJ, Fisher BM, Colhoun HM, Sattar N, Petrie JR. Insulin resistance in type 1 diabetes: what is 'double diabetes' and what are the risks? *Diabetologia* 2013; **56:** 1462–70.

44 Nadeau KJ, Regensteiner JG, Bauer TA, et al. Insulin resistance in adolescents with type 1 diabetes and its relationship to cardiovascular function. *J Clin Endocrinol Metab* 2010; **95:** 513–21.

45 Williams KV, Erbey JR, Becker D, Arslanian S, Orchard TJ. Can clinical factors estimate insulin resistance in type 1 diabetes? *Diabetes* 2000; **49:** 626–32.

46 Donga E, Dekkers OM, Corssmit EP, Romijn JA. Insulin resistance in patients with type 1 diabetes assessed by glucose clamp studies: systematic review and meta-analysis. *Eur J Endocrinol* 2015; **173:** 101–09.

47 Schauer IE, Snell-Bergeon JK, Bergman BC, et al. Insulin resistance, defective insulin-mediated fatty acid suppression, and coronary artery calcification in subjects with and without type 1 diabetes: the CACTI study. *Diabetes* 2011; **60:** 306–14.

48 Bjornstad P, Snell-Bergeon JK, Rewers M, et al. Early diabetic nephropathy: a complication of reduced insulin sensitivity in type 1 diabetes. *Diabetes Care* 2013; **36:** 3678–83.

49 Chillaron JJ, Goday A, Flores-Le-Roux JA, et al. Estimated glucose disposal rate in assessment of the metabolic syndrome and microvascualr complications in patients with type 1 diabetes. *J Clin Endocrinol Metab* 2009; **94:** 3530–34.

50 Secrest AM, Becker DJ, Kelsey SF, Laporte RE, Orchard TJ. Cause-specific mortality trends in a large population-based cohort with long-standing childhood-onset type 1 diabetes. *Diabetes* 2010; **59:** 3216–22.

51 Riddell MC, Gallen IW, Smart CE, et al. Exercise management in type 1 diabetes: a consensus statement. *Lancet Diabetes Endocrinol* 2017; **5:** 377–90.

52 Moser O, Riddell MC, Eckstein ML, et al. Glucose management for exercise using continuous glucose monitoring (CGM) and intermittently scanned CGM (isCGM) systems in type 1 diabetes: position statement of the European Association for the Study of Diabetes (EASD) and of the International Society for Pediatric and Adolescent Diabetes (ISPAD) endorsed by JDRF and supported by the American Diabetes Association (ADA). *Diabetologia* 2020; **63:** 2501–20.

53 Bermeo-Cabrera J, Almeda-Valdes P, Riofrios-Palacios J, Aguilar-Salinas CA, Mehta R. Insulin adherence in type 2 diabetes in Mexico: behaviors and barriers. *J Diabetes Res* 2018; **2018:** 3190849.

54 Polonsky WH, Anderson BJ, Lohrer PA, Aponte JE, Jacobson AM, Cole CF. Insulin omission in women with IDDM. *Diabetes Care* 1994; **17:** 1178–85.

55 Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Res Clin Pract* 2019; **157:** 107843.

56 Tandon S, Ayis S, Hopkins D, Harding S, Stadler M. The impact of pharmacological and lifestyle interventions on body weight in people with type 1 diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab* 2021; **23:** 350–62.

57 Chimen M, Kennedy A, Nirantharakumar K, Pang TT, Andrews R, Narendran P. What are the health benefits of physical activity in type 1 diabetes mellitus? A literature review. *Diabetologia* 2012; **55:** 542–51.

58 Fuchsjäger-Mayrl G, Pleiner J, Wiesinger GF, et al. Exercise training improves vascular endothelial function in patients with type 1 diabetes. *Diabetes Care* 2002; **25:** 1795–801.

59 Brazeau AS, Rabasa-Lhoret R, Strychar I, Mircescu H. Barriers to physical activity among patients with type 1 diabetes. *Diabetes Care* 2008; **31:** 2108–09.

60 Narendran P, Quann N, Nagi D, et al. Rationale and methods for the Exercise for Type 1 Diabetes Education program: a pilot randomized controlled trial of an education program to support adults with type 1 diabetes mellitus (T1DM) to undertake exercise. *BMJ Open Diabetes Res Care* 2019; **7:** e000693.

61 Watanabe M, Tuccinardi D, Ernesti I, et al. Scientific evidence underlying contraindications to the ketogenic diet: an update. *Obes Rev* 2020; **21:** e13053.

62 Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet* 2018; **391:** 541–51.

63 Leow ZZX, Guelfi KJ, Davis EA, Jones TW, Fournier PA. The glycaemic benefits of a very-low-carbohydrate ketogenic diet in adults with Type 1 diabetes mellitus may be opposed by increased hypoglycaemia risk and dyslipidaemia. *Diabet Med* 2018; **35:** 1258–63.

64 Brown RJ, Wijewickrama RC, Harlan DM, Rother KI. Uncoupling intensive insulin therapy from weight gain and hypoglycemia in type 1 diabetes. *Diabetes Technol Ther* 2011; **13:** 457–60.

65 Avgerinos I, Manolopoulos A, Michailidis T, et al. Comparative efficacy and safety of glucose-lowering drugs as adjunctive therapy for adults with type 1 diabetes: a systematic review and network meta-analysis. *Diabetes Obes Metab* 2021; **23:** 822–31.

66 Kim YJ, Hwang SD, Lim S. Effects of sodium-glucose cotransporter inhibitor/glucagon-like peptide-1 receptor agonist add-on to insulin therapy on glucose homeostasis and body weight in patients with type 1 diabetes: a network meta-analysis. *Front Endocrinol (Lausanne)* 2020; **11:** 553.

67 Petrie JR, Chaturvedi N, Ford I, et al. Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (REMOVAL): a double-blind, randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2017; **5:** 597–609.

68 Al Khalifah RA, Alnhdi A, Alghar H, Alanazi M, Florez ID. The effect of adding metformin to insulin therapy for type 1 diabetes mellitus children: a systematic review and meta-analysis. *Pediatr Diabetes* 2017; **18:** 664–73.

69 Staels F, Moyson C, Mathieu C. Metformin as add-on to intensive insulin therapy in type 1 diabetes mellitus. *Diabetes Obes Metab* 2017; **19:** 1463–67.

70 Ibáñez L, López-Bermejo A, Díaz M, Marcos MV, de Zegher F. Early metformin therapy (age 8–12 years) in girls with precocious pubarche to reduce hirsutism, androgen excess, and oligomenorrhea in adolescence. *J Clin Endocrinol Metab* 2011; **96:** e1262–67.

71 Libman IM, Miller KM, DiMeglio LA, et al. Effect of metformin added to insulin on glycemic control among overweight/obese adolescents with type 1 diabetes: a randomized clinical trial. *JAMA* 2015; **314:** 2241–50.

72 Dejgaard TF, Frandsen CS, Hansen TS, et al. Efficacy and safety of liraglutide for overweight adult patients with type 1 diabetes and insufficient glycaemic control (Lira-1): a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2016; **4:** 221–32.

73 Mathieu C, Zinman B, Hemmingsson JU, et al. 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:** 1702–10.

74 Ahrén B, Hirsch IB, Pieber TR, 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:** 1693–701.

75 Ghanim H, Batra M, Green K, et al. Liraglutide treatment in overweight and obese patients with type 1 diabetes: a 26-week randomized controlled trial; mechanisms of weight loss. *Diabetes Obes Metab* 2020; **22:** 1742–52.

76 Ratner RE, Dickey R, Fineman M, et al. Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in type 1 diabetes mellitus: a 1-year, randomized controlled trial. *Diabet Med* 2004; **21:** 1204–12.

77 Wright LA, Hirsch IB. Non-insulin treatments for type 1 diabetes: critical appraisal of the available evidence and insight into future directions. *Diabet Med* 2019; **36:** 665–78.

78 Phillip M, Mathieu C, Lind M, et al. Long-term efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes: pooled 52-week outcomes from the DEPICT-1 and -2 studies. *Diabetes Obes Metab* 2021; **23:** 549–60.

79 Kaku K, Isaka H, Sakatani T, Toyoshima J. Efficacy and safety of ipragliflozin add-on therapy to insulin in Japanese patients with type 1 diabetes mellitus: a randomized, double-blind, phase 3 trial. *Diabetes Obes Metab* 2019; **21:** 2284–93.

80 Rodbard HW, Giaccari A, Lajara R, et al. Sotagliflozin added to optimized insulin therapy leads to HbA1c reduction without weight gain in adults with type 1 diabetes: a pooled analysis of inTandem1 and inTandem2. *Diabetes Obes Metab* 2020; **22:** 2089–96.

81 Pettus J, Weinzimer SA, McCrimmon RJ, et al. Sotagliflozin in combination with optimized insulin therapy reduced HbA1c levels with a decreased daily insulin requirement after 52 weeks in adults with T1D. *Diabetes* 2018; **67** (suppl 1)**:** 5 (poster).

82 McCrimmon RJ, Henry RR. SGLT inhibitor adjunct therapy in type 1 diabetes. *Diabetologia* 2018; **61:** 2126–33.

83 Groop P-H, Dandona P, Phillip M, et al. Effect of dapagliflozin as an adjunct to insulin over 52 weeks in individuals with type 1 diabetes: post-hoc renal analysis of the DEPICT randomised controlled trials. *Lancet Diabetes Endocrinol* 2020; **8:** 845–54.

84 Garg SK, Peters AL, Buse JB, Danne T. Strategy for mitigating DKA risk in patients with type 1 diabetes on adjunctive treatment with SGLT inhibitors: a STICH protocol. *Diabetes Technol Ther* 2018; **20:** 571–75.

85 Alva S, Castorino K, Cho H, Ou J. Feasibility of continuous ketone monitoring in subcutaneous tissue using a ketone sensor. *J Diabetes Sci Technol* 2021; **15:** 768–74.

86 Lannoo M, Dillemans B, Van Nieuwenhove Y, et al. Bariatric surgery induces weight loss but does not improve glycemic control in patients with type 1 diabetes. *Diabetes Care* 2014; **37:** e173–74.

87 Mohammed N, Buckley A, Elsheikh M, et al. Bariatric surgery in the treatment of patients with obesity and type 1 diabetes: a retrospective study of clinical data. *Diabetes Obes Metab* 2021; **23:** 1562–70.

88 Höskuldsdóttir G, Ekelund J, Miftaraj M, et al. Potential benefits and harms of gastric bypass surgery in obese individuals with type 1 diabetes: a nationwide, matched, observational cohort study. *Diabetes Care* 2020; **43:** 3079–85.

89 Kirwan JP, Aminian A, Kashyap SR, Burguera B, Brethauer SA, Schauer PR. Bariatric surgery in obese patients with type 1 diabetes. *Diabetes Care* 2016; **39:** 941–48.