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Review Article

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Role of Additional GLP-1 Receptor Agonist to Insulin Regimen in Type 1 Diabetes among Pediatric Age

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ABSTRACT

Type 1 diabetes represents a major risk for future morbidity among the pediatric population, including macrovascular and microvascular complications. Additionally, strict glycemic control might require intensified insulin therapy, leading to increased risk of hypoglycemia and further weight gain, which adversely increased insulin resistance and subsequent cardiovascular risk. Multiple trials of additional antihyperglycemic agents to insulin have been made, aiming for better glycemic control and reduced the risk of cardiovascular disease. This literature review aims to address the effectiveness and safety of additional GLP-1 to insulin therapy on type 1 diabetes among the pediatric population. The main factors contributing to glycemic control include weight loss, decreased insulin requirement and subsequently decreased risk of hypoglycemia, and reduction of HbA1c. We searched in the PubMed database for relevant articles to the article. We used the following Mesh words: GLP-1 receptor agonist, type 1 diabetes, pediatric, and HbA1c. GLP-1 receptor agonist seems to have promising beneficial effects on type 1 diabetes. The addition of these agents resulted in a significant reduction in body weight and insulin requirement, leading to decreased insulin resistance and subsequent reduction in future cardiovascular risk. Nonetheless, HbA1c reduction remains an area of controversy, and further randomized multi-central clinical trials are warranted to establish the efficacy of GLP-1 receptor agonists on glycemic control (HbA1c reduction).

Key words: *GLP-1 receptor agonist, Type 1 diabetes mellitus, Insulin, Management*

INTRODUCTION

Diabetes type one (T1D) is an illness that is chronic and it is mediated by anti-self-immune response seen as pancreatic β-cells damage, leading to chronic hypoinsulinemia followed by hyperglycemia [1, 2]. T1D in childhood is considered among the frequent metabolic diseases that developed from both genetic susceptibility

and environment-related determinants, affecting all body organs [1, 3]. Additionally, in the state of hypoinsulinemia, the glucagon level started to increase during fasting and post-prandial period. Both disorders lead to increased blood sugar levels, which may need increased glycemic regulation to reduce the risk of diabetic ketoacidosis development; nevertheless, intensified insulin therapy also increases the risk of hypoglycemia [2]. Further, based on the Diabetes Control and Complications Trial (DCCT), the rates of severe hypoglycemia grew exponentially as HbA1c achieved optimal levels [4].

Another unwanted consequence is insulin-induced weight gain, which worsens insulin resistance and leads to increment in insulin dose, blood pressure, and LDL-cholesterol levels [4]. Most T1D patients developed metabolic syndrome, leading to an increased risk of vascular complications and mortality. The currently available insulin alternate therapy does not stimulate normal insulin physiology, as insulin is passively delivered to the peripheral tissues to achieve normal insulin levels in the liver. Notably, the metabolic abnormalities, such as weight gain, exaggerated post-prandial hyperglucagonemia, and accelerated gastric emptying resulted from insufficient correction of the metabolic dysfunction related to T1D or the complications of peripheral hyperinsulinemia caused by insulin replacement therapy [5].

Although various insulin products and regimens are produced on the market nowadays, blood glucose variability in T1D remains a challenge [2]. The idea of insulin adjunct therapy for T1D has arisen in reaction to the challenges according to the unanimity that 1) addition of oral preparation to insulin therapy might help to improve glycemic control; 2) This additional therapy is preferred to have an independent effect on glucose-lowering to decrease complications of diabetes. Hence, the optimal adjuvant care must achieve a reduction in requirements of insulin dose, lower Hb1c without causing an increase in the risk of hypoglycemia, reduce weight, and directly reduce the risk of cardiovascular disease (CVD), and enhance life expectancy [2, 4]. Adjuvant care can assist in regulating the antagonistic metabolic effects of T1D and the therapy of insulin, at least in some T1D individuals [5].

T1D affects almost 3 million people in the United States [6], of whom 200,000 approximately are children. The prevalence of T1D between 2001 and 2009 has increased among pediatric patients in the United States and worldwide. When children are diagnosed with T1D in the first year of life, the majority among them are more likely to be predisposed to chronic hyperglycemia for over 2 decades as they grow. By the time they reach 55 years, almost 35% of type 1 diabetic patients will die from cardiovascular disease in comparison with to only eight percent of non-diabetic males and 4% non-diabetic females. Moreover, the high risk of CVD started in preadolescence, and 14-45% of pediatric T1D have more than two CVD predisposing factors [6].

Therefore, adequate T1D management would not only be good glycemic regulation but also with controlling insulin resistance, β-cell function, and CVD, which is growing exponentially in this population [1]. Over the last two decades, new data concerning the pathophysiology and hormonal regulations of T1D resulted in the development of modern diabetes medication agents, including (GLP-1 RAs) therapy. The adjunct therapy with one of the newly developed anti glycemic agents (such as GLP-1 RAs) might provide better glycemic control and counteract the complications of insulin replacement therapy, such as weight gain and increased insulin resistance, which adversely increased the risk of CVD [1]. presently, the United States Food and Drug Administration (FDA) has appropriated only pramlintide for adjunct T1D insulin therapy, yet only 2% of adults reported taking pramlintide. However, no other noninsulin antihyperglycemic adjunct therapy has been approved for treating T1D, even though metformin has been consumed by 6six percent of type diabetes exchange contributors, which makes it the most popular adjunct type 1 diabetes therapy [7].

RESULTS AND DISCUSSION

GLP-1 RAs mechanism of action and normal physiology

The glucagon-like peptide was initially discovered as an insulinotropic hormone secreted by the intestinal mucosa by L-cells and produced in the gut after meal assimilation, which promotes insulin secretion and reduces glucagon secretion when blood glucose increased [8-10]. GLP-1 hormone exerts its effect via the receptor of GLP-1, which goes to the member of 7 transmembrane domain receptors [10]. It gained attention due to its function in the physiology of glucose metabolism as an incretin [8].

The expression of glucagon-like peptidase 1 receptors comes in various cardiovascular tissues and cell types at the mRNA and protein levels. Physiologically, glucagon-like peptide facilitates the function of the endothelium, increases ventricular contractility, and induces cytoprotective and metabolic actions on blood vessels and cardiomyocytes [8]. GLP-1 RAs are synthetic analogs or mimetics of the native human GLP-1 with better pharmacokinetics effect and more stable pharmacodynamic profiles, resulting in a more significant effect than the

endogenous GLP-1 [9]. Multiple pharmaceutical companies have developed GLP-1 RAs; for instance, six drugs have been approved to treat diabetes and/or obesity [11].

GLP-1 RAs were the most common medication used in the treatment of (T2D) over the last 14 years, either standard drug or adjuvants to metformin or insulin. It is proved that GLP-1 RAs promote decreased gastric emptying rates, improving the organ dysfunctions of diabetes [12]. Gastric-emptying represents an essential detector of glucose levels after a meal. The degree of gastric excretion directly correlates with postprandial blood glucose levels, which is the subsequent reason for the glucose assimilation from simple carbohydrates from the proximity small colon. Postprandial glucose levels can reach thirty-four percent higher in healthy individuals with rapid stomach emptiness. In T1D people and even healthy individuals, critical increased glucose levels diminish stomach excretion of solids and liquids nutrients compared to euglycemia. Eventually, individuals with long-standing diabetes will develop gastroparesis [12].

In addition, glucagon-like peptide 1 Rna's causes the glucose-dependent release of insulin and hinders glucagon release in the islet cells with decreased risk of hypoglycemia. Importantly, GLP-1 RAs reduce postprandial glycemic excursions through insulin augmentation and glucagon secretion inhibition from alpha cells [13]. Some studies have reported GLP-1R expression within the alpha cells subset, which supports the possibility that GLP-1R might directly mediate the suppression of glucagon secretion [13].

Moreover, GLP-1 RAs reduce islet inflammation and prevent or delay the evolution of experimental β-cell failure in a non-obese diabetic mouse model of autoimmune diabetes, which promotes exploration of potential therapeutic GLP-1 RAs in the management of T1D. Additionally, GLP-1 RAs enhance the survival of human islet *ex vivo* or following transplantation to animals; nonetheless, their efficacy in preserving β-cells functionality as adjuvant therapy in T1D humans remain unproven. Although preclinical studies were linking GLP-1 RAs to the reduction of β-cells inflammation and enhanced its function and survival, demonstrating clinical evidence for GLP-1 RAs in the transplanted islet setting has not been anticipated [13].

Besides, sustained GLP-1 RAs use resulted in less oral intake and subsequent weight loss, which improves insulin sensitivity in animals and humans. Additionally, the current proof indicates that GLP-1 RAs independently stimulate insulin, inhibit glucagon secretion, and do not directly influence insulin signaling or glucose uptake in the liver, muscles, or adipose tissues [13]. Beyond glycemic control, preclinical investigations have revealed a valuable consequence of GLP-1 RAs on vessels of blood, BP, lipid profile, heart failure, kidneys, liver, and inflammatory cascades [14].

Normally, Glucagon-like peptide 1 Rna's may be categorized based on their length of action; Short-acting GLP-1 RAs (exenatide and lixisenatide), which promote short-lived receptor activation and are associated with reduced postprandial glucose reductions through slowing stomach emptying and causing diminished glucose transport to the duodenum; The long-acting GLP-1 RAs (Liraglutide or exenatide ER, dulaglutide, semaglutide) agents have a longer half-life and the activation of the ongoing receptor is delivered at a preferred dose [9].

Evidence-based medicine

Short-acting GLP-1 RAs

In comparison to insulin monotherapy, eight pediatric individuals with T1D and few or no C-peptide response to meals, 2 doses of exenatide (1.25 and 2.5 μg) pre-meals. As a result, single doses of exenatide reduced glucose excursions over 300 min ($P<0.0001$) and slowed stomach emptying ($P<0.0004$) with no alteration of glucagon or C-peptide levels. However, two individuals experienced nausea with exenatide [15].

Although exenatide daily dose is thought to have some beneficial effect in T1D, two small studies have failed to prove beneficial exenatide effect on pancreatic β-cell function in long-standing or newly diagnosed T1D. The foremost literature was conducted on patients with long-standing T1D with a mean of twenty-one years of age and the study was an open-label crossover trial in 20 subjects. Exenatide has tittered gradually to 10 μg four times daily SC for 4 months duration. The study resulted in a decrease of the body weight by 4.1 kg and reduced the use of injected insulin with no β-cell function improvement (measured by plasma insulin levels) while having the glucose control at about HbA1c of 6.5%. Notably, exenatide does not affect fasting glucagon levels. The second study also investigated the efficacy of exenatide on pancreatic β-cells function, for which 18 individuals with newly diagnosed T1D were received exenatide titered gradually to 10 μg two times daily sc. Similarly, six patients who received exenatide in addition to insulin had no weight gain induced by insulin, decreased daily insulin dose, but did not have improved β-cell functionality (as measured by the plasma C-peptide levels) [16].

Furthermore, exenatide 0.03 μg/kg sc was given to eight T1D patients 15 min before an intermixed meal with acetaminophen (for stomach emptying assessment). A substantial reduction in blood glucose plasma level

excursions was reported in comparison to placebo in addition to a vast reduction of stomach emptying (assessed by time-averaged iAUC0-60 minutes for acetaminophen) in the exenatide group. Also, glucagon levels were significantly reduced with mean time-averaged iAUC0-120 min. All three findings (decreased postprandial glucose excursions, gastric emptying, and glucagon levels) are in line with the result in patients with T2D [17].

Another study was performed for eight T1D adolescents by mixed-meal tests supplemented with 13C-glucose to compare adjunct exenatide 1.25 and 2.5 μg sc with insulin monotherapy. Although the daily insulin dose was decreased by twenty percent when exenatide was added, both 1.25 and 2.5 μg doses of exenatide resulted in a major decrease in the blood glucose plasma level excursions compared with insulin monotherapy [17]. Besides, gastric emptying (measured by 13CO2 in-breath) was significantly delayed with both 1.25 and 2.5 μg exenatide compared with insulin monotherapy; nonetheless, this study did not report a significant difference in glucagon levels with the exenatide group when compared to the insulin monotherapy group [17].

In a network meta-analyses conducted by Kim *et al*., 23 RCTs were selected and compared insulin monotherapy vs. insulin in addition to GLP-1 RAs and other antihyperglycemic agents. The addition of exenatide to insulin therapy was found to decrease total body weight by 5.1 kg. More impressively, weight loss was due to the use of exenatide where it decreases the body fat, but not in lean tissue mass [18].

Long-acting GLP-1 RAs

Liraglutide 1.8 mg single dose following night fasting proves to cause a reduction in ketoacidosis (acetoacetate and β-hydroxybutyrate) and suppression of glucagon in 26 C-peptide negative T1D patients. Like exenatide, liraglutide had successfully reduced body weight and daily required insulin dose in T1D subjects with and without β-cell function and have no effect on HbA1c. In addition, 14 T1D patients with plasma C-peptide levels of <0.10 nmol/l and positive GAD antibodies, liraglutide 0.6 mg/daily sc for a week resulted in decreased plasma glucose levels, time spent with high or low levels of glucose, and the basal and bolus insulin dosage. Eight patients continued treatment for 24 weeks, for which HbA1c was decreased from 6.5% to 6.1% with decreased body weight by 4.5 Kg [16].

Another study selected T1D patients with positive or negative C-peptide levels and randomized to liraglutide 0.6 mg every day for the 1st week followed by 1.2 mg every day compared to placebo. During this four-week study, the HbA1c was not significantly reduced in the liraglutide group compared to the placebo group, the however total weight of the body was decreased by 2.3 kg, and the dosage of insulin was considerably decreased. It must be mentioned that most liraglutide-treated patients experienced gastrointestinal side effects initially but spontaneously subsided later [16].

Additionally, 100 overweight and poorly controlled T1D subjects were selected to take either liraglutide or saline solution plus an insulin regimen in a randomized, double-blind, placebo-controlled trial for twenty-four weeks. Liraglutide's initial dose was 0.6mg/daily sc, then 1.2 mg/daily for one week, and then 1.8 mg daily for another week. Likewise, the HbA1c level was not statistically different among the two groups. However, the liraglutide group had decreased hypoglycemic events, bolus and basal total insulin dose, and body weight with increased heart rate [19].

Most studies investigating liraglutide in T1D patients have reported conflicting HbA1c outcomes, showing no greater changes but rather a decrease between 0.4% and 0.9% (4.4 and 9.8 mmol/mol). Also, a significant reduction was reported in daily bolus insulin dose by 0% to 46% and 0% to 49% for basal insulin daily dose. Weight reduction was ranging between 3.6% to 6.6% compared with baseline have also been reported [17]. Further, liraglutide can decrease the frequency of prediabetes up to ninety-six percent in the SCALE trial. Groups with high weight and prediabetes who received three mg of liraglutide lost 8.4 kg over fifty-six weeks in comparison with 2.8 kg in the placebo subjects, with sixty-three percent of individuals having lost more than five percent and thirty-three percent have lost less than ten percent of their standard. It also suppresses plasma levels of ghrelin in T1D patients after overnight fasting, which is the period ghrelin levels tend to induce hunger sensation [20].

retrospective single literature has studied 11 T1D patients who received 2 mg exenatide once weekly, comparing glycemic control at baseline and three months later. HbA1c was reduced by 0.6% (6.6 mmol/mol) along with a 13% reduction in total daily insulin dose and a 3.7% reduction in body weight. Moreover, 11 T1D individuals were selected for weekly 2mg exenatide over three months; As a result, they experienced a reduction in HbA1c by 0.6%, reduced body weight by 3.7%, and reduced total insulin dosage by 13% of individuals [16]. It is worth mentioning that 5/11 participants have discontinued treatment within six months due to side effects; 4 of them were secondary to bothersome nodule formation [17].

On the other hand, a retrospective analysis was performed for normal weight, C-peptide positive T1D patients who received additional long-acting GLP-1 RAs to their insulin regimen. The control group received either liraglutide 0.6 mg sc daily for a week, then 1.2 mg daily for the second week, then 1.8 mg consequently for 12 weeks, OR dulaglutide 0.75 mg weekly OR 1.5mg weekly for 12 weeks. One of the liraglutide groups stopped the treatment in the first week due to intolerance to nausea. Surprisingly, the GLP-1 RAs group reported a reduction in HbA1c from 10.74± 0.96% to 7.4± 0.58% ($p<0.01$); body weight from 71±2.0 kg to 69±2 kg ($p=0.06$) and body mass index (BMI) reduction from 23±1 to 22±1 ($p=0.04$). The insulin requirements were reduced by 64% from 33±6 to 11±5 units ($p<0.01$). Interestingly, 5/10 patients who tolerated GLP-1 RAs therapy did not require any insulin. In addition, C-peptide levels were significantly increased, and this increment was observed equally in insulin-free patients and patients who had decreased insulin needs [21].

CONCLUSION

Although GLP-1 RAs provide a great addition to the regulation of glycemia and CVD in diabetes mellitus type 2, the function they serve in type 1 diabetes remains unclear. However, several trials have proven its significantly beneficial effect on body weight and insulin requirement without causing high danger of decreased blood sugar. The ability of glycemic regulation in terms of HbA1c reduction and improving pancreatic beta cells has been proven in animal models, but not upon clinical trials. Despite initial promising effect, no consensus yet on the benefit of GLP-1 RAs in glycemia regulation among type 1 diabetic subjects, and further randomized multi-central clinical trials would be warranted.

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REFERENCES

1. Naciu AM, Pozzilli P. Novel blood glucose lowering therapies for managing type 1 diabetes in paediatric patients. Expert Opin Pharmacother. 2018;19(4):355-64. doi:10.1080/14656566.2018.1441288.
2. Frandsen CS, Dejgaard TF, Madsbad S, Holst JJ. Non-insulin pharmacological therapies for treating type 1 diabetes. Expert Opin Pharmacother. 2018;19(9):947-60. doi:10.1080/14656566.2018.1483339.
3. Lunder M, Janić M, Japelj M, Juretič A, Janež A, Šabovič M. Empagliflozin on top of metformin treatment improves arterial function in patients with type 1 diabetes mellitus. Cardiovasc Diabetol. 2018;17(1):153. doi:10.1186/s12933-018-0797-6.
4. Livingstone R, Boyle JG, Petrie JR, REMOVAL Study Team. A new perspective on metformin therapy in type 1 diabetes. Diabetologia. 2017;60(9):1594-600. doi:10.1007/s00125-017-4364-6.
5. Lebovitz HE. Adjunct therapy for type 1 diabetes mellitus. Nat Rev Endocrinol. 2010;6(6):326-34. doi:10.1038/nrendo.2010.49.
6. Gourgari E, Dabelea D, Rother K. Modifiable risk factors for cardiovascular disease in children with type 1 diabetes: can early intervention prevent future cardiovascular events? Curr Diabetes Rep. 2017;17(12). doi:10.1007/s11892-017-0968-y
7. Bode BW, Garg SK. The emerging role of adjunctive noninsulin antihyperglycemic therapy in the management of type 1 diabetes. Endocr Pract. 2016;22(2):220-30. doi:10.4158/EP15869.RA.
8. Nauck MA, Meier JJ, Cavender MA, Abd El Aziz M, Drucker DJ. Cardiovascular actions and clinical outcomes with glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. Circulation. 2017;136(9):849-70.
9. Cornell S. A review of GLP-1 receptor agonists in type 2 diabetes: A focus on the mechanism of action of once-weekly agents. J Clin Pharm Ther. 2020;45(S1):17-27.
10. Dalsgaard NB, Brønden A, Vilsbøll T, Knop FK. Cardiovascular safety and benefits of GLP-1 receptor agonists. Expert Opin Drug Saf. 2017;16(3):351-63. doi:10.1080/14740338.2017.1281246.

11. Taylor SI. GLP-1 receptor agonists: differentiation within the class. Lancet Diabetes Endocrinol. 2018;6(2):83-5.
12. Fenske RJ, Kimple ME. Targeting dysfunctional beta-cell signaling for the potential treatment of type 1 diabetes mellitus. Exp Biol Med. 2018;243(6):586-91.
13. Drucker DJ. Mechanisms of action and therapeutic application of glucagon-like peptide-1. Cell Metabol. 2018;27(4):740-56. doi:10.1016/j.cmet.2018.03.001
14. Drucker DJ. The ascending GLP-1 road from clinical safety to reduction of cardiovascular complications. Diabetes. 2018;67(9):1710-9. doi:10.2337/dbi18-0008
15. Raman VS, Mason KJ, Rodriguez LM, Hassan K, Yu X, Bomgaars L, et al. The role of adjunctive exenatide therapy in pediatric type 1 diabetes. Diabetes Care. 2010;33(6):1294-6. doi:10.2337/dc09-1959
16. Doggrell SA. Do glucagon-like peptide-1 receptor (GLP-1R) agonists have potential as adjuncts in the treatment of type 1 diabetes? Expert Opin Pharmacother. 2018;19(15):1655-61. doi:10.1080/14656566.2018.1519547.
17. Albèr A, Brønden A, Knop FK. Short-acting glucagon-like peptide-1 receptor agonists as add-on to insulin therapy in type 1 diabetes: A review. Diabetes Obes Metab. 2017;19(7):915-25. doi:10.1111/dom.12911
18. Kim YJ, Hwang SD, Lim S. Effects of sodium-glucose cotransporter inhibitor/glucagon-like peptide-1 receptor agonist add-on to insulin therapy on glucose homeostasis and body weight in patients with type 1 diabetes: A network meta-analysis. Front Endocrinol (Lausanne). 2020;11:553. doi:10.3389/fendo.2020.00553.
19. Dejgaard TF, Frandsen CS, Hansen TS, Almdal T, Urhammer S, Pedersen-Bjergaard U, et al. Efficacy and safety of liraglutide for overweight adult patients with type 1 diabetes and insufficient glycaemic control (Lira-1): a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol. 2016;4(3):221-32. doi:10.1016/S2213-8587(15)00436-2.
20. Dandona P, Ghanim H, Chaudhuri A. Incretins: Beyond type 2 diabetes. Diabetes Obes Metab. 2018;20 Suppl 1:59-67. doi:10.1111/dom.13153.
21. Kuhadiya ND, Prohaska B, Ghanim H, Dandona P. Addition of glucagon-like peptide-1 receptor agonist therapy to insulin in C-peptide-positive patients with type 1 diabetes. Diabetes Obes Metab. 2019;21(4):1054-7. doi:10.1111/dom.13609.