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Do GLP-1 receptor agonists have a place in the treatment of people with type 1 diabetes?

Thomas Fremming Dejgaard [1], Christian Seerup Frandsen [2], Jens Juul Holst [3], Sten Madsbad [4]

[1] Department of Endocrinology and Nephrology, Copenhagen University Hospital Nordsjaelland, Hilleroed, Denmark
[2] Department of Gynaecology, University of Copenhagen, Rigshospitalet, Blegdamsvej 3, DK-2200 Copenhagen, Denmark
[3] Novo Nordisk Foundation Center for Basic Metabolic Research, and Department of Biomedical Sciences, University of Copenhagen, Copenhagen, Denmark
[4] Department of Endocrinology, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark

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ABSTRACT

The glucagon-like peptide-1 receptor agonists (GLP-1RAs) are established for the treatment of type 2 diabetes but are not currently recommended for the treatment of people with type 1 diabetes. However, during the last decade experience has been collected regarding addition of a GLP-1 RA to insulin in patients with type 1 diabetes, both from clinical trials and off-label use. Several retrospective as well as prospective observational studies without a control group have been published. Only very few placebo-controlled, randomized studies have been presented. The present narrative review assesses the efficacy and safety of the different GLP-1 RAs and the dual GLP-1/ glucose-dependent insulinotropic polypeptide (GIP) agonist tirzepatide on glycaemic control, body weight, dose of insulin and adverse events in people with type 1 diabetes.

The reduction in HbA1c has in most studies been absent or minimal (0-0.3% (3.3 mmol/mol)), partly explained by a concomitant significant reduction in dose of insulin. The reduction in body weight has been in the range of 2-7 kg. The most pronounced reduction in body weight and dose of insulin has been obtained with semaglutide and tirzepatide. In the two largest placebo-controlled, randomized studies infrequent increases in hyperglycaemia with ketosis and hypoglycaemia were registered. The only identified clinical variable impacting the effect of GLP-1 RAs on HbA1c and dose of insulin has been residual beta-cell function. Treatment with GLP-1 based therapy was associated with more gastrointestinal adverse events. The outcomes of the studies depended on the different GLP-1 RAs applied, the intervention time and the residual beta-cell function.

Thus, combination therapy is of interest in relation to weight loss in people with obesity and type 1 diabetes, and in newly diagnosed patients with residual beta-cell function aiming at prolonging remission period. More well-designed studies of high quality are of required to better identify the subgroups, who will benefit most from adding GLP-1 based therapy to insulin in people with type 1 diabetes.

Keywords: type 1 diabetes, GLP-1 receptor agonist, liraglutide, semaglutide, tirzepatide, glycaemic control, body weight, dose of insulin, adverse events.

The rationale behind treatment with GLP-receptor agonists in type 1 diabetes.

More than 50% of people with type 1 diabetes are overweight or obese, which is associated with metabolic and cardiovascular complications and reduced life expectancy compared with the general population [1]. Obesity is also associated with insulin resistance and need for higher daily dose of insulin [2]. Treatment with basal-bolus insulin regime or continuous subcutaneous insulin infusion in combination with a glucose sensor is recommended in most patients to achieve the best possible glycaemic control for reducing late diabetic complications. However, for many people with type 1 diabetes adequate glucose regulation control is very demanding, and often leads to risk of hypoglycaemia and weight gain.

The glucagon-like peptide-1 receptor agonists (GLP-1RAs) are now established agents for treatment of type 2 diabetes and protection against cardiovascular events and kidney disease, but they are not currently recommended for the treatment of people with type 1 diabetes [3]. However, during the last decade experience has been gained from both clinical trials and off-label use regarding addition of a GLP-1 receptor agonist for the therapy of patients with type 1 diabetes

GLP-1 is one of the incretin hormones secreted from the L-cells in the gut epithelium after food intake [4]. It has pleiotropic effects as it potentiates glucose-induced insulin secretion and suppresses glucagon release, inhibits gastric emptying, and reduces appetite resulting in weight loss [4]. The delay of gastric emptying may in theory reduce postprandial glucose fluctuations. GLP-1 also has anti-inflammatory effects [3]. 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 [3]. 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. Exenatide is also available once weekly administration in a depot formulation.

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 [5]. At diagnosis, most people with type 1 diabetes have a residual beta-cell function, but corresponding to only 10-30% of the insulin production seen in healthy individuals without diabetes [6,7]. After initiation of insulin treatment and control of hyperglycaemia, a short period of improvement of beta-cell function (remission period) is often observed, and insulin treatment can be paused in 10-20% of the patient [6,7]. However, the destruction of the beta-cell continues and after 3-5 years the beta-cell function is minimal or absent [6]. Especially, in children the decline in beta-cell function is very fast [6]. In a subgroup some beta-cell function can be detected after 5-10 years duration of diabetes [6,8–10]. Residual beta-cell function is associated with improved glycaemic control, lower insulin doses, less risk of hypoglycaemia, ketoacidosis and late diabetic complications [6,11]. The loss of beta-cell function is accompanied by in a defective regulation in glucagon secretion with impaired glucagon secretion during hypoglycaemia [12,13]. Consequently, treatments capable of improving beta-cell function are warranted.

Notably, treatment with GLP-1 in experimental animal models increased beta-cell proliferation and survival, reduced rate of apoptosis, and delayed autoimmune diabetes [14–17]. Therefore, GLP-1 based therapy is of potential interest in the treatment of people with type 1 diabetes with preserved beat-cell function and therefore also in newly diagnosed people with diabetes.

In the present review the efficacy and safety of adding a GLP-1 based agonist to insulin treatment in people with type 1 diabetes will be discussed. Focus will be on randomized, placebo-controlled trials. Further, the review will focus on identifying subgroups of people with type 1 diabetes where GLP-1 RA treatment might be of special interest in the future. We have previously in details discussed the effect of the native GLP-1 hormone in people with type 1 diabetes [18].

Method

A systematic literature review was performed to identify all relevant published articles concerning treatment of people with type 1 diabetes with a GLP-1 RA or a GLP-1/GIP dual agonist. We searched PubMed by combining the terms “type 1 diabetes”, “T1D”, “T1DM”, “glucagon-like peptide-1 receptor agonist”, “GLP-1 RA”, “glucagon-like peptide-1”, “GLP-1”, “albiglutide”, “exenatide“, “byetta”, “bydureon”, “trulicity”, “dulaglutide” liraglutide“, “victoza”, “semaglutide”, “ozempic”, “GLP-1/GIP dual agonist”, “tirzepatide”. We also search the reference lists of original articles, reviews and meta-analysis focusing on treatment of type 1 diabetes with GLP-1 RAs for relevant articles. We reviewed the abstract programs for European Association of the Study of Diabetes (EASD) and American Diabetes association (ADA) during the last 5 years for relevant presentations. The final search was perfomed in September 2024. 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. The studies identified differ significantly in quality of design, choice of GLP-1 based therapy, duration of the trial, and insulin treatment (e.g. basal-bolus regimen or subcutaneous insulin infusion pump therapy). Therefore, we chose to write a narrative review of the studies since it seems meaningless to perform a meta-analysis because of the heterogeneity of trials. The focus of the present review is primarily on randomized clinical trials with placebo as a comparator, but also retrospective studies without control groups are included, especially in related to semaglutide and tirzepatide. The literature review was performed by SMA, who also extracted data and assessed the quality of the studies. Only publications written in English were included in the review.

Clinical trials with GLP-1 RAs in people with type 1 diabetes

Effects of native GLP-1 in type 1 diabetes

In eleven fasting subjects with type 1 diabetes, Creutzfeldt and co-workers found that a continuous infusion of GLP-1 (1.2 pmol/kg,min) for 240 minutes

resulting in pharmacological plasma levels, reduced hyperglycamia from 13.4 to 10 mmol/l and the glucagon concentration by approximately 50%, whereas the insulin levels was only slightly increased [19]. During placebo infusion plasma glucose did not change considerable (from 14.4 mmol/l to 13.1 mmol/l).

We studied the effect of endogenous as well as exogenously infused GLP-1 on postprandial glucose metabolism in people with type 1 diabetes with and without residual beta-cell function [20]. We performed infusion of GLP-1 and on another study day we blocked the GLP-1 receptor with exendin 9-39 during a mixed meal. Infusion of GLP-1 reduced peak plasma glucose in both groups. In the group with residual beta-cell function the glucose excursions did not differ from those of control subjects without diabetes. GLP-1 reduced gastric emptying and glucagon levels in patients both with and without beta-cell function and increased C-peptide secretion in the group with beta-cell function. Blocking the GLP-1 receptor increased glucose excursions, glucagon levels, and gastric emptying. Thus, acute GLP-1 infusion regulates glucose metabolism by increasing endogenous insulin secretion, inhibiting glucagon release, and reducing rate of gastric emptying.

Liraglutide

Most studies in people with GLP-1 RAs in type 1 diabetes have been performed with liraglutide 1.8 mg once daily. In a small study without a control group liraglutide was added to insulin therapy in C-peptide negative people with type 1 diabetes (n=8) [21]. After 24 weeks, mean body weight was reduced by about 4.5 kg, HbA1c by about 0.4% (4.4 mmol/mol) and basal insulin dose from 26 unit/day to 13 units/day and bolus insulin from 25 to 14 units/day.

In a retrospective study, 27 obese patients with type 1 diabetes were treated with liraglutide 1.8 mg once daily for 180 days. Body weight was reduced from 96.2 kg to 91.6 kg [22]. HbA1c was lowered from 7.9% (63 mmol/mol) to 7.5% (58 mmol/mol) and daily total and bolus insulin doses were reduced from 73 to 60 units/day and from 40 to 29 units/day, respectively. Systolic blood pressure fell from 130 to 120 mmHg.

In a small 4-week trial including 10 people with type 1 diabetes and residual beta-cell function (mean stimulated C-peptide 0.45 nmol/l) and 19 people with type 1 diabetes without residual beta-cell function, who were randomized to treatment with or without liraglutide 1.8 mg [23]. Insulin dose decreased from a mean of 0.50 units/kg/day to 0.31 units/kg/day in people with beta-cell function and from 0.72 units/kg/day to 0.59 units/kg/day in in C-peptide negative patients treated with liraglutide. Insulin dose did not change in people treated only with insulin. HbA1c decreased in both liraglutide treated groups. Patients treated with liraglutide lost weight with a mean of 2.3 kg.

In a 12-week randomized, placebo-controlled, double-blind trial, liraglutide 1.2 mg once daily was added to insulin treatment in normal weight and poorly controlled patients with type 1 diabetes and without residual beta-cell function. Forty patients were randomized with a mean HbA1c of 8.8% (72.5 mmol/mol) [24]. Change in HbA1c was - 0.6% (6.6 mmol/mol) with liraglutide and - 0.5% (5.6 mmol/mol) with placebo. Change in body weight was -3.1 kg and +1.2 kg, respectively, from about 75 kg (mean: BMI 24 kg/m2). Mean basal insulin was 34 units/day and bolus insulin about 25 units /day. The bolus insulin decreased by - 4 units/day vs 0.0 unit/day with liraglutide and placebo, respectively. Mean blood pressure decreased -2.6 by mmHg and - 0.8 mmHg, respectively. More patients in the liraglutide group had gastrointestinal adverse events and one patient only tolerated 0.9 mg daily. Occurrence of hypoglycaemia did not differ between groups.

In a sub-study it was demonstrated that liraglutide did not inhibit glucagon secretion and that the glycemic recovery after hypoglycemia was not compromised [25]. In another study the counterregulatory hormone responses during liraglutide treatment did not differ from those obtained with placebo [26].

In the 24-week "LIRA-1 study", liraglutide 1.8 mg once daily was added to insulin therapy in overweight patients with type 1 diabetes in a double-blind, placebo-controlled design [27]. Overall, 100 patients with type 1 diabetes (HbA1c 8.7% (71.7 mmol/mol), BMI 30.1 kg/m2, body weight 93.7 kg, duration of diabetes 23 years) were randomized. Doses of basal insulin were 32 units/day and bolus insulin 27 units/day. After 24 weeks changes in HbA1c did not differ significantly between groups (- 0.5% (5.5 mmol/mol) vs - 0.3% (3.3 mmol/mol)). The number of hypoglycemic episodes was reduced by 18% with liraglutide, while glycaemic variability did not differ between groups. Body weight fell with liraglutide (-6.8 kg) but remain unchanged with placebo. The insulin dose increased in both groups during the study. Bolus insulin was 5.8 units/day and basal insulin 5.3 units/day lower in the liraglutide group compared with placebo, but when adjusted for body weight the insulin doses did not differ between groups. Postprandial glucagon concentration and gastric emptying did not differ between groups during a mixed meal. Pulse rate increased (7.5 beats/min) and systolic blood pressure decreased 6 mmHg with liraglutide compared to no changes with placebo. Liraglutide was associated with more nausea, dyspepsia, diarrhea and vomiting.

The ADJUNCT ONE and TWO are the largest double-blind, randomized studies performed in people with type 1 diabetes where liraglutide was added to insulin treatment. In ADJUNCT ONE 1398 adults were randomized to 0.6, 1.2 or 1.8 mg of liraglutide or placebo for 52 weeks [28]. Mean HbA1c was 8.2% (66 mmol/mol), insulin dose about 61 unit/day, duration of diabetes 21 years, BMI 29.5 kg/m2 (body weight 86 kg). Placebo corrected reductions in HbA1c were 0.6 mg: -0.09% (0.9 mmol/mol), 1.2 mg: -0.15% (1.6 mmol/mol) and 1.8 mg: - 0.20% (2.2 mmol/mol). The corresponding doses of primarily bolus insulin were reduced (estimated ratios from start to end of treatment) with 1.2 mg: 0.95, and with 1.8 mg: 0.92, but not with 0.6 mg: 1.0.

Body weight was dose-dependently reduced with all liraglutide doses compared with placebo: -2.2 kg, -3.6 kg and -4.9 kg, respectively. Rates of symptomatic hypoglycaemia increased with all doses of liraglutide, and incidents of hyperglycaemia with ketosis (plasma

glucose > 16.7 mmol/l and plasma ketone > 1.5 mmol/l) increased significantly for liraglutide 1.8 mg. In total eight cases of diabetic ketoacidosis in the liraglutide groups were registered compared with none in the placebo group. Severe hypoglycaemia was not recorded. The gastrointestinal adverse effect increased dose-dependently and discontinuation of trial occurred in 4.9%, 12.6% and 14.7% of participants, respectively for liraglutide compared with 3.4% with placebo. Registered quality of life was higher with liraglutide. The authors conclude that the results questioned the clinical usefulness of GLP-1 RAs in people with type 1 diabetes.

In a subgroup analysis of 239 C-peptide positive subjects the reduction in HbA1c for 1.8 mg and 1.2 mg was (0.83% (9.1mmol/mol) and 0.71% (7.8 mmol/mol) was greater than for C-peptide negative subjects. The C-peptide positive subjects also had fewer events of hypoglycaemia and hyperglycaemia with ketosis.

In ADJUNCT TWO 835 persons with type 1 diabetes were randomized to 0.6 mg, 1.2 mg or 1.8mg liraglutide added to an individual capped total daily dose of insulin or placebo and followed for 26 weeks [29]. Mean baseline HbA1c 8.1% (65 mmol/mol) decreased significantly versus placebo at week 26 (1.8 mg: - 033% (3.6 mmol/mol), 1.2 mg: -0.22 (2.4 mmol/mol), 0.6 mg: -0.23 (2.5 mmol/mol); placebo 0.01% (0.1 mmol/mol)). BMI was 28.9 kg/m2 (body weight 84 kg), and liraglutide reduced body weight by -5.1 kg, - 4.0 kg, and -2.5 kg, respectively, versus – 0.2 kg for placebo. Total insulin dose was 59 units/day before treatment and was reduced at week 26 in the liraglutide groups, explained primarily by a reduction in postprandial dose of insulin by about – 3 to – 5.5 unit /day. There was a higher number of symptomatic and documented symptomatic hypoglycaemic episodes, but only with liraglutide 1.2 mg, and no difference between groups with respect to severe hypoglycaemia. More patients in the 1.8 mg group obtained the composite endpoint of HbA1c < 7.0 with no severe hypoglycaemia. Hyperglycaemic episodes did not differ between groups, but incidents of hyperglycaemia with ketosis were more frequent in the 1.8 mg group compared with placebo.

The C-peptide positive group (n=125) showed an improved treatment effect on HbA1c (1.8 mg: -0.77% (8.4 mmol/mol)) compared with -0.27% (2.9 mmol/mol) with placebo) and only one episode of hyperglycaemia with ketosis was observed among the C-peptide positive patients. The liraglutide group reported improved quality of life compared with placebo. Thus, the results and conclusions from ADJUNCT TWO were in accordance with those of ADJUNCT ONE.

In a post hoc analysis of both ADJUNCT studies, treatment effects of liraglutide were evaluated in the participants divided according to HbA1c < or > 8.5% (69.4 mmol/mol), body mass index < or > 27 kg/m2, and insulin regimen (basal bolus or continuous subcutaneous insulin infusion) [30]. For both trials the results recorded at the week 26 follow-up, showed that neither the reduction in HbA1c, body weight, nor the daily insulin dose differed significantly in relation to baseline HbA1c or BMI. Also, the risk of clinically significant hypoglycaemia, or hyperglycaemia with ketosis did not differ according to baseline HbA1c, BMI, or insulin regimen. The only identified variable impacting the effect of liraglutide was residual beta-cell function.

In a dedicated 26-week study, patients with overweight and insufficient glycaemic control (n=44) were given liraglutide 1.8 mg daily or placebo added to insulin pump treatment in a randomized, double-blind, placebo-controlled design [31]. HbA1c was reduced by - 0.5% (5.5 mmol/mol) from a baseline of 8.2% (66 mmol/mol) with liraglutide compared to + 0.2% (2.3 mmol/mol) with placebo. Body weight was reduced by 6.3 kg from 85 kg with liraglutide compared with placebo, where the weight was stable. Liraglutide reduced insulin dose by 8 units/day, or 16% of total dose (48 unit/day). Primarily bolus insulin was reduced, while no change was observed with placebo, but the differences between groups disappeared when adjusting for body weight. Time in range (3.9-10 mmol/l) increased with liraglutide (57% vs 45% at week 26) compared with placebo. Risk of hypoglycaemia and ketoacidosis did not differ between groups. Systolic blood pressure decreased with 7 mmHg with liraglutide while no changes were found with placebo. More gastrointestinal adverse events were registered with liraglutide compared with placebo. Changes in treatment satisfaction increased more in the liraglutide group.

In a secondary analysis fat mass was decreased by -4.6 kg and lean mass by -2.5 kg [32]. Interestingly, energy intake from added sugars decreased by 27%, while intake of carbohydrate, protein and fat did not differ between groups.

Preservation of residual beta-cell function has been an aim in several studies. In a randomized, parallel-group, placebo-controlled double dummy, double-blind trial, adults with type 1 diabetes and a mean time from diagnosis of about 11 weeks (n= 308) were randomized to treatment with an IL-21 antibody or liraglutide as monotherapy or in combination or placebo, all as adjunct to insulin therapy for preservation of beta-cell function [33]. The hypothesis was that combining immunomodulation with a GLP-1 RA would ensure beta-cell survival. IL-21 has been linked to diabetes progression in animal and in humans probably because of the central role of IL-21 in promoting trafficking of CD8+ lymphocytes to the pancreas [34]. Beta-cell function was evaluated as area under the C-peptide curve during a mixed meal. Age was 28 years, BMI 24 kg/m2, HbA1c 7.1% (54 mmol/mol), weight 72 kg and daily dose of insulin 0.31 units/kg. After 54 weeks of treatment, meal-stimulated C-peptide secretion decreased significantly less from randomization with the combination (10%), compared with liraglutide (32%) or IL-21 (25%) alone or placebo (39%), and the C-peptide secretion was 48 % greater with the combination compared with placebo. In the IL-21 or liraglutide groups the C-peptide responses did not differ from that of placebo. Despite greater doses of insulin in the placebo group, the decrease in HbA1c was greater with the active combination treatment (0.5% (5.5 mmol/mol) vs 0.1% (1.1 mmol/mol)). The rate of hypoglycaemia was lower in the liraglutide alone group than in the placebo group. However, 26 weeks after treatment cessation, the effects were lost.

In the multicenter, randomized, double-blind "New-Lira" study, the effect of liraglutide on beta-cell function was tested in newly diagnosed patients with type 1 diabetes [35]. In total, 68 patients with duration of 4 weeks of type 1 diabetes and a mean age of 28 years were randomized to liraglutide 1.8 mg or placebo. Body weight was about 74 kg (BMI 23.5 kg/m2), HbA1c 8.4% (68 mmol/mol) and daily dose of insulin about 22 unit/day. Peak C-peptide concentration was during a mixed meal at randomization 0.9 nmol/l. The patients were followed for 52 weeks during active treatment and for 6 weeks after treatment. Mixed meal tests were performed at randomization, at end of treatment (52 weeks) and at follow-up (58 weeks).

At week 52 the AUC C-peptide and other indices of beta-cell function improved compared with the placebo group, but 6 weeks after end-of-treatment the groups again co-aligned. AUC glucagon did not differ between groups at any time points.

With liraglutide treatment, the total daily dose of insulin decreased with 30% from 0.30 units/kg/day to 0.23 units/kg/day compared with an increase from 0.29 units/kg/day to 0.43 units/kg/day with placebo at week 52, but with no difference during follow-up. A period with no need for insulin was observed in 13 versus two patients for liraglutide and placebo. In these patients, the period lasted for a median of 12 weeks for liraglutide versus 6 weeks for placebo treated patients, respectively. At week 52 a reduction of 15 mmol/mol in HbA1c was found in both groups. Body weight was at end-of treatment 3 kg lower in the liraglutide group. Among 10 inflammatory markers measured, reduced levels of TNF-alfa (21%) and IL-10 (26%) were observed. Biochemically verified hypoglycaemia was registered more often in the placebo group, where also three incidents of severe hypoglycaemia occurred compared with none in the liraglutide group. The adverse events with liraglutide were predominantly gastrointestinal and transient. Two patients completed the study with 1.2 mg doses. No differences in quality of life were found between the groups. Thus, the "New-Lira study" illustrates the beneficial effects of liraglutide in patients with newly diagnosed type 1 diabetes, but also shows that the effect disappears when treatment with liraglutide is stopped.

Taken all the studies with liraglutide together, the effect of liraglutide on HbA1c has been conflicting with improvement in HbA1c from 0.4% (4.4 mmol/mol) to 0.9% (9.8 mmol/mol) over 12-24 weeks in small non-randomized studies, while other randomized, placebo-controlled studies found no effect on HbA1c. Most trials reported reduction in daily dose of insulin and in body weight (up to 6.8 kg for liraglutide 1.8 mg). The reduction in doses of insulin was less when corrected for body weight and was often insignificant when compared with those of placebo groups. Information on "patient reported outcomes" is limited in the studies. In the "New Lira" study the treatment satisfaction did not differ between liraglutide and placebo, but the perceived frequency of low blood glucose events was significantly lower in liraglutide treated patients. Adverse events were primarily gastrointestinal in nature, transient and similar to those described for people with type 2 diabetes. Liraglutide lowered systolic blood pressure and increased heart rate.

Exenatide

Patients with long-standing type 1 diabetes and some residual beta-cell function were treated with exenatide four times daily without and with daclizumab (to diminish the underlying autoimmunity and to curb a potential autoimmune reactivation), but without any improvement in beta-cell function after 6 to 9 months treatment, when evaluated by an arginine and a mixed meal tests [36]. The participants lost about 4.1 kg and the dose of insulin was reduced from 0.55 units/kg/day to 0.48 units/kg/day.

During single meal test studies exenatide has been added to insulin treatment in adolescents (n=8) with type 1 diabetes and reduces postprandial hyperglycaemia compared with insulin monotherapy; the treatment was associated with delayed gastric emptying [37].

Eighteen newly diagnosed people with type 1 diabetes were randomized to insulin alone, insulin plus exenatide twice daily or insulin + sitagliptin 100 mg daily for one year, starting one month after diagnosis [38]. The reduction in dose of insulin was greatest with insulin+ exenatide (55.7 units/day to 16.5 units /day), but dose of insulin was also lowered with insulin + sitagliptin (47.8 units/day to 24.2 units/day) compared with insulin alone (59.3 units/day to 44.2 units/day). The incidence of hypoglycaemia did not differ between groups. Neither exenatide nor sitagliptin had any effect on C-peptide responses to a mixed meal test compared with before treatment.

In a mechanistic study, Ghazi and coworkers studied the acute metabolic effects of exenatide in patients with type 1 diabetes and residual beta-cell function during a mixed meal and an intravenous glucose test [39]. During the meal test glucose levels were suppressed, while the insulin secretion related to ambient glucose levels was increased, glucagon levels were suppressed, and gastric emptying delayed. During the intravenous glucose test exenatide had no effect on insulin secretion.

The effects of 6 months treatment with exenatide were studied in adults with type 1 diabetes [40]. Fourteen patients with duration of diabetes of 20.5 years participated in the crossover study of 6 months treatment with exenatide 10 mcg four times a day and 6 months off exenatide. Changes in fasting and postprandial blood glucose and changes in insulin sensitivity before and after each study period were assessed. Exenatide was associated with reduced postprandial blood glucose responses but also with higher fasting glucose concentration, without any net changes in HbA1c. Exenatide increased insulin sensitivity (40%) evaluated by a hyperinsulinaemic-euglycaemic clamp, and the authors concluded that improvement in insulin sensitivity was beyond the effect expected from the weight reduction. Weight loss was 4.2 kg. Dose of insulin was reduced from 0.54 units/kg/day to 0.47 units /kg/day with exenatide, primarily resulting from a reduction in meal dose of insulin.

The randomized, double blind, placebo-controlled MAG1C trial is the largest trial with exenatide [41].

Overall, 108 patients with type 1 diabetes were randomized to exenatide 10 mcg three times daily or placebo injections for 26 weeks. Diabetes duration was 21 years. Body weight 87 kg, (BMI 28.4 kg/m2), basal dose of insulin about 30 units/day and prandial insulin dose was also around 30 units /day. A minimal C-peptide production was detected in 13% and 9% participants in the exenatide and placebo groups, respectively. In total, 23 participants discontinued treatment (17 in the exenatide group and six in the placebo group).

From a baseline of 8.3% (66.4 mmol/mol) HbA1c changed by - 0.3% (3.2 mmol/mol) in the exenatide and - 0.19% (2.1 mmol/mol) in the placebo group, respectively. No difference between the groups was found in fasting plasma glucose and 7-points self-monitoring blood glucose (SMBG) profiles. CGM measurements showed that mean plasma glucose concentration, time in range, time in hyperglycemia or risk of hypoglycemia did not differ between groups at week 26. Total insulin dose was reduced by 9.0 units/day in the exenatide group compared with placebo, primarily because of a reduction in prandial doses of insulin. Body weight was lowered by 4.4 kg with exenatide. Blood pressure or albuminuria did not differ between groups, but heart rate increased by 3.9 bpm with exenatide. No incidence of diabetic ketoacidosis was recorded. More gastrointestinal adverse events were registered in the exenatide group.

In a secondary analysis, exenatide changed total fat mass by -2.6 kg and lean body mass by -1.1 kg [42]. Exenatide did not change levels of interleukin-1 and 6, tumor necrosis factor (TNF)-alfa, C-reactive protein, N-terminal prohormone of brain natriuretic peptide, or 8-oxo-7,8-dihydroguanosine (RNA oxidation marker) and 8-oxo-7,8-dihydro-2-deoxyguanosine (DNA oxidation marker). Thus, exenatide had no effect on biomarkers of cardiovascular disease risk.

The authors conclude that short acting exenatide does not seem to have a future as standard add-on treatment to insulin therapy.

Exenatide once weekly

In a retrospective observational study, 11 patients receiving continuous subcutaneous insulin infusion (HbA1c 7.7% (60,7 mmol/mol)) were treated for 3 months with 2 mg of exenatide once-weekly [43]. Three months after initiation GLP-1 RA treatment, HbA1c was reduced by 0.6% (6.6 mmol/mol), body weight by 3.7 kg, and total dose of insulin by 13% (12.9 unit/day including 9.3 units/day in bolus). From month three to month six, 5 patients stopped treatment with exenatide because of gastrointestinal intolerance and subcutaneous nodule formation.

Albiglutide

In a randomized trial, albiglutide 50 mg weekly versus placebo was studied in newly diagnosed people with type 1 diabetes during the course of 52 weeks [44]. Fifty patients were treated with albiglutide and 15 with placebo. Of these, 40 and 12 participants completed the study. The patients were enrolled 4-8 weeks after diagnosis, had a stimulated C-peptide > 0.2 nmol/l and were treated with basal-bolus insulin therapy. Mean duration of diabetes was 52 days at randomization, body weight was about 67.5 kg and baseline HbA1c was 7.3% (56 mmol/mol). After 52 weeks the C-peptide and glucagon response during a mixed meal as well as HbA1c or daily dose of insulin and risk of hypoglycaemia did not differ between groups. The profile of gastrointestinal adverse events was consistent with other GLP-1 RAs. It should be noted that albiglutide has limited effect on HbA1c and body weight even in people with type 2 diabetes [3].

Semaglutide

In a letter to the Editor of New Engl J Med, the efficacy of semaglutide was analyzed in 10 patients with type 1 diabetes between the age of 21 to 39 years and a mean HbA1c of 11.7% (104 mmol/mol), who had started semaglutide up to 0.5 mg weekly within 3 months after diagnosis and were followed for one year [45]. Semaglutide treatment was associated with the elimination of prandial insulin in all patients and basal insulin in sevenpatients and reduced HbA1c to a mean of 5.7% (39 mmol/mol) after 12 months.

In another study also without a control group, 10 pump treated patients with overweight were treated with semaglutide and followed for 6 months [46]. Body weight decreased from 82.8 kg (30.9 kg/m2) to 70.0 kg and total insulin dose was reduced from 45.6 units/day to 38.5 units/day after 6 months. HbA1c did not change significantly during the follow-up.

Tirzepatide

Tirzepatide is a dual GLP-1/GIP agonist approved for treatment of type 2 diabetes and overweight. Tirzepatide is very potent also when compared with semaglutide 1 mg or 2.4 mg. In people with type 2 diabetes the weight loss has been about 11-13 kg, while in obese people without diabetes the weight loss is about 19-22 kg [47].

In a retrospective study, 62 intensively treated (basal-bolus regimen n= 10 or insulin pump treatment n=52) patients with type 1 diabetes patients and overweight were treated with tirzepatide for one year. The control group consisted of 37 matched patients with lower BMI (35.6 vs 32.8 kg/m2), weight and daily dose of insulin (76 vs 62 units/day) group.

The mean dose of tirzepatide was 9.7 mg/week, thus the majority did not reach the highest dose for people with type 2 diabetes 15 mg. Mean decrease in BMI and weight were 6.5 BMI-units (kg/m2) and 18.5 % vs 1.2% in the control group. HbA1c decreased by 0.67% (7.3 mmol/mol) in the tirzepatide group compared with -0.02% (0.22 mmol/mol) 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 compared with the control group. Neither hypoglycaemia nor diabetic ketoacidosis were reported.

In a retrospective observational study, people with type 1 diabetes treated with automatic insulin delivery system were treated for 8 months with tirzepatide (n=11). HbA1c was 7.0% (53.0 mmol/mol) and a BMI 39.6 kg/m2 at baseline [48]. The daily dose of insulin was

reduced from a mean of 73.9 units/day to 51.7 units/day (basal insulin was reduced by 31% and bolus insulin by 43%, primarily due to a reduction in bolus insulin from 31.4 units/day to 17.9 units/day. Dose reduction from 2 to 8 months was modest. Time in range increased by 7% without increase in time below 3.4 mmol/l (70 mg/dl), and HbA1c was reduced with - 0.5% (5.5 mmol/mol) and weight by 9% from 114.3 kg. The authors recommend a dose reduction of about 25 % of total dose of insulin when initiating tirzepatide in patient treated with an automatic insulin infusion pump. The insulin reduction may depend on HbA1c, and people with higher HbA1c may require less reduction in dose of insulin.

In a retrospective observational study in 26 adults with type 1 diabetes treatment with tirzepatide reduced HbA1c by - 0.45% (4.9 mmol/mol) at 3 months and -0.6% (6.6 mmol/mol) after 8 months of treatment [49]. Body weight was reduced by 10.1%, and glucose time in range (3.9 to 10.0 mmol/l) increased with 12.6%. The total dose of insulin (85.2 units/day) was reduced by 24.3%. Two patients discontinued tirzepatide treatment.

At European Association for the Study of Diabetes (EASD) 2024, (Snell-Bergeon j et al, OP 243) the efficacy of semaglutide and tirzepatide was assessed in retrospective chart review of 100 patients with type 1 diabetes; 50 who were prescribed semaglutide and 50 who were prescribed tirzepatide. Nearly all participants were overweight or obese (mean BMI 34 kg/m2) and were compared with 50 matched control subjects. HbA1c was 7.3% (56 mmol/mol). Follow-up was up to one year. Body weight declined 5.4 kg with semaglutide, and -14.4 kg with tirzepatide when compared with controls. The change in HbA1c was larger in the semaglutide (-0.42% (4.6 mmol/mol)) and tirzepatide (-0.62% (6.8 mmol/mol)) treated groups than in controls. No severe hypoglycemia or ketosis were registered.

The limitations of the studies with tirzepatide are that the studies are retrospective, without a control group and the titration of dose of insulin was not uniform among physicians.

Conclusions

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 therapy has been of interest as add-on therapy to insulin treatment in people with type 1 diabetes because of its pleiotropic effects on glucose control and body weight, but the results have been conflicting. Most studies with GLP-1RAs in people with type 1 diabetes are small with few participants, often without a control group and seldomly carried out in a placebo-controlled design. The improvement in HbA1c with the use of exenatide is minimal or absent, and with liraglutide 1.8 mg daily, the reduction in HbA1c has been in the range of -0.1 to -0.3% (1-3 mmol/mol), while greater improvements have been reported with the more potent GLP-1 Ra semaglutide and the dual GLP-1/GIP agonist tirzepatide. Notably, in the placebo-controlled studies, aggressive insulin titration in both the GLP-1 RA and placebo groups may have lessened a difference in HbA1c. In most studies a significant reduction in daily dose of insulin, often particularly a reduction in prandial insulin has been reported. In the largest trial with exenatide the weight loss was about 4 kg, and with liraglutide the weight losses have ranged from -2 to -7 kg. With semaglutide and tirzepatide the weight loss has been up to 13% to 18%, respectively. Treatment with GLP-1 RAs do not seem to compromise counter regulation after hypoglycaemia. The different mode of action of the short acting exenatide and the long acting GLP-1 RAs may explain the difference in postprandial glucose profile, i.e. the pronounced effect of exenatide on gastric emptying. Systolic blood pressure was reduced with GLP-1 RAs in most studies. The adverse events observed with GLP-1 based therapy have been similar to those reported in people with type 2 diabetes or obesity and were often transient. Some cases with diabetic ketoacidosis have been reported, probably explained by too large reductions in dose of insulin in participants without residual beta-cell function.

In ADJUNCT ONE and TWO, the two largest studies (n=2233) with liraglutide, an increased risk of hyperglycaemia with ketosis was registered because of a too optimistic reduction in dose of insulin [28,29]. Also, more hypoglycaemic events were observed in the liraglutide groups compared with placebo. In people with residual beta-cell function the reduction in HbA1c was about 0.6% (6.6 mmol/mol) primarily explained by stimulation of the endogenous insulin secretion [28,29].

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 [35]. 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 [33]. In both studies the effect on the beta-cell function disappeared a few weeks after termination of therapy.

Thus, the arguments for use of a GLP-1 RA in people with type 1 diabetes are several. Many patients with type 1 diabetes have "double" diabetes because of overweight or obesity, which is characterized by insulin resistance and higher daily doses of insulin [2]. Overweight also increases the risk of cardiovascular diseases as discussed below. Furthermore, insulin resistance seems to be a risk factor for development of late diabetic complications [2].

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 diseases in people with type 2 diabetes and in overweight and obese people without diabetes [3,50]. Diabetic kidney disease is still a problem in people with type 1 diabetes and GLP-1 RAs reduce the risk of progression of kidney disease; thus, 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 [51].

In patients with residual beta-cell function, GLP-1 RAs may reduce HbA1c, dose of insulin and risk of hypoglycemia. GLP-1 RAs may also prolong the remission period without insulin and the following period where only a single daily injection of basal insulin is needed to regulate glycaemic control. This will undoubtedly improve quality of life and adherence to treatment. Lastly, type 1 diabetes is also diagnosed in people over the age of 30-40 years, who may have a preserved beta-cell function during many years, where treatment with a GLP-1 RA can induce remission and postpone insulin treatment for years [6].

Final comments on GLP-1 based therapy in type 1 diabetes

In the future, the focus on GLP-1 based therapy in people with type 1 diabetes will probably increase. Considerable daily life experience exists in many diabetic clinics, but more randomized clinical studies of high quality are needed, using not only HbA1c but also time in range as endpoints. Effects of semaglutide and tirzepatide on body weight and dose of insulin will be of interest to investigate in greater detail. Both patients with newly diagnosed diabetes, but also patients with long-standing diabetes, cardiovascular and/or kidney disease as well as obesity should be targeting populations to allow identification of the groups of patients that may benefit the most from GLP-1 based therapy as add-on to insulin treatment.

Conflict of interest:

TFD has served on advisory boards for Medtronic, Boehringer Ingelheim, Novo Nordisk and Eli Lilly, has received lecture fees from Boehringer Ingelheim, Sanofi, Novo Nordisk, and AstraZeneca and received research support from AstraZeneca and Novo Nordisk. CSF has received lecture feew fron Novo Nordisk A/S. JJH is a member of advisory boards for NovoNordisk. SMA has served as Advisory boards: AstraZeneca; Boehringer Ingelheim; Intarcia Therapeutics; Novo Nordisk; Sanofi, Abbott Lab, Bayer, Amgen. Lecture fees: AstraZeneca; Novo Nordisk, MSD. Research Grant Recipient: Novo Nordisk; Novo Nordisk foundation, Boehringer Ingelheim. Support for attending meetings and/or travel: Novo Nordisk, Boehringer-Ingelheim, Bayer

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