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Glucagon-Like Peptide-1 Receptor Agonists as A Possible Intervention to Delay The Onset of Type 1 Diabetes: A New Horizon

GLP-1 RA for T1DM

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Abstract

Type 1 diabetes (T1D) arises from an autoimmune response that damages pancreatic β-cells, causing insulin deficiency. The only treatment for this disease is intensive insulin therapy, which requires multiple daily injections or continuous subcutaneous insulin infusion with frequent monitoring of blood glucose. Despite advances in closed-loop hybrid pumps and continuous glucose monitoring devices, 75% of subjects with T1D maintain an A1c above 7%. Moreover, there is a significant disease burden and emotional burden associated with the diagnosis and management of T1D. Our latest study, published in the New England Journal of Medicine (NEJM), demonstrates that Semaglutide, a GLP-1 receptor agonist, enables patients newly diagnosed with T1DM to sustain glucose control for 12 months without requiring insulin therapy. In all these subjects, fasting c-peptide was 0.6 and increased following Semaglutide. This finding, combined with the evidence that individuals with T1D retain 50% of their insulin secretory capacity intact when diagnosed, implies that initiating Semaglutide earlier in individuals at risk of T1D could potentially delay the onset of T1D and the need for insulin treatment in this population. Teplizumab is the only FDA-approved treatment shown to delay the onset of T1D by 32 months. There is an urgent need to develop future therapies that can further delay the onset of T1D. The debate on T1D risk screening continues, especially for those without a family history, with the benefits of early detection being weighed against the financial and emotional implications. Our research suggests that early screening of T1D combined with interventions like GLP-1 RA could significantly delay the onset of T1D in subjects at high risk of this disease. This approach offers a promising avenue for improving the quality of life for T1D patients and needs to be investigated in prospective randomized controlled clinical trials.

Key Words: Type 1 Diabetes; Semaglutide; GLP-1 Receptor Agonists; Insulin Therapy; Autoimmune Response; Blood Glucose Monitoring; β-Cell Preservation; Early Screening; Teplizumab; Randomized Controlled Trials

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Core Tip: New research suggests a novel approach to treating type 1 diabetes (T1D) by using glucagon-like peptide-1 receptor agonists (GLP-1 RA), specifically semaglutide, to significantly improve blood glucose control and potentially slow the progression of the disease in newly diagnosed patients. This strategy, which leads to less insulin dependence and better metabolic markers, could change the way T1D is managed in a big way. At the same time, the study supports early T1D risk screening, especially in groups with high risk, so that early interventions can be made, evaluating the benefits against the possible emotional and financial effects. This dual approach shows that there are bright futures for improving the lives of patients with T1D.

INTRODUCTION

Type 1 diabetes (T1D) is a chronic disease that has long posed therapeutic challenges. This ailment, rooted in the autoimmune destruction of pancreatic β-cells by T-cells, results in a severe decline of β-cell activity and an eventual complete lack of insulin [1-3]. The only treatment for this disease is intensive insulin therapy, which requires multiple daily injections or continuous subcutaneous insulin infusion with frequent monitoring of blood glucose. Despite advances in closed-loop hybrid pumps and continuous glucose monitoring devices, 75% of subjects with T1D maintain an A1c above 7%. Moreover, there is a significant disease burden and emotional burden associated with the diagnosis and management of T1D. Even with modern medical breakthroughs, many T1D sufferers still grapple with maintaining optimal blood sugar levels. Intensive insulin therapies, though advantageous, can sometimes lead to hypoglycemia, presenting a therapeutic conundrum [4, 5].

THE POTENTIAL OF GLP-1 RA

Researchers observed promising results in a study examining the potential benefits of GLP-1RAs for T1D patients with positive C-peptide levels. Our recent exploration, as published in the New England Journal of Medicine (NEJM), sheds light on a hopeful path. We delved into the impact of semaglutide, a GLP-1 RA, within three months on ten newly diagnosed T1D patients. These individuals began with an average glycated hemoglobin of 11.7±2.1% and a fasting C-peptide of 0.65±0.33 ng/mL, all undergoing standard insulin treatments [6]. Introducing semaglutide and dietary modifications led to the discontinuation of prandial insulin for all participants within a quarter year. Impressively, by half a year, seven had ceased using basal insulin. A year later, the average glycated hemoglobin decreased to 5.7±0.4%, while the fasting C-peptide surged to an average of 1.05±0.40 ng/mL. Continuous glucose assessments revealed an 89±3% time-in-range [6].

In a 12-week randomized placebo-controlled clinical trial, researchers investigated the impact of adding liraglutide, a GLP-1 receptor agonist, to the insulin regimen of patients with T1D. The study included 72 participants, with a division between those receiving liraglutide and those on a placebo. The results demonstrated that patients who received higher doses of liraglutide (1.2 mg and 1.8 mg) experienced a significant weekly reduction in average blood glucose levels and a notable reduction in HbA1c in the 1.2 mg group. Furthermore, glycemic variability decreased in the 1.2 mg group, and there was a marked weight loss in the groups receiving the two higher doses of liraglutide [7].

The study entailed a retrospective analysis of 11 normal-weight T1D patients treated with GLP-1RA in conjunction with insulin. Notable findings included a significant reduction in HbA1c levels from 10.74 ± 0.96% to 7.4 ± 0.58% after 12 ± 1 wk of GLP-1RA therapy. Additionally, there was a noteworthy decline in total insulin dose by 64% and a minor weight reduction. Importantly, C-peptide concentrations, indicative of endogenous insulin production, surged significantly, enhancing pancreatic beta-cell

function. Remarkably, 50% of the study participants achieved freedom from insulin therapy while on GLP-1RA therapy over the study duration [8].

In the ADJUNCT ONE Treat-To-Target Randomized Trial, the addition of liraglutide to insulin therapy in type 1 diabetes was assessed over 52 wk in 1,398 adults. Participants were administered liraglutide (at concentrations of 1.8, 1.2, or 0.6 mg) or a placebo in conjunction with insulin. The study found that HbA1c levels reduced by 0.34–0.54% from an initial 8.2%, insulin doses diminished more with liraglutide compared to the placebo, and there was a notable weight reduction in the liraglutide cohorts. However, liraglutide recipients experienced elevated rates of symptomatic hypoglycemia, and the 1.8 mg liraglutide group saw a significant rise in hyperglycemia with ketosis. Consequently, despite its benefits, the increased adverse events suggest caution in the broader clinical application of liraglutide for T1D [9].

IMMUNOTHERAPY: A SPECTRUM OF OUTCOMES

Various immunotherapies, including Teplizumab, Otelixizumab, and Abatacept, have displayed promise but are not without complications. For example, Otelixizumab users have reported headaches, fevers, and rashes, typical reactions to anti-CD3 antibodies [10, 11]. Teplizumab has been linked to skin issues, leukopenia, respiratory infections, and lymphopenia [12-14]. Most issues with Abatacept were related to the infusion process [15, 16].

THE DEBATE ON SCREENING

The question of T1D risk screening remains contentious, especially for those without familial ties to the condition. A study by Ziegler in Bavaria showcased the viability of screening children during standard pediatric appointments, pinpointing 280 children with multiple autoantibodies, 43 of whom later developed T1D [5, 17]. The means of early identification and action are clear. Yet, the financial and emotional tolls of screening warrant consideration. Nevertheless, research indicates that psychosocial screenings can pinpoint vulnerable families [18]. Moreover, regions with a high prevalence of

diabetic ketoacidosis (DKA) could economically justify presymptomatic T1D screenings [19].

CONCLUSION

Our findings suggest that early T1D screening, combined with interventions such as GLP-1 RA, could significantly impede the progression of the disease, especially in high-risk obese individuals. Pediatric professionals should exercise heightened caution with patients prone to T1D due to genetic or autoimmune factors. As we venture further into this realm, the prospect of an enhanced quality of life for T1D patients becomes increasingly tangible.

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