THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 13 Issue 9

RESEARCH ARTICLE

Treatment of people with type 1 diabetes with Semaglutide or Tirzepatide – Relevant in the future?

Sten Madsbad [1]

[1] Department of Endocrinology, Hvidovre Hospital, University of Copenhagen, Copenhagen, Denmark

OPEN ACCESS

PUBLISHED
30 September 2025

CITATION
Madsbad, S., 2025. Treatment of people with type 1 diabetes with Semaglutide or Tirzepatide – Relevant in the future? Medical Research Archives, [online] 13(9). https://doi.org/10.18103/mra.v13i9.6925

DOI
https://doi.org/10.18103/mra.v13i9.6925

ISSN
2375-1924

ABSTRACT

For many people with type 1 diabetes optimizing glucose control is very demanding, and often leads to risk of hypoglycaemia and weight gain and more than half of people with type 1 diabetes are overweight or obese. Glucagon-like peptide-1 (GLP-1) based pharmacotherapy is established as treatment of people with type 2 diabetes and obesity but are not recommended for treatment of type 1 diabetes. GLP-1 based pharmacotherapy has also beneficial effects on cardiovascular and kidney disease, which also are complications to type 1 diabetes. Prescription of GLP-1 based pharmacotherapy has become increasing popular as add-on treatment to insulin in type 1 diabetes. The most potent GLP-1 receptor agonist semaglutide and the dual GLP-1/glucose-dependent insulinotropic peptide tirzepatide have been investigated in small trials, primarily retrospective chart reviews in type 1 diabetes. The present narrative review assesses up to August 2025 the efficacy and safety of semaglutide and tirzepatide on glycaemic control, body weight, dose of insulin and adverse events. Two small, randomized trial has been published with semaglutid reporting weight loss of 5.3 kg and 9.2 kg, reduction of daily dose of insulin up to 30%. The reduction in HbA1c was about - 0.3% to - 0.5% with increased continuous glucose monitoring (CGM) time in range. With tirzepatide the weight loss has been between 10-20 kg and with major reduction (up to> 30%) in dose of insulin combined with small reduction in HbA1c but with increased CGM time in range. Hypoglycaemia and ketoacidosis have not been a problem in the studies with semaglutide and tirzepatide. The effect of semaglutide and tirzepatide on risk of cardiovascular and kidney disease in people with type 1 diabetes has not been investigated. Major, long-term, randomized, placebo-controlled trials to define the place of GLP-1 based pharmacotherapy in the treatment algorithm of people with different phenotypes of type 1 diabetes are warranted.

Keywords: Type 1 diabetes, GLP-1 receptor agonist, GLP-1/GIP agonist. Semaglutide, Tirzepatide

Introduction: Type 1 diabetes, overweight and GLP-1 based pharmacotherapy

Type 1 diabetes is a disease in which pancreatic beta-cell destruction caused by an autoimmune attack leads to absolute insulin deficiency, requiring lifelong insulin treatment [1]. The Diabetes Control and Complication Trial (DCCT) underscored that strict glycemic control protect against micro - and macrovascular complications [2]. Treatment with basal-bolus insulin regimen or insulin pump including automatic insulin delivery (AID) in combination with a continuous glucose monitoring (CGM) is recommended in most patients to achieve the best possible glycaemic control for reducing late diabetic complications [3]. However, for many people optimizing glucose control is very demanding, and often leads to risk of hypoglycaemia and weight gain [3,4]. More than two-third of people with type 1 diabetes fails to obtain a HbA1c below the recommended 7% and with 70% or more time spent in the CGM target range of glucose (3.9-10.0 mmol/l), even when treated with the most advanced automatic insulin delivery (AID) pumps combined with CGM [5,6]. The explanation of the poor glycemic control is often suboptimal postprandial glucose regulation.

GLP-1 is one of the incretin hormones secreted from the L-cells in the gut epithelium after food intake [7]. It has pleiotropic effects as it potentiates glucose-induced insulin secretion without causing hypoglycaemia, suppresses glucagon release, inhibits gastric emptying, and reduces appetite resulting in weight loss [7]. A delay of gastric emptying in combination with a suppression of glucagon secretion may in theory reduce postprandial glucose fluctuations [8]. GLP-1 also has anti-inflammatory and immunomodulatory effects [9]. The GLP-1 RAs differ in efficacy with respect to their effect on HbA1c and body weight in people with type 2 diabetes: albiglutide< exenatide< dulaglutide< liraglutide< semaglutide< tirzepatide with semaglutide and tirzepatide being the most potent [9]. Exenatide has the shortest half-life and is administered twice-daily, followed by liraglutide once-daily, while albiglutide, dulaglutide, semaglutide and tirzepatide are for once-weekly administration [9]. Exenatide is also available in a depot formulation for once weekly administration [9]. Semaglutide can also be administrated as a tablet once daily, but when absorbed, primarily from the stomach to the systemic circulation, the half-life is about one week like the subcutaneous injected semaglutide [9].

The glucagon-like peptide-1 receptor agonist (GLP-1RA) semaglutide is now an established treatment of type 2 diabetes and protection against cardiovascular events including heart failure, kidney disease, metabolic dysfunction-associated steatotic liver disease (MASLD), and reduces blood pressure, but they are not currently recommended for the treatment of people with type 1 diabetes [10]. The US Food and Drug administration (FDA) labelling warns about an increased risk of hypoglycemia in person using insulin [10]. The unimolecular GLP-1/glucose-dependent insulinotropic polypeptide (GIP) dual agonist, tirzepatide, has been approved for treatment of type 2 diabetes and in 2023 also for treatment of overweight and obesity, but not for type 1 diabetes [10]. Tirzepatide has demonstrated beneficial effect on cardiovascular disease, including heart failure, sleep apnoea and MASLD [10]. During the last decade experience has gained from both clinical trials and off-label use regarding addition of GLP-1 based pharmacotherapy in patients with type 1 diabetes. Among US adults with type 1 diabetes the prescriptions for GLP-1 based pharmacotherapy have increased across BMI categories in a dose-dependent manner [11]. In 2020-2023 the frequency of obesity in people with type 1 diabetes was about 38% and 7.1% of individuals had severe obesity (BMI > 40 kg/m^2), and the frequencies were higher in female than in males [11]. GLP-1 prescriptions among patients with type 1 diabetes were in the same period 5.7% among adults with normal weight, and 33.1% among those with severe obesity (BMI > 40 kg/m^2) [11]. Semaglutide accounted for 45% and tirzepatide with 8.5% of prescriptions.

Most of previous studies in people with type 1 diabetes have been performed with liraglutide once daily, which has been available since 2006. From 2018 the very potent GLP-1 agonist semaglutide 1 mg OW and since 2022 semaglutide 2.4 mg OW has been available and in 2023 the more potent dual GLP-1/GIP agonist tirzepatide was approved for treatment of type 2 diabetes and obesity. With the increasing prevalence of obesity and cardiovascular diseases in individuals with type 1 diabetes there is a growing interest in use of GLP-1 based pharmacotherapy. In the present review focus is on semaglutide and tirzepatide as add on therapy in people with type 1 diabetes and on future used of GLP-1 based therapy in type 1 diabetes.

Rationale for use of GLP-1 based therapy in people with type 1 diabetes

More than 50% of people with type 1 diabetes are overweight or obese, which is associated with cardiometabolic complications: the metabolic syndrome, kidney-, and liver disease as well as sleep apnea and reduced life expectancy compared with the general population [4,12]. Both in people with or without type 2 diabetes and established cardiovascular disease semaglutide has reduced the risk of a CVD events with about 20% and progression of diabetic kidney disease compared with placebo treatment [10] Tirzepatide has shown beneficial effects on cardiovascular diseases, inclusive heart failure, MASLD and sleep apnea [10]. Obesity is also associated with insulin resistance and the need for higher daily dose of insulin as well as the risk of suboptimal glucose control [12]. The obese patient with type 1 diabetes displays the same cardiovascular risk profile known from type 2 diabetes: hypertension, low HDL, high triglycerides, too many small dense LDL particles and low-grade inflammation, often referred to as “double diabetes” [12]. Insulin resistance is also associated with an increased risk of late diabetic complication [12]. Given the growing pandemic of obesity among people with type 1 diabetes and that traditional lifestyle modification with diet and exercise is often complicated in type 1 patients because of risk of hypoglycemia and frequently with poor results in relation to weight loss. Therefore, the argument for use of potent GLP-1 based treatment in obese people with type 1 diabetes is that the expected weight loss with semaglutide is between 5 kg to 15 kg

and with tirzepatide between 1o kg to 20 kg, which theoretically induces a reduction in dose of insulin, reduces risk of hypoglycemia and should add some cardiometabolic and renal benefits [10]. Especially, in type 1 patients treated with a very high dose of insulin GLP-1 based therapy is tempting and of interest. Therefore, semaglutide and tirzepatide may serve as valid add-on therapy to insulin in people with type 1 diabetes.

Method

A systematic literature review was performed to identify all relevant published articles concerning treatment of people with type 1 diabetes with semaglutide and tirzepatide. PubMed was served by combining the terms "type 1 diabetes", "T1D", "T1DM", "semaglutide", and "tirzepatide". We also search the reference lists of original articles, reviews and meta-analysis focusing on treatment of type 1 diabetes for relevant articles. The final search was performed in July 2025. Endpoints of interest included: number of patients, HbA1c, time in range (TIR), body mass index (BMI), baseline body weight, weight loss, dose of insulin, hypoglycaemia, hyperglycaemia with ketosis, duration of study and adverse events. Only publications written in English were included in the review.

Treatment of adults with type 1 diabetes with semaglutide

At present, two randomized, placebo-controlled trials are published investigating semaglutide OW as add-on to insulin treatment in people with type 1 diabetes [13,14].

In a randomized, double-blind, cross-over study in patients treated with automatic insulin pump delivery (AID) once weekly semaglutide up to 1 mg was added as adjunct therapy [13]. Twenty-eight people with type 1 diabetes were included with a mean age of 45 years, mean duration of diabetes 28 years and with a mean HbA1c of 7.4%. Seven participants were overweight and 18 were obese (mean BMI 32.2 kg/m^2) with a mean body weight of 91.3 kg. The design of the study included an 11 weeks uptitration period for semaglutide followed by 4 weeks follow-up. Cross-over time was 2 weeks. Primary endpoint was CGM time in range (TIR) (3.9-10 mmol/l). Twenty-four participants completed the trial, two on 0.25 mg, six on 0.5 mg, and 16 participants were on 1 mg OW. TIR for the last 4 weeks of each intervention was 74.2% with semaglutide and 69.4% with placebo, which was significant different. Time spent in hypoglycemia (< 3.9 mmol/l) did not differ between treatments, while time >10 mmol/l was less with semaglutide. Reduction in HbA1c was - 0.5% with semaglutide compared with placebo. A greater reduction in HbA1c was reported in people with detectable plasma C-peptide compared to participants without detectable C-peptide. Daily dose of insulin was reduced with - 11.3 units/day with semaglutide compared with placebo, driven by a reduction in both basal (-3.5 units/day) and bolus insulin. Weight was reduced by - 5.3 kg (5.1%) with semaglutide compared with placebo. Weight loss was positively associated with improvement in glycemic control. Notable, daily carbohydrate intake was reduced with 36 gram with semaglutide compared with placebo. HDL cholesterol was significant lower during semaglutide, while other lipids did not differ between treatments. Two participants had episodes of euglycaemic ketosis, which did not lead to ketoacidosis. The most common adverse events with semaglutide were gastrointestinal of nature. Limitation of the study are the small sample size, the short duration of the study and the more often follow-up in the outpatient clinic in the semaglutide group, which may have affected the results.

Shah and coworkers performed an intriguing randomized, double-blind, placebo-controlled 26-week trial (ADJUST-T1D) in 72 adults with type 1 diabetes using automatic insulin delivery (AID) systems and continuous glucose monitoring (CGM) [14]. Notable, the improvement in glycemia with AID systems is largely attributed to improvement in overnight glycaemia, while postprandial excursions are still a challenge to control. The mean age was 40 years, with a mean duration of diabetes of 23 years, a mean HbA1c of 7.8%, and a mean weight of 102 kg (mean BMI 35 kg/m^2). Participants were randomized to receive semaglutide OW up to 1 mg or placebo. The percentage of patients completing the trial was 94% with semaglutide and 92% with placebo. The primary composite endpoint (70% of time spent with a sensor glucose between 3.9 - 10 mmol/l, less than 4% of time spent with sensor glucose below 3.9 mmol/l and a 5% reduction in body weight) was obtained in 13 patients with semaglutide and 0 patient in the placebo group ($p<0.001$). The placebo-controlled reduction in HbA1c was - 0.3% point. At week 26, 50% in the semaglutide group and 22.2% in the placebo group obtained a HbA1c less than 7.0%. The improvement in CGM metrics was obtained during daytime and was equal to about 2 hours per day more in TIR, probably explained by the delayed gastric emptying and reduced food intake. The reduction in body weight was -9.2 kg vs -0.4 kg, respectively. The placebo-controlled reduction in total dose of insulin was - 22.3 units/day, corresponding to about 30% reduction from baseline. The placebo-controlled reduction in basal insulin was - 9.8 units/day and -12.5 units/day in bolus insulin with semaglutide. The adverse events were the well-known from GLP-1 based pharmacotherapy, primarily from the gastrointestinal tract. There was no ketoacidosis reported and severe hypoglycemia was reported in two patients in each group.

In a prospective cohort study of 12 weeks, 89 adults with type 1 diabetes treated with multiple injections or insulin pumps, all used CGM (ENDIS study) [15] were randomized into three comparable groups, receiving empagliflozin (n = 30), semaglutide (n = 30), and a control group (n = 29). At baseline and after 12 weeks treatment endothelial function was measured as FMD (brachial artery flow-mediated dilation) and FBF (forearm blood flow) as reactive hyperemia with strain gauge plethysmography). Pulse wave velocity (PWV) and peripheral resistance were measured as parameters of arterial stiffness. After 12 weeks body weight was reduced by -2.49 kg with empagliflozin and - 4.3 kg with semaglutide. The reduction in HbA1c was - 0.24% and - 0.29%, respectively. TIR did not differ between treatments. Reduction in daily dose of insulin was -5.1 units/day with empagliflozin and -8.5 units/day with semaglutide (- 1.1 units/day in the control group).

Improvement in FMD was significant in both intervention groups compared to controls (empagliflozin group 2.0-fold, and Semaglutide group 1.9-fold), with no difference between the two groups. FBF was statistically insignificant improved in both groups compared to controls (empagliflozin group 1.39-fold and semaglutide group 1.22-fold). In arterial stiffness parameters, improvements were seen only in the semaglutide group, with a decline in peripheral resistance by 5.1% ($p = 0.046$). The authors conclude that for arterial stiffness, semaglutide seems better, but both drugs positively impact endothelial function. No events of severe hypoglycemia or ketoacidosis were reported.

In a letter to the Editor of New Engl J Med, the efficacy of semaglutide was analyzed retrospective in 10 patients with type 1 diabetes between the age of 21 to 39 years and a mean HbA1c of 11.7% and a mean fasting C-peptide of 0.21 nmol/l. Semaglutide up to 0.5 mg weekly was initiated within 3 months after diagnosis and the patients were followed for one year [16,17]. Semaglutide treatment was associated with the elimination of prandial insulin in all patients and basal insulin in seven patients and reduced HbA1c to a mean of 5.7% and TIR was 89% after 12 months. No severe hypoglycemia was observed. No data on weight changes was reported. This study illustrates the efficacy of semaglutide in newly diagnosed subjects with type 1 diabetes and residual beta-cell function.

In another retrospective study also without a control group, 11 pump treated patients with overweight were treated with semaglutide 0.5 mg OW and followed for 6 months [18]. Body weight decreased from 82.8 kg (BMI: 30.9 kg/m^2) to 74.0 kg, and total insulin dose was reduced from 45.6 units/day to 38.5 units/day after 6 months. Intake of carbohydrate decreased from 137 gram to 109 gram/day at six months. HbA1c and TIR did not change significantly during the follow-up.

In a retrospective chart review of 23 patients with type 1 diabetes, 86% of whom were overweight or obese and treated with semaglutide. Overall, 61% used automatic insulin delivery (AID) and 78% CGM [19]. The mean duration of diabetes was 23 years. The follow-up was 7 to 50 months. Six participants were treated with 0.25 mg OW, five with 0.5 mg OW, eight with 1.0 mg OW and four were on 2.0 mg OW. The weight loss was on average - 5% (about 3.75 kg). No significant change in glycemic control was reported (TIR and HbA1c). Daily dose of insulin decreased slightly form a mean of 47.7 to 46.9 units/day. The results suggested that the therapeutic benefit of semaglutide was primary a modest weight loss rather than to improve glycemic control.

In another retrospective chart review of 50 overweight or obese people with long-term type 1 diabetes, who had been treated with semaglutide for 1 year were compared with a matched control group [20]. All patients used CGM with or without an insulin pump. After 12 months the mean dose of semaglutide was 0.92 mg OW. There was a significant decrease in body weight (mean -7.2 kg (7.6%)) compared with a weight gain of 0.95 kg in the control group. The reduction in HbA1c was - 0.60% and - 0.17%, respectively. The CGM glucose standard deviation (SD) and coefficient of variation improved with semaglutide, while time above range or time below range did not differ compared with the control group. The changes in dose of insulin did not differ. No episode of hypoglycaemia and ketoacidosis were reported.

In a two-year study the effect of semaglutide on weight and glucose outcome was evaluated in a retrospective chart review after 12 and 24 months.[21]. Sixty-seven adults with type 1 diabetes, mean duration of diabetes of 16.6 years, 18 participants used insulin pump treatment and 49 used multiple injection of insulin. At 24 months, TIR improved from 46% to 71%, CV% of glucose was reduced from 46.3% to 33.6%, HbA1c improved from 8.2% to 7.1%. Daily dose of insulin decreased from 1.4 to 0.7 units/kg /day. Significant reduction in body weight was reported and no hospitalization for ketoacidosis occurred.

In a real-world retrospective study in 30 T1D treated with semaglutide and with a mean follow up of 255 days [22] the reduction in body weight was - 8.2 kg (8.4%) and HbA1c was reduced by - 0.5%. CGM metrics did not improve.

In a multicenter study by Almohareb of 144 patients with type 1 diabetes, 92 particpants were treated with semaglutide [23]. Twenty-one decided to stop treatment with semaglutide. Data on body weight, HbA1c and dose of insulin in the semaglutide treated group were not reported, but severe hypoglycemia and ketoacidosis were not a problem.

Hence, treatment with semaglutide up to 1 mg once weekly reduced body weight in the same range as reported in people with type 2 diabetes treated with semaglutide 1 mg OW (5-6 kg), but not in the same range as observed in the STEP obesity trial in people without diabetes treated with semaglutide 2.4 mg weekly, where the mean body weight was about 15% [10]. In some of the studies semaglutide treatment induced a minor improvement in HbA1c and TIR. Ketoacidosis and hypoglycemia were not a problem, probably explained by that most of the participants used CGM. The minimal improvement in HbA1c seems to be explained by a significant reduction in daily dose of insulin and that many of the participants were well-controlled before treatment with semaglutide.

Treatment of type 1 diabetes with tirzepatide

In a retrospective review study adult people with type 1 diabetes and a body mass index over 27 kg/m^2 and treated with multiple insulin injection or insulin pumps in combination with CGM were treated with tirzepatide for at least 6 months [24]. Eighty-four patients were included in the study together with 38 matched control subjects. Diabetes duration was 28 years, HbA1c 7.1 %. BMI differ between the groups (33.3 kg/m^2 in control subjects and 35.2 kg/m^2 in the tirzepatide group) and in total insulin dose 63 vs 78 units/day, respectively. The median dose of tirzepatide was 10 mg OW. After 21 months the weight loss was -23.4% (26.8 kg) with tirzepatide while the control subjects gained 1.8% (0.8 kg). The BMI

decrease was -9 kg/m^2 among tirzepatide users. HbA1c decreased -0.5% and -0.24% in the tirzepatide and control groups, respectively, while the increase in TIR did not differ significantly between groups. In the tirzepatide group the mean reduction in dose of insulin was - 38 units/day, corresponding to -0.2 units/kg compared with -2.4units/day in control group. The reduction in bolus insulin was - 22.3 units/day compared with +1.0 units/day, respectively. The reduction in total cholesterol, LDL, triglycerides and systolic blood pressure were significant with tirzepatide, while no statistical changes were reported in the control group. eGFR was stable with tirzepatide during follow-up.

In a retrospective study, 62 intensively treated (basal-bolus regimen n=10 or insulin pump treatment n=52) patients with type 1 diabetes and overweight were treated with tirzepatide for one year [25]. The control group consisted of 37 matched patients with lower BMI (35.6 vs 32.8 kg/m^2), body weight and daily dose of insulin (76 vs 62 units/day). The mean dose of tirzepatide was 9.7 mg/week. Thus, most participants did not reach the highest dose for people with type 2 diabetes which is 15 mg. Mean decrease in BMI and weight were - 6.5 BMI-units (kg/m^2) and - 18.5 % (21.1kg) vs - 1.2% in the control group. HbA1c decreased by - 0.67% in the tirzepatide group compared with - 0.02% in the control group, and the total dose of insulin decreased by -22.8 vs + 5.0 units/day. Time in range was higher with tirzepatide and time > 10 mmol/l lower compared with the control group. Neither events of hypoglycaemia nor diabetic ketoacidosis were reported.

In a retrospective study, people with type 1 diabetes treated with AID pumps were treated for 8 months with tirzepatide (n=11). Basal HbA1c was 7.0% and mean BMI 39.6 kg/m^2 [26]. The daily dose of insulin was reduced from a mean of 73.9 units/day to 51.7 units/day (basal insulin was reduced from 47 units/day to 32.4 units/day and bolus insulin from 31.4 units/day to 17.9 units/day). Dose reduction from 2 to 8 months was modest. Total insulin dose units/day per kg also decreased by 25%, which may indicate an increase in insulin sensitivity. TIR increased by 15.3%, most pronounced during daytime without increase in time below 3.9 mmol/l. HbA1c was reduced with - 0.5% and weight by 9% from 114.3 kg to 105.7 kg. Carbohydrate intake was reduced from 120 gram to 45 gram/day. The authors recommend a dose reduction of about 25 % of total dose of insulin when initiating tirzepatide in patient treated with an AID pump, although the insulin reduction may depend on HbA1c, and people with higher HbA1c may require less reduction in dose of insulin.

In a retrospective study in 26 adults with type 1 diabetes (mean BMI 36.7 kg/m^2) treatment with tirzepatide over 8 months reduced HbA1c by - 0.45% at 3 months and - 0.6% after 8 months [27]. Body weight was reduced by - 10.1%, and glucose TIR (3.9 to 10.0 mmol/l) increased with 12.6% points together with that time over range (> 10 mmol/l) was reduced. The total dose of insulin (85.2 units/day) was reduced by - 24.3 units/day. Two patients discontinued tirzepatide treatment and one severe hypoglycaemia was reported.

In a retrospective study with up to 12 months follow-up included 51 TID patients mostly treated with insulin pumps and CGM were treated with tirzepatide OW. Basal BMI was > 27 kg/m^2 and 41% had obesity class 3. The reduction in HbA1c was - 0.9% and an increase in TIR from 51% to 69% with an reduction in time above range (>10 mmol/l) from 48% to 29% at 8 months [28]. The body weight was reduced with - 8.5% after 8 months and - 12.2% at 12 months. The reduction in insulin was - 32% (25 units/day). About one-third have adverse events, the most common was nausea (14%). No ketoacidosis was reported but four patients had hypoglycaemia, though not severe.

The efficacy of semaglutide and tirzepatide was assessed in a retrospective chart review of 100 patients with type 1 diabetes; 50 who were prescribed semaglutide and 50 were prescribed tirzepatide [29]. Nearly all participants were overweight or obese (mean BMI 34 kg/m^2) and were compared with 50 matched control subjects. Mean HbA1c was 7.6% in the semaglutide, 7.0% in the tirzepatide and 7.3% in the control group. About 64% to 86% were pump users, mostly AID systems. Daily dose of insulin was 70.3 units/day, 76.5 units/day and 61.6 units/day, respectively. Follow-up was up to one year, and median dose of semaglutide was 0.5 mg OW and 7.5 mg OW for tirzepatide. The vast majority of participants have at least 6 months follow-up an more than half about 9 months follow-up data. Body weight declined – 9.7 kg (9.1%) with semaglutide, and - 22.4 kg (21.4%) with tirzepatide. The change in HbA1c was -0.54% with semaglutide and -0.68% in the tirzepatide group. Body weight and HbA1c did not change significantly in the control group. Reduction in total dose of insulin was -4.1 units/day with semaglutide, -26.4 units/day with tirzepatide and + 3.9 units/day in the control group. The reduction in daily dose of insulin for semaglutide and tirzepatide was greater for bolus insulin compared with reduction in basal insulin. No severe hypoglycemia or ketosis were registered.

The studies show that a mean reduction in body weight of 10% or more is realistic during treatment with tirzepatide in combination with a major reduction (> 20%) in daily dose of insulin. The improvement in HbA1c has been about 0.5% in combination with a greater TIR. The limitations of the studies with tirzepatide are that the studies are retrospective, often without a control group and the titration of dose of insulin was not uniform among physicians.

Discussion

In the present review the focus is on semaglutide and tirzepatide as add-on to insulin therapy in people with type 1 diabetes. In most of the studies semaglutide and tirzepatide improved glycaemic control with a mean reduction in HbA1c of - 0.20% to - 0.60%, and with increased CGM measured TIR and a reduction in time of glucose > 10 mmol/l as well as reduction in glycemic variability. This is of interest since TIR has been shown to be a predictor of microvasculare complications [30].The studies also demonstrated a reduction in daily dose of insulin, most pronounced with tirzepatide explained by

the mechanism of action of GLP-1 on appetite and the decreased need of insulin, which have anabolic effects. Reduction in daily intake of carbohydrate in combination with the delay in gastric emptying probably in part explain the improved glycaemic control. Treatment with semaglutide and tirzepatide was associated with a considerable weight loss, most evident with tirzepatide. The most common side effects with semaglutide and tirzepatide were the well-known from the gastrointestinal tract (nausea, vomiting, constipation or diarrhea), mostly mild-to-moderate and transient. Hypoglycaemia or ketoacidoses have not been a problem in the reviewed studies.

Two minor placebo-controlled, randomized studies have been published with semaglutide and none with tirzepatide. The other studies discussed have been retrospective observational studies often without a control group and with small number of participants and short duration of follow-up. The participants have typically been highly selected patients treated with AID pumps and CGM. No doubt, major well-design studies are warranted to clarify the efficacy, safety and limitation of GLP-1 based pharmacotherapy in T1D.

Two randomized placebo-controlled studies have been published with semaglutide up to 1 mg OW. In the first study weight loss was - 5.3 kg compared with placebo. Reduction in HbA1c was - 0.5% and TIR improved with less time with glucose above 10 mmol/l. The reduction in daily dose of insulin was -14.6 units/day compared with + 7.7 units/day during placebo treatment. In the second randomized, placebo-controlled trial the reduction in body weight was - 9.2 kg compared with -0.4 kg in the placebo group [14]. The placebo-controlled reduction in daily dose of insulin was - 22.3 units/day. Several retrospective minor trials have reported similar results. The adverse events were the well-known with GLP-1 based pharmacotherapy. No episode of severe hypoglycemia and ketoacidosis were reported.

In the retrospective studies with tirzepatide with a mean dose up to about 10 mg OW impressive reduction in body weight up to - 23.4% and in dose of insulin up to - 38 units per day were reported. The reduction in HbA1c was up to - 0.9%, but was in most studies smaller, although clinically relevant (HbA1c reduction > 0.3%). Note, that the reduction in body weight in the studies also depends on the duration of follow-up. From the studies in obese people without diabetes the experience is that to obtain a weight loss of about 20 % required a follow-up of about one year [10]. In the trials with tirzepatide in people with type 2 diabetes the weight loss has been in the range of 10-15 kg [10].

In both the semaglutide and tirzepatide studies insulin titration with major reduction in daily dose of insulin has lessen the reduction in HbA1c and in some of studies the patients were already well-controlled leaving less space for improvement. Nevertheless, the TIR improved in most of studies including a reduction in time of glucose > 10 mmol/l.

People with type 1 diabetes have an about 2-3 fold increase in mortality of cardiovascular diseases, and GLP-1 RAs, especially semaglutide, has been shown to reduce cardiovascular disease in people with type 2 diabetes and in overweight and obese people without diabetes [9,31]. Diabetic kidney disease is still a problem in people with type 1 diabetes and in the dedicated "FLOW" study in patients with type 2 diabetes, semaglutide reduced the risk of progression of kidney disease and the mortality of cardiovascular diseases [32]. Tirzepatide has in the SURPASS - CVOT including participants with type 2 diabetes demonstrated a 16% lower rate of all-cause mortality and an eight percent lower rate of major adverse cardiovascular events (MACE) compared with the GLP-1 RA dulaglutide, which in the REWIND trial reduced MACE and stroke significantly compared with placebo (Press release, E Lilly Juli 31, 2025). Therefore, major long-term randomized, placebo-controlled trials of semaglutide and tirzepatide will be of interest in people with type 1 diabetes, overweight or obesity and in high risk for cardiovascular and kidney disease to generate evidence of the use in people with type 1 diabetes. At present, the Steno 1 study is ongoing using multifactorial intervention including semaglutide to reduce cardiovascular disease in type 1 diabetes [33]. The aim is to enroll 2000 high risk individuals, who will be followed for 5 years. The effect of semaglutide in individual with type 1 diabetes is also investigated in the randomized trial of Semaglutide for Diabetic Kidney Disease in type 1 diabetes, REMODEL T1D (clinical Trials .gov ID NCTO5822609) and in the OBES1TY trial (Clinical Trial.gov ID NCT06909006) in individual with kidney disease and obesity, respectively. In the minor (n=60) RESET1 study the effect of semaglutide on the carotid femoral pulse velocity is investigated [34]. The long-term glycaemic and other metabolic outcomes as well as safety for tirzepatide in people with type 1 diabetes are evaluated in phase 3 trials (SURPASS-T1D-1; NCT06914895 and SURPASS-T1D-2; NCT06962280).

In previous studies with the short acting exenatide the improvement in HbA1c was minimal or absent, and with liraglutide 1.8 mg daily, the small reduction in HbA1c has been in the range of -0.1% -0.6%. In the largest randomized, placebo-controlled trial with exenatide the weight loss was about - 4 kg, and with liraglutide the weight losses have ranged from 2-7 kg, and the reduction in daily dose of insulin between 5 to 10 units/day, reviewed in https://esmed.org/MRA/mra/article/view/6110. In ADJUNCT ONE and TWO trials an increased risk of hypoglycaemia and ketosis was reported, but the use of CGM was low in the earlier studies making it more difficult to titrate insulin and monitor glycemic control accurately [35,36]. Today, the glucose sensors and advanced pumps are commonplace and hypoglycaemia and hyperglycaemia with ketosis can be identified early as discussed in a recent consensus report [37]. In studies with liraglutide the glucagon responses during hypoglycemia did not differ from responses during placebo and thus treatment with GLP-1 based therapy seems not to increase the risk for severe hypoglycemia [38,39].

The greatest benefit of adding GLP-1 based pharmacotherapy in patients with type 1 diabetes seems to be in people with some residual beta-cell function. In ADJUNCT ONE and TWO, the two largest studies

(n=2233) with liraglutide the reduction in HbA1c in people with residual beta-cell function was about - 0.6%, which was greater than in people without residual beta-cell function, and possible explained by stimulation of the endogenous insulin secretion [35,36]. Residual beta-cell function was the only identified variable impacting the effect of liraglutide on glycaemic control regardless of level of glycaemic control, BMI and insulin regime. Lower risk of hypoglycaemia was found in participants with residual beta-cell function. In the "New Lira" study, which included patients with type 1 diabetes and with a mean duration of diabetes of about 4 weeks, liraglutide reduced total insulin dose from 0.30 units/kg/day to 0.23 units/kg/day while the dose increased from 0.29 units/kg/day to 0.43 units/kg/day in the placebo group after 1 year follow-up [40]. A period without need for insulin was observed in 13 vs two patients and in these patients the period lasted for 12 vs 6 weeks, respectively. In another study where patients were randomized to liraglutide, IL-21 antibody or a combination or placebo, the effect of liraglutide alone did not differ from placebo [41]. In both studies the effect on the beta-cell function disappeared a few weeks after termination of therapy. Thus, GLP-1 based pharmacotherapy has not until today prevented the loss of C-peptide

Noteworthy, treatment with semaglutide in 10 patients with type 1 diabetes, who had started semaglutide up to 0.5 mg weekly within 3 months after diagnosis [16,17] was associated with the elimination of prandial insulin in all patients and basal insulin in seven patients and reduced HbA1c to a mean of 5.7% and TIR was 89% after 12 months.

Preservation of the residual beta-cell function is of major interest since it is associated with improved glycaemic control, lower insulin doses, less risk of hypoglycaemia, ketoacidosis and late diabetic complications [42,43]. The loss of beta-cell function is accompanied by a defective regulation in glucagon secretion with impaired glucagon secretion during hypoglycaemia [44,45]. Therefore, major randomized long-term studies with semaglutide and tirzepatide from time of diagnosis and in patients with long-term diabetes and residual beta-cell function are justified, also in relation to whether long-term treatment with GLP-1 based pharmacotherapy may protect the beta-cell mass from autoimmune destruction. Notable, treatment with GLP-1 in experimental animal models increased beta-cell proliferation and survival, reduced rate of apoptosis, and delayed autoimmune diabetes [46–49].

Practical pearls on the use of semaglutide and tirzepatide in people with type 1 diabetes

Because of the risk of gastrointestinal side effects, the initiation of semaglutide or tirzepatide should be with the lowest dose and with a gradual uptitration every fourth week. Alternatively, a more flexible titration regimen with longer intervals between injections and smaller uptitration dose can be attemted, if the patient has gastrointestinal symptoms. It is very important to inform the patients about the adverse events with semaglutide and tirzepatide and how to mitigate the side effects by eating slowly, small meals, and avoid fatty and spice food. When initiation the GLP-1 based treatment the total dose of insulin has been recommended to be reduced with about 20%, mostly in relation to bolus meal insulin to avoid hypoglycemia. Of course, the magnitude of reduction should be based on diabetes control, risk of hypoglycaemia and ketosis as well as type of GLP-1 RA and with less reduction or no reduction in people with a HbA1c > 8%. During the titration of dose of insulin, the focus should be on risk of developing hypoglycaemia or ketoses or ketoacidosis and the patient should be educated in how to monitor glucose and ketone metabolism. The use of semaglutide and tirzepatide may require changes in "the insulin to carbohydrate ratio" and timing of the mealtime bolus insulin. In patient with residual insulin secretion the need of mealtime insulin dose may be severely reduced or stopped, especially in people with reduced carbohydrate intake. Normal weight people should monitor body weight to avoid underweight. During weight loss and reduced food intake focus on protein (>1.2 gram/kg/day) and vitamin intake in combination with exercise including resistance training should optimally be part of the treatment to protect against sarcopenia and malnutrition. Altogether, clinical protocols focusing on insulin titration, glucose monitoring and healthy weight loss during treatment with GLP-1 based pharmacotherapies are deserved to improve safety and efficacy of the treatment.

Conclusion

Despite great developments regarding insulin analogues and technical advances it is still difficult for many people with type 1 diabetes to obtain optimal glycaemic control. GLP-1 based pharmacotherapy as add-on therapy to insulin treatment in people with type 1 diabetes have improved glycaemia evaluated by HbA1c and TIR. One argument for use of a GLP-1 RA is that many patients with type 1 diabetes have "double" diabetes because of overweight or obesity, which is characterized by insulin resistance and high daily doses of insulin [12]. Insulin resistance also increases the risk of cardiovascular and microvascular diseases [12]. Several studies have demonstrated the beneficial effect of weight loss with semaglutide or tirzepatide in overweight or obese people with type 1 diabetes.

Tirzepatide and semaglutide have in people with overweight and obesity with and without type 2 diabetes protect against cardiovascular and kidney disease, which also is severe complications to type 1 diabetes. Randomized placebo-controlled trials are undergoing to study the beneficial effect of GLP-1 based treatment on cardiovascular and kidney diseases.

Overall, most of the studies with semaglutide and tirzepatide are small with few participants, of short duration and of poor quality. Often retrospective chart reviews without a control group and including highly selected patients treated with insulin pumps, eventually AID and CGM. The use of CGM may explain that severe hypoglycamia or diabetic ketoacidosis have not been a problem in the studies. Randomized, placebo-controlled high quality long-term studies are still missing to define

the place of GLP-1 pharmacotherapy in the treatment algorithm of people with different phenotype and treatments modalities. A major hurdle in the use of GLP-1 based pharmacotherapy is the cost and absent reimbursement and the need of closely follow-up to adjust insulin therapy and dose of GLP-1 pharmacotherapy in people with type 1 diabetes.

Disclosures

Sten Madsbad; Advisory boards: AstraZeneca; Boehringer Ingelheim; Novo Nordisk; Sanofi, Abbott Lab, Bayer, Amgen. **Lecture fees**: Novo Nordisk, MSD, E Lilly. **Research Grant Recipient**: Novo Nordisk; Novo Nordisk foundation, Boehringer Ingelheim. Grants were paid to the institution Hvidovre hospital, University of Copenhagen (no personal fee). None of the grants have any relation to the work presented in the paper. **Support for attending meetings and/or travel:** Novo Nordisk, Boehringer-Ingelheim, Bayer. SMA has **served as PI** in relation to development of drugs for treatment of Type 2 diabetes and obesity in collaboration with Novo Nordisk and Bayer with funds paid to the institution where he is employed (no personal fee), and with no relation to the work reported in this paper. **Consultant** for Netdoktor.

Funding:

No financial support was received for writing the review and publication of this article.

References

1. DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. *Lancet*. 2018;391(10138):2449-2462. doi:10.1016/S0140-6736(18)31320-5
2. Braffett BH, Bebu I, Lorenzi GM, et al. The NIDDK Takes on the Complications of Type 1 Diabetes: The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study. *Diabetes Care*. 2025;48(7):1089-1100. doi:10.2337/dc24-2885
3. 6. Glycemic Goals and Hypoglycemia: Standards of Care in Diabetes—2025. *Diabetes Care*. 2024;48(Supplement_1):S128-S145. doi:10.2337/dc25-S006
4. Bailey R, Calhoun P, Garg SK. Weight Gain and Glycemic Control in Adults with Type 1 Diabetes in the T1D Exchange Registry. *Diabetes Technol Ther*. 2024;26(3):156-160. doi:10.1089/dia.2023.0389
5. Karakus KE, Akturk HK, Alonso GT, Snell-Bergeon JK, Shah VN. Association Between Diabetes Technology Use and Glycemic Outcomes in Adults With Type 1 Diabetes Over a Decade. *Diabetes Care*. 2023;46(9):1646-1651. doi:10.2337/dc23-0495
6. Jacobs PG, Levy CJ, Brown SA, et al. Research Gaps, Challenges, and Opportunities in Automated Insulin Delivery Systems. *J Diabetes Sci Technol*. 2025;19(4):937-949. doi:10.1177/19322968251338754
7. Holst JJ. The physiology of glucagon-like peptide 1. *Physiol Rev*. 2007;87(4):1409-1439. doi:10.1152/physrev.00034.2006
8. Johansen NJ, Dejgaard TF, Lund A, et al. Efficacy and safety of meal-time administration of short-acting exenatide for glycaemic control in type 1 diabetes (MAG1C): a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2020;8(4):313-324. doi:10.1016/S2213-8587(20)30030-9
9. Madsbad S, Holst JJ. Cardiovascular effects of incretins: focus on glucagon-like peptide-1 receptor agonists. *Cardiovasc Res*. 2023;119(4):886-904. doi:10.1093/cvr/cvac112
10. Madsbad S, Holst JJ. The promise of glucagon-like peptide 1 receptor agonists (GLP-1RA) for the treatment of obesity: a look at phase 2 and 3 pipelines. *Expert Opin Investig Drugs*. 2025;34(3):197-215. doi:10.1080/13543784.2025.2472408
11. Xu Y, Echouffo Tcheugui JB, Coresh J, et al. Trends in obesity and glucagon-like peptide-1 receptor agonist prescriptions in type 1 diabetes in the United States. *Diabetes Obes Metab*. 2025;27(6):2967-2976. doi:10.1111/dom.16300
12. Kilpatrick ES, Rigby AS, Atkin SL. Insulin resistance, the metabolic syndrome, and complication risk in type 1 diabetes: "double diabetes" in the Diabetes Control and Complications Trial. *Diabetes Care*. 2007;30(3):707-712. doi:10.2337/dc06-1982
13. Pasqua MR, Tsoukas MA, Kobayati A, Aboznadah W, Jafar A, Haidar A. Subcutaneous weekly semaglutide with automated insulin delivery in type 1 diabetes: a double-blind, randomized, crossover trial. *Nat Med*. 2025;31(4):1239-1245. doi:10.1038/s41591-024-03463-z
14. Shah VN, Akturk HK, Kruger D, et al. Semaglutide in Adults with Type 1 Diabetes and Obesity. *NEJM evidence*. Published online June 2025:EVIDoa2500173. doi:10.1056/EVIDoa2500173
15. Navodnik MP, Janež A, Žuran I. The Effect of Additional Treatment with Empagliflozin or Semaglutide on Endothelial Function and Arterial Stiffness in Subjects with Type 1 Diabetes Mellitus-ENDIS Study. *Pharmaceutics*. 2023;15(7). doi:10.3390/pharmaceutics15071945
16. Dandona P, Chaudhuri A, Ghanim H. Semaglutide in Early Type 1 Diabetes. *N Engl J Med*. 2023;389(10):958-959. doi:10.1056/NEJMc2302677
17. Dandona P, Chaudhuri A, Ghanim H. More on Semaglutide in Early Type 1 Diabetes. Reply. *N Engl J Med*. 2024;390(3):292. doi:10.1056/NEJMc2311608
18. Grassi BA, Teresa Onetto M, Sánchez C, Tapia N, Mena F. Effect of low dose Semaglutide in people with Type 1 Diabetes and excess weight. *Diabetes Res Clin Pract*. 2024;209:111593. doi:10.1016/j.diabres.2024.111593
19. Orrange S, Humphrey T, Fayne E, Peters A. Semaglutide for Weight Reduction in Type 1 Diabetes: Promising Results With Uncertain Glycemic Impact. *J Diabetes Sci Technol*. 2025;19(2):593-594. doi:10.1177/19322968241304779
20. Garg SK, Kaur G, Haider Z, Rodriquez E, Beatson C, Snell-Bergeon J. Efficacy of Semaglutide in Overweight and Obese Patients with Type 1 Diabetes. *Diabetes Technol Ther*. 2024;26(3):184-189. doi:10.1089/dia.2023.0490
21. Al Hayek A, Klonoff DC, Al Zahrani WM, Ibrahim SE, Al Dawish MA. Evaluating the effect of Semaglutide as add-on therapy on glycemic control and continuous glucose monitoring outcomes in adults with type 1 diabetes: A two-year real-world data study. *J Diabetes Complications*. 2025;39(7):109064. doi:10.1016/j.jdiacomp.2025.109064
22. Cohen N, Yeung A, Jenkins A. Real-world experience of adjunct weekly semaglutide in Type 1 diabetes. Is it worth it? *Diabetes Res Clin Pract*. 2025;219:111979. doi:10.1016/j.diabres.2024.111979
23. Almohareb SN, Alfayez OM, Aljuaid SS, et al. Effectiveness and Safety of GLP-1 Receptor Agonists in Patients with Type 1 Diabetes. *J Clin Med*. 2024;13(21). doi:10.3390/jcm13216532
24. Garg SK, Kaur G, Renner D, et al. Cardiovascular and Renal Biomarkers in Overweight and Obese Adults with Type 1 Diabetes Treated with Tirzepatide for 21 Months. *Diabetes Technol Ther*. 2025;27(3):152-160. doi:10.1089/dia.2024.0481
25. Garg SK, Akturk HK, Kaur G, Beatson C, Snell-Bergeon J. Efficacy and Safety of Tirzepatide in Overweight and Obese Adult Patients with Type 1 Diabetes. *Diabetes Technol Ther*. 2024;26(6):367-374. doi:10.1089/dia.2024.0050
26. Karakus KE, Klein MP, Akturk HK, Shah VN. Changes in Basal and Bolus Insulin Requirements with Tirzepatide as an Adjunctive Therapy in Adults with Type 1 Diabetes Using Tandem Control-IQ. *Diabetes Ther*. 2024;15(7):1647-1655. doi:10.1007/s13300-024-01592-9
27. Akturk HK, Dong F, Snell-Bergeon JK, Karakus KE, Shah VN. Efficacy and Safety of Tirzepatide in Adults

With Type 1 Diabetes: A Proof of Concept Observational Study. *J Diabetes Sci Technol*. Published online February 2024:19322968231223990. doi:10.1177/19322968231223991
28. Rivera Gutierrez R, Tama E, Bechenati D, et al. Effect of Tirzepatide on Body Weight and Diabetes Control in Adults With Type 1 Diabetes and Overweight or Obesity. *Mayo Clin Proc*. 2025;100(2):265-275. doi:10.1016/j.mayocp.2024.07.006
29. Snell-Bergeon JK, Kaur G, Renner D, Akturk HK, Beatson C, Garg SK. Effectiveness of Semaglutide and Tirzepatide in Overweight and Obese Adults with Type 1 Diabetes. *Diabetes Technol Ther*. 2025;27(1):1-9. doi:10.1089/dia.2024.0328
30. Bezerra MF, Neves C, Neves JS, Carvalho D. Time in range and complications of diabetes: a cross-sectional analysis of patients with Type 1 diabetes. *Diabetol Metab Syndr*. 2023;15(1):244. doi:10.1186/s13098-023-01219-2
31. Lind M, Svensson AM, Kosiborod M, et al. Glycemic control and excess mortality in type 1 diabetes. *N Engl J Med*. 2014;371(21):1972-1982. doi:10.1056/NEJMoa1408214
32. Perkovic V, Tuttle KR, Rossing P, et al. Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes. *N Engl J Med*. 2024;391(2):109-121. doi:10.1056/NEJMoa2403347
33. Stougaard EB, Andersen MR, Bagger JI, et al. The Steno 1 study: Multifactorial intervention to reduce cardiovascular disease in type 1 diabetes-rationale and protocol of the prospective, randomized, open-labelled multicentre study. *Diabetes Obes Metab*. Published online July 2025. doi:10.1111/dom.16606
34. Frampton R, Snaith JR, Hocking S, Holmes-Walker J, Olsen N, Greenfield JR. Reducing cardiometabolic risk with semaglutide in type 1 diabetes (RESET1): Study protocol of a phase 2 double-blinded randomised placebo-controlled trial. *Diabet Med*. 2024;41(10):e15377. doi:10.1111/dme.15377
35. 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(10):1702-1710. doi:10.2337/dc16-0691
36. 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(10):1693-1701. doi:10.2337/dc16-0690
37. Shah VN, Peters AL, Umpierrez GE, et al. Consensus Report on Glucagon-Like Peptide-1 Receptor Agonists as Adjunctive Treatment for Individuals With Type 1 Diabetes Using an Automated Insulin Delivery System. *J Diabetes Sci Technol*. 2025;19(1):191-216. doi:10.1177/19322968241291512
38. Pieber TR, Deller S, Korsatko S, et al. Counter-regulatory hormone responses to hypoglycaemia in people with type 1 diabetes after 4 weeks of treatment with liraglutide adjunct to insulin: a randomized, placebo-controlled, double-blind, crossover trial. *Diabetes Obes Metab*. 2015;17(8):742-750. doi:10.1111/dom.12473
39. Frandsen CS, Dejgaard TF, Andersen HU, et al. Liraglutide as adjunct to insulin treatment in type 1 diabetes does not interfere with glycaemic recovery or gastric emptying rate during hypoglycaemia: A randomized, placebo-controlled, double-blind, parallel-group study. *Diabetes Obes Metab*. 2017;19(6):773-782. doi:10.1111/dom.12830
40. Dejgaard TF, Frandsen CS, Kielgast U, et al. Liraglutide enhances insulin secretion and prolongs the remission period in adults with newly diagnosed type 1 diabetes (the NewLira study): A randomized, double-blind, placebo-controlled trial. *Diabetes Obes Metab*. 2024;26:4905-4915. doi:10.1111/dom.15889
41. von Herrath M, Bain SC, Bode B, et al. Anti-interleukin-21 antibody and liraglutide for the preservation of β-cell function in adults with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Diabetes Endocrinol*. 2021;9(4):212-224. doi:10.1016/S2213-8587(21)00019-X
42. Madsbad S. Prevalence of residual B cell function and its metabolic consequences in Type 1 (insulin-dependent) diabetes. *Diabetologia*. 1983;24(3):141-147. doi:10.1007/BF00250151
43. Lachin JM, McGee P, Palmer JP. Impact of C-peptide preservation on metabolic and clinical outcomes in the Diabetes Control and Complications Trial. *Diabetes*. 2014;63(2):739-748. doi:10.2337/db13-0881
44. Dinneen S, Alzaid A, Turk D, Rizza R. Failure of glucagon suppression contributes to postprandial hyperglycinemia in IDDM. *Diabetologia*. 1995;38(3):337-343. doi:10.1007/BF00400639
45. Madsbad S, Hilsted J, Krarup T, et al. Hormonal, metabolic and cardiovascular responses to hypoglycaemia in Type 1 (insulin-dependent) diabetes with and without residual B cell function. *Diabetologia*. 1982;23(6):499-503. doi:10.1007/BF00254298
46. Skyler JS. Prevention and reversal of type 1 diabetes--past challenges and future opportunities. *Diabetes Care*. 2015;38(6):997-1007. doi:10.2337/dc15-0349
47. Zhang J, Tokui Y, Yamagata K, et al. Continuous stimulation of human glucagon-like peptide-1 (7-36) amide in a mouse model (NOD) delays onset of autoimmune type 1 diabetes. *Diabetologia*. 2007;50(9):1900-1909. doi:10.1007/s00125-007-0737-6
48. Buteau J. GLP-1 receptor signaling: effects on pancreatic beta-cell proliferation and survival. *Diabetes Metab*. 2008;34 Suppl 2:S73-7. doi:10.1016/S1262-3636(08)73398-6
49. Buteau J, El-Assaad W, Rhodes CJ, Rosenberg L, Joly E, Prentki M. Glucagon-like peptide-1 prevents beta cell glucolipotoxicity. *Diabetologia*. 2004;47(5):806-815. doi:10.1007/s00125-004-1379-6

