Glucagon-like Peptide-1 Receptor Agonist Treatment in Type 1 Diabetes: A Review of Current Evidence and Rationale for Use

Michael A. Tsoukas, MD, FRCPC

About the Author

Dr. Michael Tsoukas is an Associate Professor of Medicine, Division of Endocrinology at the McGill University Health Centre and Clinician Investigator of the Research Institute of McGill and Hygea Medical Clinic. He completed his residency training at Tuft's University and subsequently trained in Endocrinology at McGill University. He later pursued a post-graduate research fellowship in diabetes and obesity at Harvard University (Beth Israel Deaconess Medical Center), with a focus on GLP-1 receptor pharmacotherapy, brain signaling, and enterohormone treatments. Further training involved pathophysiological regulation of novel molecules such as SGLT-2 inhibitors and GLP-1 receptor agonists important in energy homeostasis, diabetes, and obesity.

Affiliations

Division of Endocrinology, McGill University Health Centre

Introduction

Type 1 diabetes (T1D) is characterized by a progressive decline of insulin production due to a marked destruction of pancreatic β cells. Intensive insulin therapy is the pillar of T1D management. More recently, continuous glucose monitoring devices, closed-loop systems (CLS) and smarter connected insulin pen systems have all significantly helped individuals to improve glycemic control. However, despite these advances, more than three-quarters of the adult T1D population does not achieve recommended glycemic targets.[1] In addition, aggressive insulin intensification potentiates weight gain and the risk of recurrent hypoglycemic events. Recent significant increase in rates of obesity has also led to a sharp increase in T1D patients who concurrently have adiposity-based chronic disease, increasing their insulin resistance and predisposition for cardiovascular events.[2] While insulin will remain the basis of T1D management, there is an unmet need for individualized adjunctive therapeutic approaches focusing on the prevention of diabetic complications in addition to glycemic control. One such adjunctive therapy currently being explored in T1D are the glucagon-like peptide-1 receptor agonists (GLP-1RAs), a popular and robust approach in Type 2 diabetes (T2D) to mimic the natural endogenous GLP-1 incretin. This brief review will focus on the rationale and existing evidence for the use of GLP-1RAs in the management of T1D.

Background and Rationale

GLP-1RAs are well recognized for exerting multifaceted effects through activation of the widely dispersed GLP-1 receptor.[3] Data has shown predominant expression in the pancreatic islet cells, hypothalamus area of the central nervous system, and gastrointestinal (GI) tract.[4] This class of medication, commercially available since 2005, has been rigorously studied in the T2D population. In most cardiovascular outcome trials for T2D, GLP-1RAs have demonstrated profound reductions in major adverse cardiovascular events in atherosclerotic disease, all of which were independent of glycemic improvement.[4] In sub-group analyses, renal protective effects were also likely linked to reductions in albuminuria,[5] and certain GLP-1 mimetics have demonstrated improvements in non-alcoholic steatohepatitis, with reductions in liver enzymes and hepatic lipid accumulation.[6] Additionally, GLP-1RAs are routinely used in the pharmacotherapy of obesity due to their positive effects on the satiety

and food perception centres of the hypothalamus, and the slowing of gastric emptying.[7]

With the wealth of evidence of GLP-1RA in T2D and obesity management, the logical approach would be the use of these agents in T1D patient subgroups. Indeed, off-label use as adjunctive therapy to insulin is becoming increasingly common in practice. However, what are the potential beneficial mechanisms in a T1D population, and are there any evidence-based studies to support their use.

Potential Beneficial Properties for T1D

The complete benefits of GLP-1RAs in T1D are not fully elucidated; as a result, controversy exists over their off-label use. However, four main properties of GLP-1RAs have been proposed as having potential beneficial action in T1D (**Figure 1**).

1. Weight Loss Properties

Contrary to established perceptions, obesity is equally prevalent in the T1D population as it is in the general population.[8] Weight loss in T1D subgroups improves insulin resistance and can lower the total daily requirements of insulin. Two studies using liraglutide have been conducted in patients with T1D and overweight/obesity. One six-month trial demonstrated significant weight loss with thermogenesis and increased lipid oxidation as the main weight loss mechanisms.[9] Another study in a T1D cohort showed significant placebo-adjusted benefits with liraglutide on prolonged satiety, as well as decreased food consumption and food desire following standardized meal tests.[10] Insulin requirements are decreased with weight loss and, by association, cardiometabolic disease progression is potentially mitigated.

2. Suppression of Glucagon-mediated Gluconeogenesis

GLP-1RAs may offer glycemic improvement via their anti-glucagon property. The glucagonostatic effect exerted is important for potential efficacy in T1D given that the insulinotropic effect is less pertinent to individuals with inadequate β-cell function.[3] Two studies have demonstrated continued endogenous GLP-1 secretion following the ingestion of mixed meals in individuals with T1D, irrespective of residual β-cell function.[11,12] One probable pathway includes paracrine inhibition of α-cells, whereby GLP-1 receptor activation of δ-cells of the pancreas stimulates somatostatin release, which inhibits glucagon-stimulated increase in gluconeogenesis.[13] In doing so, improved glycemic control in target range with less hyperglycemia range, blood glucoses can potentially be achieved.

3. Inhibition of Gastric Emptying

Gastric emptying is a complex phenomenon in the T1D population, complicated by neuropathy, enterohormonal changes, modified neurotransmitters, and glycemia levels.[3] In some cases, gastric motility may be increased causing diarrhea, while in most cases motility is slowed causing gastroparesis. Authors of the EDIC trial observed altered gastric emptying in 47% of participants, most of which was asymptomatic.[14] This suggests that nearly half of the T1D population is affected by underlying GI autonomic neuropathy. These alterations affect post-prandial glycemia levels significantly. In T1D adolescents and young adults, one study (n=8) demonstrated delayed gastric emptying five hours postprandially with short-acting exenatide that was associated with reduced glucose excursions.[15] A longer trial in overweight people without diabetes

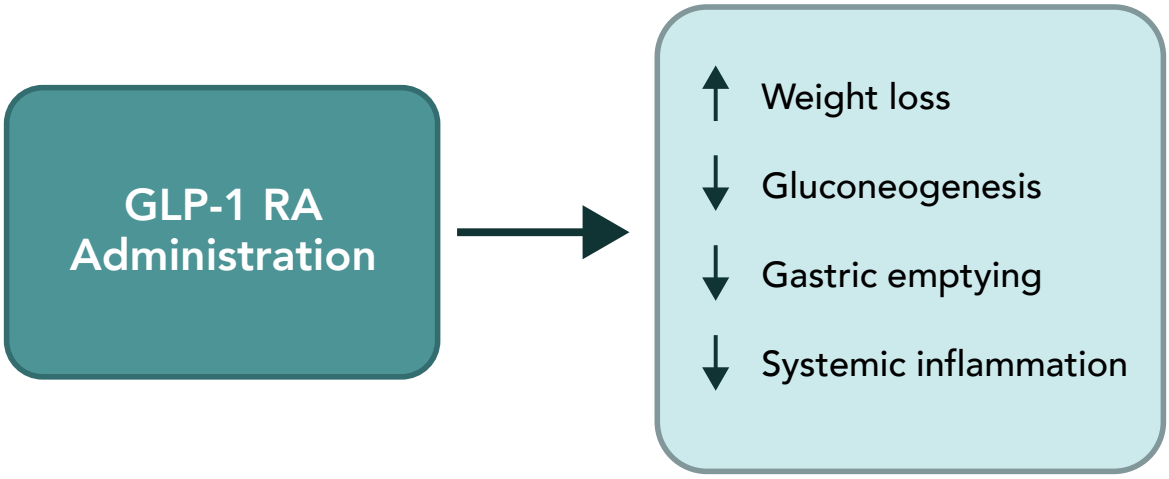

Figure 1. Potential beneficial mechanisms of GLP-1RAs in T1D; *courtesy of Dr. Michael A. Tsoukas.*

reported a marked reduction in gastric emptying and postprandial glycemia after eight weeks with once-weekly exenatide 2.0 mg.[16]

It is also known that acute changes in blood glucose concentration, both hyperglycemia and hypoglycemia, have a marked, reversible effect on gut motility.[17] Overall, the benefits of GLP-1RAs reflect improved post-prandial glycemic levels with less risk of glucose excursions. Finally, GI mechanoreceptors in gastroparesis relay a message of satiety to the brain, thereby also decreasing food intake which may, in turn, indirectly improve glycemic control.

4. Anti-inflammatory Properties

Systemic inflammation is well known to increase insulin resistance.[1819] Liraglutide treatment is reported to decrease levels of pro-inflammatory TNF-α and IL-6 as well as macrophage activation while increasing levels of the anti-inflammatory adiponectin.[20] Furthermore, high-sensitivity CRP and serum markers of endothelial function such as P-selectin, ICAM and VCAM have also been shown to improve with GLP-1 RA administration.[21] GLP-1RAs thus help with reducing inflammation which may have beneficial effects on glycemic control and atherosclerotic disease prevention.

T1D Clinical Studies Using GLP-1RAs

The majority of clinical studies examining GLP-1RAs in T1D have focused on examining the safety and efficacy of short-acting agents such as twice-daily exenatide and daily liraglutide, each as adjunct-to-insulin therapy for T1D in both multiple daily injection (MDI) and continuous subcutaneous insulin infusion (CSII) cohorts.[3]

Published evidence consistently demonstrates weight loss, decreases in total daily insulin requirements, and modest improvements in glycemic control with the use of GLP-1RAs. Of note, data on the more recent commercially available GLP-1RAs, such as semaglutide and dulaglutide, and dual co-agonists such as tirzepatide, have not yet been published; however, studies are in progress.

a) Exenatide

The use of short-acting exenatide in two clinical trials did not yield any significant HbA1c-lowering benefit nor improved time in range (3.9–10.0 mmol/L) vs placebo.[22,23] In the MAGIC trial, the authors noted an insignificant change in HbA1c from baseline, suggesting no clear HbA1c-lowering benefit with exenatide.[23] Furthermore, C-peptide levels did not differ among groups. However, a significant reduction in body weight and total daily insulin needs with no increased risk of hypoglycemia was reported.[22]

b) Liraglutide

i. MDI-only cohorts

The most robust MDI-only trial intervention was the Lira-1 trial which investigated daily liraglutide 1.8 mg in an overweight, sub-optimally controlled T1D population.[24] The primary outcome revealed a significant decrease of 0.4% HbA1c early in the study, while, by the end-of-trial period, no statistical significance was demonstrated. Interestingly, there was a marked reduction in body weight and total daily insulin requirements in the liraglutide-treated group, but no changes in glycemic variability or blood pressure. Furthermore, there were fewer reported hypoglycemic events vs placebo.

ii. Mixed MDI and CSII cohorts

Several clinical studies have examined liraglutide in a mixed MDI and CSII population. In a two-way trial using liraglutide in T1D adults with overweight and obesity, the authors reported a non-significant treatment effect of 0.29% HbA1c reduction from baseline.[9] Of note, the intervention group experienced a significant within-group HbA1c reduction of 0.41%, suggesting an overall underpowered intervention. Other findings included reductions in body weight which uniquely were further characterized by dual-energy X-ray absorptiometry and magnetic resonance imaging of total body fat mass and distribution. At present, the ADJUNCT program comprises the two largest double-blind, randomized, placebo-controlled trials to have investigated once-daily liraglutide as adjunct-to-insulin therapy for T1D.[25,26] Three different doses of daily liraglutide were analyzed in the ADJUNCT ONE study in 1,389 T1D adults over one year.[25] There was a dose-dependent decrease in HbA1c with all three doses, as well as a significant reduction in total body weight. The subsequent ADJUNCT TWO study examined liraglutide treatment tested on top of individualized capped insulin dosing in 831 participants. Compared to ADJUNCT ONE, the findings showed a similar body weight reduction but a more meaningful dose-dependent HbA1c-lowering effect with a decrease of 0.35% for the 1.8 mg dose.[26]

iii. CSII and Closed-Loop system studies

Only limited preliminary studies have explored the possibility of combining GLP-1 RA with Closed-Loop System (CLS) technology as an adjunctive hormonal therapy. Using a randomized, double-blind parallel

Author (year) and n sample size	Insulin Administration Modality	Comparator/ Intervention	Primary Endpoints	Additional Outcomes and Comments
Johansen et al.[23] (2020) n=105	MDI only cohort	Exenatide 10 µg tid vs placebo	HbA1c -0.1% (P=0.36)	• No run-in period • Double-blinded study
Dejgaard et al.[24] (2016) n=100	MDI only cohort	Liraglutide 1.8 mg daily vs placebo	HbA1c -0.2% (P=0.18)	• Reduced bolus insulin intake 5.8 units/day (P=0.023) • Double-blinded
Mathieu et al.[25] (2016) n=1389	2.5% MDI 27.5% CSII	Liraglutide 0.6 mg vs 1.2 mg vs 1.8 mg daily vs placebo	HbA1c -0.2% (P=0.0019)	• Increased hypogylcemic events • Significant body weight loss (-2.2 kg to -4.9 kg) • Decrease in total daily insulin requirements: 9 units/day (P<0.01)
Ahren et al.[26] (2016) n=831	74.5% MDI 25.5% CSII	Liraglutide 0.6 mg vs 1.2 mg vs 1.8 mg daily with use of capped insulin vs placebo	HbA1c -0.35% (P<0.0001)	• Significant body weight loss (-2.3 kg to -4.9 kg)
Ghanim et al.[9] (2020) n=64	31% MDI 69% CSII	Liraglutide 1.8 mg daily vs placebo	HbA1c -0.29% (P=0.1)	• Decrease in bolus insulin requirements: 4.0 units/day (P=0.021) • Significant body weight loss 4.2 kg (P=0.002)
Dejgaard et al.[27] (2020) n=44	CSII only cohort	Liraglutide 1.8 mg daily vs placebo	HbA1c -0.7% (P<0.001)	• Decrease in total insulin requirements: 7.7 units/day (P=0.008) • No run-in period

Table 1. Summary of selected trials examining GLP-1RAs in T1D. MDI: multiple daily injection insulin; CSII: continuous subcutaneous insulin infusion; HbA1c: glycated hemoglobin; *courtesy of Dr. Michael A. Tsoukas.*

design, the Lira Pump trial is the only trial to date that has examined liraglutide administration in a population of CSII-treated, overweight T1D adults.[27] Change from baseline in HbA1c after 26 weeks was the most profound statistically-significant, placebo-corrected reduction (-0.6% as early as 13 weeks, and -0.7% by end of study). Furthermore, significant improvements were noted for body weight loss, glucose time in target ranges and total daily insulin requirements. The study was limited by a smaller sample size of (n=44); however a robust study design including adjustments for insulin sensitivity factors, carbohydrate ratios and basal rate modification was performed at the onset of treatment.

Table 1 shows a brief summary of findings from selected major interventional clinical trials.

Conclusion

While off-label use of GLP-1RAs as adjunctive therapy to insulin in T1D is becoming more common in practice, evidence of HbA1c reduction supporting its use is limited. Nonetheless, the current clinical evidence base does consistently demonstrate:

a) an indisputable weight loss effect, improving underlying adiposopathy of T1D, especially in view of the growing population with overweight/obesity; b) decreases in insulin requirements/total daily dosing for most study populations; and c) glycemic benefits in HbA1c lowering of approximately 0.5% reduction, although the improvement observed with placebo often diluted the treatment effect.[3] The proposed beneficial mechanistic effects of GLP-1RAs on gluconeogenesis suppression, delayed gastric emptying and anti-inflammation, also favour their use. Furthermore, clinical trials have examined the safety and efficacy of short-acting agents such as twice-daily exenatide and daily liraglutide as adjunct-to-insulin therapy for T1D in both MDI and CSII cohorts. However, no published data currently exists for more novel GLP-1RAs and dual co-agonists available commercially and used regularly in practice for T2DM patients.

As global diabetes treatment strategies increasingly prioritize cardiometabolic disease prevention and weight loss, the high value of these molecules would be of potential benefit in T1D patients with overweight/obesity and those with high-risk/pre-existing cardiovascular and renal disease. However, dedicated cardiovascular outcomes studies in T1D would bridge the knowledge gap and potentially reveal therapeutic potential. Other T1D subgroups, such as patients with advanced insulin delivery devices experiencing labile blood sugars and high rates of hypoglycemia may benefit from these molecules as well. Despite off-label use in practice, further work is needed to redirect GLP-1RAs as an indicated adjunctive therapy for an individualized treatment approach for T1D.

Acknowledgement:

We gratefully acknowledge Alessandra Kobayati, PhD for her substantial original conceptualization and detailed review analysis of the topic. These invaluable contributions were instrumental in the creation of this article.

Correspondence

Dr. Michael A. Tsoukas
Email: michael.tsoukas@mail.mcgill.ca

Financial Disclosures

Speaker honoraria: AstraZeneca, Boehringer-Ingelheim, Eli Lilly, Janssen, and NovoNordisk.

References

1. Foster NC, Beck RW, Miller KM, , et al. State of type 1 diabetes management and outcomes from the T1D exchange in 2016–2018. Diabetes Technol Ther. 2019 Jan 18;21(2):66-72.
2. Vergès B. Cardiovascular disease in type 1 diabetes: A review of epidemiological data and underlying mechanisms. Diabetes Metab. 2020 Nov;46(6):442-449.
3. Kobayati A, Haidar A, Tsoukas MA. Glucagon-like peptide-1 receptor agonists as adjunctive treatment for type 1 diabetes: Renewed opportunities through tailored approaches? Diabetes Obes Metab. 2022;24:769-787.
4. Marx N, Hussain M, Lehrke M, Verma S, Sattar N. GLP-1 receptor agonist for the reduction of atherosclerotic cardiovascular risk in patients with type 2 diabetes. Circulation 2022;146:1882-1894.
5. Mosenzon O, Schechter M, Leibowitz G. Kidney outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes. Adv Chronic Kidney Dis. 2021;28:347–60.
6. Nevola R, Epifani R, Imbriani S, et al. GLP-1 receptor agonists in non-alcoholic fatty liver disease: current evidence and future perspectives. In J Mol Sci 2023;24(2):1703
7. Drucker DJ. GLP-1 physiology informs the pharmacotherapy of obesity. Molecular Metabolism 2027;57:101351
8. Fellinger P, Fuchs D, Wolf P, et al. Overweight and obesity in type 1 diabetes equal those of the general population. Wien Klin Wochenschr. 2019 Feb;131(3-4):55-60.
9. Ghanim H, Batra M, Green K, et al. Liraglutide treatment in overweight and obese patients with type 1 diabetes: A 26-week randomized controlled trial; mechanisms of weight loss. Diabetes Obes Metab. 2020 Oct 1;22(10):17421752.
10. Dubé M-C, D'Amours M, Weisnagel SJ. Effect of liraglutide on food consumption, appetite sensations and eating behaviours in overweight people with type 1 diabetes. Diabetes Obes Metab. 2020;22(8):1417-1424.
11. Vilsbøll T, Krarup T, Sonne J, et al. Incretin secretion in relation to meal size and body weight in healthy subjects and people with type 1 and type 2 diabetes mellitus. J Clin Endocrinol Metab. 2003 Jun 1;88(6):2706-2713.
12. Kielgast U, Holst JJ, Madsbad S. Antidiabetic actions of endogenous and exogenous GLP-1 in type 1 diabetic patients with and without residual ?-cell function. Diabetes. 2011 May;60(5):1599-1607.
13. Drucker DJ. Mechanisms of action and therapeutic application of glucagon-like peptide-1. Cell Metab. 2018 Apr 3;27(4):740-756.
14. Bharucha AE, Batey-Schaefer B, Cleary PA, et al. Delayed gastric emptying is associated with early and long-term hyperglycemia in type 1 diabetes mellitus. Gastroenterology. 2015 May 14;149(2):330-339.
15. Raman VS, Mason KJ, Rodriguez LM, Hassan K, et al. The role of adjunctive exenatide therapy in pediatric type 1 diabetes. Diabetes Care. 2010 Jun;33(6):1294-1296.
16. Jones KL, Huynh LQ, Hatzinikolas S, et al. Exenatide once weekly slows gastric emptying of solids and liquids in healthy, overweight people at steady-state concentrations. Diabetes Obes Metab. 2020;22(5):788-797.
17. Horowitz M, Rayner CK, Marathe CS, et al. Glucagon-like peptide-1 receptor agonists and the appropriate measurement of gastric emptying. Diabetes Obes Metab. 2020;22(12):2504-2506.
18. Tsalamandris S, Antonopoulos AS, Oikonomou E, et al. The role of inflammation in diabetes: current concepts and future perspectives. Eur Cardiol. 2019 Apr;14(1):50-59.
19. Polyzos S, Kountouras J, Tsoukas MA. Circulating homocysteine in nonalcoholic fatty liver disease. Eur J Intern Med. 2015 Mar;26(2):152-153.
20. Hogan AE, Gaoatswe G, Lynch L, et al. Glucagon-like peptide 1 analogue therapy directly modulates innate immune-mediated inflammation in individuals with type 2 diabetes mellitus. Diabetologia 2014;57(4):781-784.
21. Tardio V, Kellett S, Bidal-St-Aubin M, et al. Effects of incretin therapy and bariatric surgery on inflammation in obese patients. Obes Med. 2019;13:13-20.
22. Rother KI, Spain LM, Wesley RA, et al. Effects of exenatide alone and in combination with daclizumab on beta-cell function in long-standing type 1 diabetes. Diabetes Care. 2009 Dec;32(12):2251-2257.
23. 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 Apr 1;8(4):313-324.
24. Dejgaard TF, Frandsen CS, Hansen TS, et al. Efficacy and safety of liraglutide for overweight adult patients with type 1 diabetes and insufficient glycaemic control (Lira-1): a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol. 2016 Mar;4(3):221-232.
25. 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 Oct 1;39(10):1702-1710.
26. 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 Oct 1;39(10):1693-1701.
27. Dejgaard TF, Schmidt S, Frandsen CS, et al. Liraglutide reduces hyperglycaemia and body weight in overweight, dysregulated insulin-pump-treated patients with type 1 diabetes: The Lira Pump trial-a randomized, double-blinded, placebo-controlled trial. Diabetes Obes Metab. 2020 Apr;22(4):492-500.