

# World Journal of *Diabetes*

*World J Diabetes* 2024 February 15; 15(2): 129-307



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The primary aim of *World Journal of Diabetes (WJD, World J Diabetes)* is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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**INDEXING/ABSTRACTING**

The *WJD* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJD* as 4.2; IF without journal self cites: 4.1; 5-year IF: 4.5; Journal Citation Indicator: 0.69; Ranking: 51 among 145 journals in endocrinology and metabolism; and Quartile category: Q2.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: *Yu-Xi Chen*; Production Department Director: *Xu Guo*; Editorial Office Director: *Jia-Ru Fan*.

**NAME OF JOURNAL**

*World Journal of Diabetes*

**ISSN**

ISSN 1948-9358 (online)

**LAUNCH DATE**

June 15, 2010

**FREQUENCY**

Monthly

**EDITORS-IN-CHIEF**

Lu Cai, Md. Shahidul Islam, Michael Horowitz

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/1948-9358/editorialboard.htm>

**PUBLICATION DATE**

February 15, 2024

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<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>

## Glucagon-like peptide-1 receptor agonists as a possible intervention to delay the onset of type 1 diabetes: A new horizon

Mahmoud Nassar, Ajay Chaudhuri, Husam Ghanim, Paresh Dandona

**Specialty type:** Endocrinology and metabolism

**Provenance and peer review:**

Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0  
Grade B (Very good): B, B  
Grade C (Good): 0  
Grade D (Fair): 0  
Grade E (Poor): 0

**P-Reviewer:** Cai L, United States;  
Shalaby MN, Egypt

**Received:** November 3, 2023

**Peer-review started:** November 3, 2023

**First decision:** December 6, 2023

**Revised:** December 17, 2023

**Accepted:** January 16, 2024

**Article in press:** January 16, 2024

**Published online:** February 15, 2024



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### Abstract

Type 1 diabetes (T1D) is a chronic autoimmune condition that destroys insulin-producing beta cells in the pancreas, leading to insulin deficiency and hyperglycemia. The management of T1D primarily focuses on exogenous insulin replacement to control blood glucose levels. However, this approach does not address the underlying autoimmune process or prevent the progressive loss of beta cells. Recent research has explored the potential of glucagon-like peptide-1 receptor agonists (GLP-1RAs) as a novel intervention to modify the disease course and delay the onset of T1D. GLP-1RAs are medications initially developed for treating type 2 diabetes. They exert their effects by enhancing glucose-dependent insulin secretion, suppressing glucagon secretion, and slowing gastric emptying. Emerging evidence suggests that GLP-1RAs may also benefit the treatment of newly diagnosed patients with T1D. This article aims to highlight the potential of GLP-1RAs as an intervention to delay the onset of T1D, possibly through their potential immunomodulatory and anti-inflammatory effects and preservation of beta-cells. This article aims to explore the potential of shifting the paradigm of T1D management from reactive insulin replacement to proactive disease modification, which should open new avenues for preventing and treating T1D, improving the quality of life and long-term outcomes for individuals at risk of T1D.

**Key Words:** Type 1 diabetes; Semaglutide; Glucagon-like peptide-1 receptor agonists; Insulin therapy; Autoimmune response; Blood glucose monitoring; B-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, 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.

**Citation:** Nassar M, Chaudhuri A, Ghanim H, Dandona P. Glucagon-like peptide-1 receptor agonists as a possible intervention to delay the onset of type 1 diabetes: A new horizon. *World J Diabetes* 2024; 15(2): 133-136

**URL:** <https://www.wjgnet.com/1948-9358/full/v15/i2/133.htm>

**DOI:** <https://dx.doi.org/10.4239/wjd.v15.i2.133>

## INTRODUCTION

Type 1 diabetes (T1D) is a chronic disease that has long posed therapeutic challenges. This ailment, rooted in the autoimmune destruction of pancreatic  $\beta$ -cells by T-cells, results in a severe decline of  $\beta$ -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 GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS

Researchers observed promising results in a study examining the potential benefits of Glucagon-like peptide-1 receptor agonists (GLP-1RAs) for T1D patients with positive C-peptide levels. Our recent exploration, as published in the New England Journal of Medicine, sheds light on a hopeful path. We delved into the impact of semaglutide, a GLP-1RA, within three months on ten newly diagnosed T1D patients. These individuals began with an average glycated hemoglobin of  $11.7\% \pm 2.1\%$  and a fasting C-peptide of  $0.65\% \pm 0.33\%$  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  $5.7\% \pm 0.4\%$ , while the fasting C-peptide surged to an average of  $1.05 \pm 0.40$  ng/mL. Continuous glucose assessments revealed an  $89\% \pm 3\%$  time-in-range[6].

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  $10.74\% \pm 0.96\%$  to  $7.4\% \pm 0.58\%$  after  $12 \pm 1$  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[7].

In the Adjunct One Treat-To-Target Randomized Trial, the addition of liraglutide to insulin therapy in T1D was assessed over 52 wk in 1398 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[8].

## 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[9,10]. Teplizumab has been linked to skin issues, leukopenia, respiratory infections, and lymphopenia[11-13]. Most issues with Abatacept were related to the infusion process[14,15].

## 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 *et al*[5] in Bavaria showcased the viability of screening children during standard pediatric appointments, pinpointing 280 children with multiple autoantibodies, 43 of whom later developed T1D[5,16]. 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[17]. Moreover, regions with a high prevalence of diabetic ketoacidosis could economically justify presymptomatic T1D screenings[18,19]. The timing and approach to screening are debated, focusing on the balance between cost and comprehensive detection[18,20,21].

## CONCLUSION

Our findings suggest that early T1D screening, combined with interventions such as GLP-1RA, 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.

## FOOTNOTES

**Author contributions:** All authors have contributed equally to this work; All authors have read and approved the final manuscript.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

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**Country/Territory of origin:** United States

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**S-Editor:** Li L

**L-Editor:** A

**P-Editor:** Li L

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