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GLP-1 Agonists in Type 1 Diabetes Mellitus: A Review of the Literature

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Abstract

Objective: To review the use of GLP-1 agonists in patients with type 1 diabetes mellitus (T1DM). **Data Sources:** A search using the MEDLINE database, EMBASE, and Cochrane Database was performed through March 2016 using the search terms *glucagon-like peptide 1* (GLP-1) *agonists, incretin, liraglutide, exenatide, albiglutide, dulaglutide, type 1 diabetes mellitus*. **Study Selection and Data Extraction:** All English-language trials that examined glycemic end points using GLP-1 agonists in humans with T1DM were included. **Data Synthesis:** A total of 9 clinical trials examining the use of GLP-1 agonists in T1DM were identified. On average, hemoglobin A_{1C} (A1C) was lower than baseline, with a maximal lowering of 0.6%. This effect was not significant when tested against a control group, with a relative decrease in A1C of 0.1% to 0.2%. In all trials examined, reported hypoglycemia was low, demonstrating no difference when compared with insulin monotherapy. Weight loss was seen in all trials, with a maximum weight loss of 6.4 kg over 24 weeks. Gastrointestinal adverse effects are potentially limiting, with a significant number of patients in trials reporting nausea. **Conclusion:** The use of GLP-1 agonists should be considered in T1DM patients who are overweight or obese and not at glycemic goals despite aggressive insulin therapy; however, tolerability of these agents is a potential concern. Liraglutide has the strongest evidence for use and would be the agent of choice for use in overweight or obese adult patients with uncontrolled T1DM.

Keywords

GLP-1 agonists, diabetes, type 1 diabetes, exenatide, liraglutide, dulaglutide, albiglutide

Introduction

Type 1 diabetes mellitus (T1DM) affects approximately 1.25 million American adults and children and accounts for 5% to 10% of all patients with diabetes.[1] Insulin therapy is the cornerstone treatment of T1DM and is successful in preventing diabetic ketoacidosis, an immediate and potentially fatal consequence of insulin deficiency. However, adequate glucose control to prevent long-term complications, such as diabetic nephropathy, peripheral neuropathy, and retinopathy, is often difficult to attain with insulin alone. This was seen in a study spanning over a total of 30 years, in which hemoglobin A_{1C} (A1C) averaged 7.2% in patients receiving intensive insulin treatment and remained above goal at 10 years (7.9%) and 30 years (8.0%) after study initiation.[2] Intensive insulin therapy that does not achieve A1C goals could place the patient at increased risk for long-term complications.[3] Owing to an increased prevalence of obesity in T1DM and its association with insulin resistance, innovative approaches to glucose control have become necessary.[4] An explosion of novel antidiabetic treatments have recently come into the market, but only pramlintide (Symlin), an analog of amylin, has gained Food and Drug Administration (FDA) approval for T1DM. This has begged the question as to which, if any, of these new agents could have utility in T1DM? Glucagon-like peptide 1 (GLP-1) has been shown to have insulinotropic and glucagonostatic properties, making GLP-1 agonists an ideal area for investigation in T1DM.[5,6]

Data Sources

To obtain relevant literature, a search using MEDLINE, EMBASE, and the Cochrane Database was performed, through March 2016, using the key terms *type 1 diabetes mellitus* together with *GLP-1 agonists, incretin, liraglutide, exenatide, albiglutide*, and *dulaglutide*, respectively. References of all articles were reviewed for relevant citations. Studies eligible for inclusion in this review were English-language, human clinical trials of GLP-1 agonists

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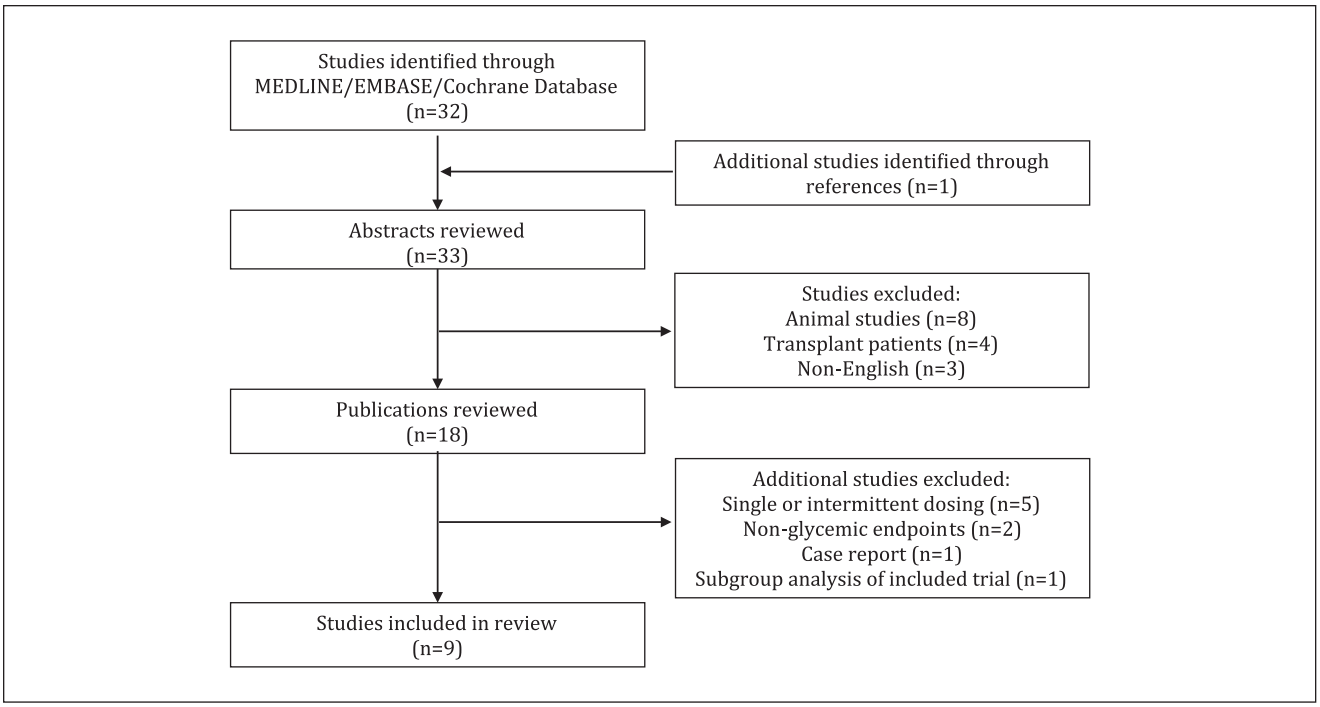

Figure 1. Flowchart of study inclusion.

that reported glycemic outcomes. Glycemic outcomes are defined as A1C or plasma glucose measurements. Studies in patients who had undergone islet transplantation or that utilized either single or intermittent dosing were excluded from this review. A total of 9 trials met inclusion criteria. Details regarding study inclusion are reported in Figure 1.

Pathophysiology

T1DM results from autoimmune destruction of the pancreatic β-cells, causing insulin deficiency. As a consequence, patients require exogenous insulin for treatment. Although the rate and extent of destruction of β-cells is highly variable, measurable residual function remains in nearly 100% of newly diagnosed patients after the first year.[5] Remaining insulin secretion can be measured indirectly through obtaining serum concentrations of C-peptide, which is cleaved from proinsulin during endogenous insulin production in equimolar amounts to insulin. The hallmark of diagnosis of T1DM is the presence of autoantibodies to at least 1 known autoimmune marker, though this can occur before any clinical signs or symptoms of diabetes are present.[7] In addition to insulin deficiency, several other underlying metabolic disturbances have been implicated in T1DM, including excess production of glucagon in the presence of hyperglycemia leading to inappropriate gluconeogenesis, increased levels of free fatty acids, rapid gastric emptying, and decreased sensation of satiety.[5,8] Provision of exogenous insulin fails to address these other manifestations of endocrine dysfunction, leading to potential targets of therapy for T1DM.

Gaps in Treatment

Currently, there are only 2 treatment modalities approved for T1DM in the United States: insulin and pramlintide. Treatment with exogenous insulin has been the mainstay of management of T1DM patients for decades, and a plethora of insulin analogs are currently available; however, intensive insulin therapy causes hypoglycemic episodes (62 incidents/100 patient-years) and weight gain of approximately 4.6 kg over a period of 10 years.[9] In addition, many patients fail to reach A1C goals despite aggressive treatment.[2] Pramlintide, an analog of amylin, has many actions similar to GLP-1 agonists, including delayed gastric emptying, decreased glucagon secretion, and increased satiety. In clinical trials, use of pramlintide 3 or 4 times daily in T1DM patients led to reductions in A1C of 0.29% and 0.34%, respectively, over 52 weeks.[10] Unfortunately, it has been associated with hypoglycemia in T1DM, a cause for concern.[10] Metformin has been studied in T1DM with mixed results on changes in insulin sensitivity and without statistically significant changes in A1C.[11,12] Currently, dipeptidyl peptidase-4 (DPP4) and sodium-glucose cotransporter 2 (SGLT-2) inhibitors are also under investigation for use in T1DM.[13-16] Over the past decade, GLP-1 agonists

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have been the most rigorously studied noninsulin agents for T1DM. Several proof-of-concept studies showed reductions in postprandial hyperglycemia and serum glucose area under the curve (AUC) following single doses of up to 3 days of therapy.[17,18] Below, we discuss the role of GLP-1 in T1DM, evidence for specific GLP-1 agonists in T1DM, and clinical implications in depth.

GLP-1 Agonists in T1DM

GLP-1 is an endogenous hormone that regulates secretion of both insulin and glucagon in response to meals. In the presence of postprandial hyperglycemia, GLP-1 stimulates insulin release from β cells and suppresses glucagon release from pancreatic α cells. It is hypothesized that a paradoxical increase in glucagon in T1DM could be responsible for the erratic blood glucose control often seen in patients appropriately treated with insulin therapy; thus, GLP-1 agonists could have utility in T1DM.[5,6] Because GLP-1 activity is a glucose-dependent mechanism, risk for hypoglycemia is low.[19] Additionally, GLP-1 slows gastric emptying through effects on the autonomic nervous system and acts centrally to increase satiety. The resultant decrease in oral intake is thought to be the mechanism that induces weight loss.[20] This effect is observed regardless of baseline weight and has led to FDA approval of 1 agent, liraglutide, as an adjunct to diet and exercise for weight loss in obese, nondiabetic patients.[5,19,20] These agents are available as subcutaneous injections with varying dosing intervals.

Evidence for the use of GLP-1 agonists in T1DM is limited and varies based on agent. Various proof-of-concept studies for both exenatide and liraglutide demonstrated a decrease in plasma glucose when added to insulin therapy.[17,18,21,22] This led to additional clinical trials for GLP-1 agonists in T1DM, evaluating extended GLP-1 use and corresponding glycemic outcomes. Each will be discussed independently, including relevant published studies and those currently in process.

Exenatide

Exenatide was first approved for use in the United States as a twice-daily, immediate release subcutaneous injection. Several years later, an extended release formulation was additionally approved. Drug levels of the twice daily preparation are detectable for only 6 to 7 hours after dosing, which results in intermittent stimulation of the GLP-1 receptor.[6] The once-weekly formulation allows for continuous stimulation of the GLP-1 receptor and has been noted to have significantly increased gastric emptying as compared with twice-daily dosing.[6] Use of exenatide to augment insulin therapy in T1DM patients has been evaluated since 2009.[20] The majority of studies in T1DM utilize the immediate release formulation. Although data are conflicting and limited, these data have been used to shape GLP-1 use in T1DM. A review of published data reveals 3 studies utilizing exenatide beyond a single dose, all in adult patients (Table 1).[16,20,23] Clinical trials range from 3 to 18 months, limiting available long-term outcomes; however, the clinical findings are useful to consider in T1DM patients.

The first clinical trial to explore GLP-1 agonist use in T1DM patients simultaneously evaluated the impact of an immunomodulator (daclizumab) and exenatide on β-cell function and glycemic control.[20] Rother et al[20] executed a 4-arm crossover clinical trial with insulin, exenatide, and daclizumab in various combinations: insulin monotherapy, insulin + exenatide, insulin + exenatide + daclizumab, or insulin + daclizumab. Participants underwent an optimization period for 2 to 4 months to achieve improved glycemic control. The optimization period was followed by a 4-month run-in phase, which prohibited any major changes to their insulin regimen and diabetes management. Patients were randomized to group A, insulin or insulin + exenatide, or group B, exenatide + daclizumab + insulin or daclizumab + insulin. After 6 months of treatment, patients in each group switched treatment arms to alter receipt of exenatide. The dose and frequency were titrated from exenatide 2.5 μg twice daily to 10 μg 4 times daily; however, no data are provided about the number of patients reaching the 40-μg daily exenatide doses. With each exenatide titration, the authors noted corresponding reductions in insulin doses. An independent examination of exenatide patients demonstrated no effect on C-peptide secretion or fasting glucagon, likely because of an average duration of T1DM of 21 years. Interestingly, exenatide did not alter A1C during the study period but did improve weight loss without dropout because of gastrointestinal (GI) adverse drug reactions (ADRs).[20] A subgroup analysis of this study also evaluated insulin sensitivity in 13 exenatide patients enrolled within the larger trial.[24] In these patients, exenatide was associated with improved insulin sensitivity, specifically pertaining to postprandial blood glucose control.[24]

Insulin augmentation with exenatide has also been compared with augmentation with sitagliptin in adult patients newly diagnosed with T1DM within the previous month.[16] Patients were randomized to 1 of 3 treatment arms: insulin monotherapy, insulin + exenatide, or insulin + sitagliptin. All 3 treatment arms showed improvement in A1C and decreased insulin requirements at 1 year. Similar to previous studies, treatment with exenatide had no impact on C-peptide secretion. Two patients reported nausea with exenatide; however, neither participant withdrew from the study.[16]

Finally, a recent retrospective analysis was completed in patients receiving weekly extended-release exenatide.[23] Patients served as their own controls, and data was collected at baseline and 3 months after beginning treatment. Statistically significant improvements in A1C, body mass index (BMI), and insulin requirement were seen at 3 months.[23]

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Table 1. Summary of Studies of Exenatide in Patients With T1DM.[a]

Author(s)	Study Design and Inclusion Criteria	Baseline Characteristics	Number of Patients	Study Duration	Change in A1C	Change in Plasma Glucose	Change in Insulin Dose	Change in Weight or BMI	Comments
Rother et al[20,b]	• Prospective • Randomized • Open-label crossover • Exenatide vs exenatide/daclizumab vs daclizumab vs insulin monotherapy Inclusion criteria • 18-60 Years of age • BMI >25 kg/m^2 • Diagnosis for ≥5 years	• Age 39 years • Duration of disease 21.3 years • A1C 7.3% ± 1.1% • BMI 25.9 kg/m^2	20	18 Months	−0.13% with exenatide	NR	−0.07 IU/kg/d[c] from baseline	−4.1 kg[c] from baseline	• Exenatide 2.5 µg twice daily titrated to 10 µg 4 times daily, as tolerated • Daclizumab 2 mg/kg IV once monthly • No GI ADRs reported • Hypoglycemia similar between exenatide groups (1.21 episodes per week on exenatide)
Hari Kumar et al[16,b]	• Prospective • Randomized • Open label • Exenatide vs sitagliptin vs insulin monotherapy Inclusion criteria • >18 Years of age • C-peptide >0.1 ng/mL	• Age 28 years • Duration of disease 1.1 months • A1C 9.7% ± 0.8% • BMI 21.5 kg/m^2	18	12 Months	−0.3% difference with exenatide	NR	• −24.1 IU/d • −0.4 IU/kg/d	−4.5 kg from baseline	• Exenatide 5 µg twice daily titrated to 10 µg twice daily, as tolerated • Nausea in 11% (n = 2) • Hypoglycemia similar between groups (3 episodes reported with exenatide)
Traina et al[23]	• Retrospective • No comparator Inclusion criteria • >18 Years of age • Diagnosis for >6 months	• Age 53 years • Duration of disease 39 years • A1C 7.70% ± 0.95% • BMI 29.8 kg/m^2	11	3 Months	−0.6%[c] from baseline	−12.3 mg/dL from baseline	• Bolus: −7.8 IU/d[c] from baseline • Basal: −3.3 IU/d from baseline	−1.7 kg/m^{2c} from baseline	• Exenatide dose not provided • Hypoglycemia events increased by 3.7 episodes in the first 28 days

Abbreviations: A1C, hemoglobin A_{1C}; ADR, adverse drug reactions; BMI, body mass index; GI, gastrointestinal; IU, international units; IV, intravenous; NR, not reported; T1DM, type 1 diabetes mellitus.

[a]All study groups were on insulin therapy; data are reported as mean values for the overall study.

[b]Results listed are insulin + exenatide relative to insulin therapy alone (placebo).

[c]Statistically significant ($P < 0.05$).

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To date, exenatide has safety and efficacy data for up to 18 months in T1DM, the longest of any GLP-1 agonist.[20] Supplementing insulin therapy with exenatide led to lowered total daily dose (TDD) of insulin, up to 24 IU/d, and delayed gastric emptying, with corresponding weight loss. The sample size was limited, with no more than 20 patients included in any single study. Comparator groups were not consistent and included other antidiabetic drugs (sitagliptin) and immunomodulator therapy (daclizumab).[16,20,23] Study design was also inconsistent across studies, with 1 study including a run-in phase that was not clearly described.[20] Prospective research has been limited to immediate release formulations of exenatide; however, a recent retrospective analysis shows promise for extended-release formulations.[23] Prospective investigations with extended-release exenatide are under way, currently targeting adult patients with established T1DM.[25]

Liraglutide

Liraglutide, the second approved GLP-1 agonist, is a once-daily preparation with a half-life of 11 to 15 hours.[6] This results in continuous stimulation of the GLP-1 receptor, compared with twice-daily exenatide, which only results in intermittent exposure.[6] Liraglutide is the most widely studied GLP-1 agonist in adult T1DM patients, as an add-on therapy to insulin. Six clinical trials were identified, and a summary of available clinical data is outlined in Table 2.[8,26-30] Results of the 3 placebo-controlled trials are listed in terms of liraglutide plus insulin relative to insulin therapy alone (placebo).[26-28] All studies involving liraglutide were done in adult patients. Despite the limited number of patients and varying study durations in the clinical trials, results are relatively consistent across studies. Patients in the studies tended to be younger (<50 years old) in age, without any residual β-cell function, and many patients were on insulin pumps and underwent continuous glucose monitoring during the study period. The studies contained a mix of patients who were above A1C goal and those who were at goal; however, most studies included patients who were not at glycemic targets. Similarly, the studies were a mix of normal-weight and overweight patients, although normal weight predominated.

In regard to glycemic control, studies consistently showed an approximate 0.2% to 0.5% A1C lowering when liraglutide was added on to insulin therapy. In trials without a control group, this result was always statistically significant.[8,29,30] Conversely, in placebo-controlled trials, there was no significant difference in A1C lowering.[26-28] Additionally, plasma glucose decreased by roughly 20 mg/dL when liraglutide was added to insulin. This effect was not statistically significant when the studies contained a comparator group. The nonsignificant difference in glycemic control in studies when compared with insulin alone can likely be explained by insulin regimens being titrated toward desired goals.

A similar effect was observed among the trials in regard to TDD of insulin. TDD of insulin was reported differently among studies, including international units (IU)/d, IU/kg/d, or as a percentage reduction. In all trials, the reduction of TDD of insulin was statistically significant. The overall effect was approximately 4 to 5 IU/d, 0.1 to 0.2 IU/kg/d, or 20%. Part of this observed reduction may be explained by patients' weight loss during the study period. Overall, addition of liraglutide exhibited a modest, but significant, reduction of TDD of insulin in the studies identified.

Other effects reported include weight loss and GI ADRs. All 6 trials reported effects of liraglutide on body weight.[8,26-30] Liraglutide produced a statistically significant reduction in body weight, averaging 2.3 to 6.8 kg over a 4- to 24-week period, respectively. This effect was seen regardless of baseline body weight or BMI of the study population; however, it was more pronounced in the trials that included overweight patients with T1DM.[26,30] It appears that liraglutide produces a modest reduction in body weight, which may or may not be a desired effect depending on the patient's baseline weight. GI ADRs were frequently reported in clinical trials. Nausea was the most common GI ADR, ranging from 11% to 100%.[8,26-30] In studies with a control group, GI ADRs were more common in the liraglutide group, which may present a potential barrier in clinical practice. Liraglutide was initiated at 0.6 mg subcutaneously once daily and titrated up to 1.2 or 1.8 mg once daily in all trials to lessen the risk of GI ADRs. Incidence of hypoglycemia either did not differ or was observed significantly less often compared with insulin alone or compared with a time period prior to initiation of liraglutide.[8,26-30] Drop-out rates as a result of ADRs were similar across all trials, and the difference was not statistically significant when compared with placebo.[26,27]

A recently published, double-blinded, randomized, placebo-controlled trial, the Lira-1 study, recruited 100 participants with uncontrolled T1DM (A1C > 8%) who were overweight (BMI > 25 kg/m^2).[26] This is the largest clinical trial of GLP-1 agonists in T1DM to date and warrants targeted discussion. The primary outcome of A1C lowering at 24 weeks was nonsignificant, with an absolute reduction of 0.5% from baseline and an additional lowering of 0.2% as compared with placebo ($P = 0.18$). Additionally, a decrease of TDD was not significant when adjusted for decrease in weight ($P = 0.1162$). Body weight, on the other hand, was significantly reduced by 6.8 kg as compared with placebo at 24 weeks ($P = 0.01$). Patients in the liraglutide group reported significantly less perceived hypoglycemia episodes than those in the placebo group, though there was no difference in rates of hypoglycemia during the 6-day continuous glucose monitoring periods at 0, 12, and 23 weeks.[26]

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Table 2. Summary of Studies of Liraglutide in Patients With T1DM.[a]

Author(s)	Study Design and Inclusion Criteria	Baseline Characteristics	Number of patients	Study duration	Change in A1C	Change in Plasma Glucose	Change in Insulin Dose	Change in Weight or BMI	Comments
Dejgaard et al[26,b]	• Double blind • Randomized • Placebo controlled • Liraglutide vs placebo Inclusion criteria • >18 Years of age • BMI >25 kg/m^2 • A1C >8% • Diagnosis for >1 year	• Age 48 years • Duration of disease 22.5 years • A1C 8.7% ± 0.7% • BMI 30 kg/m^2	100	24 weeks	• −0.5% liraglutide • −0.3% placebo • −0.2% difference	Similar between groups	• −11.2 IU/d[c] liraglutide vs placebo • −0.1 IU/kg/d liraglutide vs placebo	• −5.9 kg liraglutide • 0.2 kg placebo • −6.8 kg[c] difference in weight	• Liraglutide 0.6 mg once daily titrated to 1.2 mg at week 1 and 1.8 mg at week 2, as tolerated • More GI ADRs in liraglutide • Nausea 90% • Vomiting 14% • 8% Dropout in liraglutide • Hypoglycemia events: ○ Liraglutide: 1.3/patient ○ Placebo: 1.8/patient
Frandsen et al[27,b]	• Double blind • Randomized • Placebo controlled • Liraglutide vs placebo Inclusion criteria • 18-70 years of age • BMI 18-28 kg/m^2 • A1C ≥8% • No β-cell function • Caucasian descent • Diagnosed age 5-40 years	• Age 38 years • Duration of disease 19 years • A1C 8.8% ± 0.2% • BMI 23 kg/m^2	40	12 Weeks	• −0.6% liraglutide • −0.5% placebo • −0.1% difference	Similar between groups	• Bolus: −4 IU/d[c,d] liraglutide vs placebo • Basal: −0.1 IU/d liraglutide vs placebo	• −3.1 kg liraglutide • 1.1 kg placebo • −4.0 kg[c] difference in weight	• Liraglutide 0.6 mg once daily titrated to 1.2 mg at week 1, as tolerated • More GI ADRs in liraglutide • Nausea 65% • Vomiting 10% • 10% Dropout in liraglutide • Hypoglycemia events per patient-day: ○ Liraglutide: 0.37/patient ○ Placebo: 0.42/patient
Kielgast et al[28,b]	• Unblinded • Randomized • Placebo controlled • Liraglutide vs placebo Inclusion criteria • 18-50 years of age • BMI 18-27 kg/m^2 • A1C ≤8.5% • Caucasian descent • Diagnosed age 5-40 years	• Age 32 years • Duration of disease not specified • A1C 7.1% • BMI 24 kg/m^2	29	4 Weeks	• −0.26 to −0.47% liraglutide • −0.18% placebo • −0.2% difference	Similar between groups	• −0.1 To −0.2 IU/kg/d[c] liraglutide vs placebo	• −2.3 kg liraglutide • 0.2 kg placebo • −2.1 kg[c] difference in weight	• Liraglutide 0.6 mg once daily titrated to 1.2 mg at week 1, as tolerated • More GI ADRs in liraglutide • Nausea 95% • Vomiting 11% • Drop-out rates not specified • Hypoglycemia similar

(continued)

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Table 2. (continued)

Author(s)	Study Design and Inclusion Criteria	Baseline Characteristics	Number of patients	Study duration	Change in A1C	Change in Plasma Glucose	Change in Insulin Dose	Change in Weight or BMI	Comments
Varanasi et al[29]	• Unblinded • No comparator Inclusion criteria • On insulin with CGM	• Age 40 years • Duration of disease 24 years • A1C 6.6% ± 0.5% • BMI 24 kg/m^2	14	24 Weeks	−0.4%[c] from baseline	−20 mg/dL (Fasting)[c] from baseline	−0.18 IU/kg/d[c] from baseline	−4.5 kg[c] from baseline	• Liraglutide 0.6 mg once daily titrated to 1.2 mg at week 1, and 1.8 mg at week 2, as tolerated • Nausea, constipation, headache 14% • Hypoglycemia: 2% of time during CGM
Harrison et al[8]	• Retrospective • No comparator Inclusion criteria • Follow-up visit more than 4 weeks after GLP-1 initiated	• Age 37 years • Duration of disease 17 years • A1C 7.4% ± 0.7% • BMI 26 kg/m^2	11	20 Weeks	• −0.4% at 10 weeks[c] from baseline • −0.8% at 20 weeks[c] from baseline	−23 mg/dL[c] from baseline	−19.2%[c] from baseline	−3 kg[c] from baseline	• Liraglutide 0.6 mg once daily titrated to a maximum of 1.8 mg over a mean of 7.5 weeks • Nausea 100% • Hypoglycemia similar ○ 5.8% at 10 weeks ○ 7.4% at 20 weeks
Kuhadiya et al[30]	• Retrospective • No comparator Inclusion criteria • None specified	• Age 48 years • Duration of disease not specified • A1C 7.89% ± 0.13% • BMI 33 kg/m^2	27	24 Weeks	−0.4%[c] from baseline	−21 mg/dL[c] (4 Weeks) from baseline	−0.1 IU/kg/d[c] from baseline	−4.6 kg[c] from baseline	• Liraglutide 0.6 mg once daily titrated to 1.2 mg at week 2, and 1.8 mg at week 3, as tolerated • Nausea 40% • Hypoglycemia episodes: ○ Before: 6/month ○ After: 4/month

Abbreviations: A1C, hemoglobin A_{1C}; ADR, adverse drug reaction; BMI, body mass index; CGM, continuous glucose monitoring; GI, gastrointestinal; IU, international units.
[a]All study groups were on insulin therapy; data are reported as mean values for the overall study.
[b]Results listed relative to insulin therapy alone (placebo).
[c]Statistically significant ($P < 0.05$).
[d]Bolus insulin only.

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Although the trials included a limited number of patients overall, the effects of liraglutide were seen consistently among studies. Liraglutide, when added to insulin, produces a modest reduction in A1C and reduces plasma glucose by about 20 mg/dL. In addition, it reduces TDD of insulin and body weight. However, liraglutide may increase the incidence of GI ADRs. It may be beneficial as add-on therapy in patients with uncontrolled T1DM (above A1C goal) in whom weight reduction is desired (ie, overweight or obese patients). A randomized clinical trial to further investigate the use of liraglutide in overweight and obese patients treated with insulin pumps is currently ongoing.[31]

Comparison to Pramlintide

As discussed earlier, the only noninsulin agent currently approved for T1DM is pramlintide. Only 1 study has been published comparing pramlintide to a GLP-1 agonist, exenatide, in T1DM.[21] This was a single-day, proof-of-concept study. In comparison to insulin monotherapy, exenatide significantly reduced postprandial plasma glucose and glucagon secretion, whereas pramlintide did not. More patients in the exenatide group experienced nausea, with 1 patient experiencing vomiting that was resolved by administration of ondansetron. Limitations to this study include small sample size (10 patients completed the trial) and limited duration. The authors did not reveal the frequency of hypoglycemia in either group.[21]

Discussion

The use of GLP-1 agonists has been studied in patients on aggressive insulin regimens in both newly diagnosed and established T1DM. Prospective trials are limited in number, and sample sizes are small in all studies. Additionally, 1 study with liraglutide was only 4 weeks long, making it difficult to draw conclusions regarding A1C lowering based on this study alone.[28] However, all other studies included in the analysis were 10 weeks or more in duration. As a whole, A1C lowering with GLP-1 agonists has been modest—up to a maximum of 0.6%.[23] Though all trials showed a trend toward lower A1C with addition of a GLP-1 agonist, results were not statistically significant in trials with comparators for any agent.

Comparison of Available Agents

Liraglutide and exenatide have the most robust findings of available noninsulin therapies to support use in T1DM. Specifically, liraglutide has the most published data. A total of 221 total patients participated in liraglutide trials, though a single study contained 100 of those patients.[26] Conversely, exenatide has the most data for long-term use in T1DM, with 1 trial extending for 18 months[20]; however, the total number of patients enrolled among studies was 49, significantly less than for liraglutide. Dosing was inconsistent in exenatide studies, and more frequent dosing is required with the immediate-release formulation as compared with liraglutide. Results remained relatively consistent among trials, with a trend toward lower A1C seen with both liraglutide and exenatide. The additional benefit of weight loss may offset the lack of A1C lowering when compared with titrated insulin therapy. It is difficult to draw conclusions for albiglutide and dulaglutide because clinical trials utilizing these agents have yet to be published.

Considerations for Use

GLP-1 agonists have a low risk of hypoglycemia that is perhaps decreased when compared with insulin monotherapy, likely because of a decrease in TDD of insulin. This is also a potential advantage over pramlintide, which has been associated with significantly more hypoglycemic episodes when compared with insulin monotherapy in clinical trials, although this could have been a result of a study protocol that did not allow for insulin adjustment.[10] Weight-lowering effects could be advantageous in overweight or obese individuals and may contribute to the decrease in TDD of insulin observed in trials. The Lira-1 trial, which included overweight or obese patients, demonstrated a weight loss of 6.8 kg with liraglutide over insulin monotherapy at 24 weeks, which was a 6.4% decrease from baseline body weight.[26] Because patients experienced weight loss regardless of baseline weight in clinical trials, GLP-1 agonists should not be used in patients with low to normal BMIs.

Products vary widely in reconstitution procedures, storage requirements, and dosing schedules. Adding a GLP-1 agonist will increase the total number of injections, which is a potential barrier for compliance. For patients who are concerned about additional injections, once-weekly dosing schedules could be advantageous; however, the longer-acting GLP-1 agonists have not been prospectively studied in the setting of T1DM. Nonetheless, overall injection burden with GLP-1 agonists is less when compared with pramlintide, which is administered prior to all major meals. Cost is a limiting factor and should be discussed with the patient prior to starting therapy. The average wholesale prices of exenatide and liraglutide for a 30-day supply are $694.32 and $831.06, respectively.[32,33]

Controversial safety concerns have led to a boxed warning regarding the development of thyroid C-cell tumors, especially in patients with a personal or family history of specific thyroid tumors.[34-36] There is additional concern for pancreatitis identified in postmarketing reports.[37,38] GI adverse effects—namely nausea, vomiting, and diarrhea—were nearly ubiquitous in clinical trials.[8,16,20,23,26-30] Titrating doses per manufacturer recommendations should reduce these effects, but some

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patients may find the nausea to be intolerable. Other common adverse effects include injection site reactions and small, but significant, increases in heart rate.[39]

Special Populations

For patients with severe renal impairment (creatinine clearance <30 mL/min), exenatide is not recommended. There have been postmarketing reports of acute kidney injury, sometimes requiring hemodialysis, with exenatide.[40,41] Use of liraglutide in patients with moderate renal dysfunction and end-stage renal disease (ESRD) has been studied in patients with type 2 diabetes mellitus.[42,43] Both groups were more susceptible to GI adverse effects than those with normal renal function.[42,43] Dose titration of liraglutide should be done with caution in patients with renal dysfunction, and reduced treatment doses may be required.[42,43] No studies investigating use of GLP-1 agonists have been completed in T1DM patients with renal dysfunction.

To date, only exenatide has been studied in pediatric patients with T1DM[17]; 8 patients 15 to 18 years old participated in a 3-part study. Participants had baseline insulin requirements captured over 5 hours following a standard carbohydrate load. For the remaining 2 parts, participants received single doses of exenatide 1.25 and 2.5 μg in addition to exogenous insulin therapy with an identical carbohydrate load. Each exenatide dose was separated by 3 weeks. During the 5-hour study period, both doses of exenatide demonstrated immediate glucose reduction and statistically significant decreases in postprandial hyperglycemia and glucose AUC. Because of the limited study duration, questions remain regarding the long-term safety and efficacy in pediatric patients.[17]

Future Directions

The impact of GLP-1 agonists on the long-term complications of T1DM, including cardiovascular events, has not been studied. Prospective trials for use in renal impairment and pediatric patients, as well as utilizing long-acting formulations, are needed. Albiglutide, a long-acting, once-weekly GLP-1 agonist, is currently under investigation in T1DM.[44] Additionally, studies addressing cost-effectiveness and quality of life would be beneficial in helping elucidate the role of these agents in therapy.

Conclusion

As a whole, GLP-1 agonists are safe and potentially effective as add-on therapy to insulin in select T1DM patient populations—namely, those who are overweight or obese and not at glycemic goals despite aggressive insulin therapy. GI ADRs are relatively common with these agents, and slow titration using manufacturer guidelines should be utilized to lessen risk of nausea. At the current time, liraglutide has the strongest evidence for use, as demonstrated by total number of patients studied and consistency of dosing and results in clinical trials, and would be the agent of choice for use in T1DM at this time. Further studies on long-term effects of GLP-1 agonists on A1C lowering and related complications of T1DM would be advantageous in directing further use of these agents outside of their weight-lowering and insulin-sparing effects.

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