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Peer Review of *World Journal of Diabetes*, Dimiter Avtanski, PhD, Director, Endocrine Research Laboratory, Friedman Diabetes Institute, Lenox Hill Hospital, New York, NY 10022, United States. davtanski@northwell.edu

AIMS AND SCOPE

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.

WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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EDITORIAL

Glucagon-like peptide-1 agonists: Role of the gut in hypoglycemia unawareness, and the rationale in type 1 diabetes

Hyder O Mirghani

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Abstract

Type 1 diabetes is increasing and the majority of patients have poor glycemic control. Although advanced technology and nanoparticle use have greatly enhanced insulin delivery and glucose monitoring, weight gain and hypoglycemia remain major challenges and a constant source of concern for patients with type 1 diabetes. Type 1 diabetes shares some pathophysiology with type 2 diabetes, and an overlap has been reported. The above observation created great interest in glucagon-like peptide-1 receptor agonists (GLP-1) as adjuvants for type 1 diabetes. Previous trials confirmed the positive influence of GLP-1 agonists on β cell function. However, hypoglycemia unawareness and dysregulated glucagon response have been previously reported in patients with recurrent hypoglycemia using GLP-1 agonists. Jin *et al* found that the source of glucagon dysregulation due to GLP-1 agonists resides in the gut. Plausible explanations could be gut nervous system dysregulation or gut microbiota disruption. This review evaluates the potential of GLP-1 agonists in managing type 1 diabetes, particularly focusing on their impact on glycemic control, weight management, and glucagon dysregulation. We provide a broader insight into the problem of type 1 diabetes mellitus management in the light of recent findings and provide future research directions.

Key Words: Glucagon-like peptide-1 receptor agonists; Glucagon response; Hypoglycemia unawareness; Gut; Type 1 diabetes

Core Tip: Poor glycemic control, nonadherence to insulin, vascular complications, and obesity remain major challenges in type 1 diabetes management. Glucagon-like peptide-1 receptor (GLP-1) agonists have been shown to address the above issues without significant hypoglycemia. The rationale for GLP-1 agonist use is based on the shared pathophysiology of type 1 and type 2 diabetes. The recent evidence of gut involvement in GLP-1 agonists induced hypoglycemia unawareness and glucagon dysregulation is of great concern and the emerging role of GLP-1 agonists in gut microbiota dysregulation and diversity could change diabetes management including type 1 diabetes. The use of GLP-1 agonists should be individualized.

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INTRODUCTION

Type 1 diabetes is increasingly diagnosed among children and adolescents, and glucagon-like peptide-1 receptor agonists (GLP-1) are increasingly used in patients with type 1 diabetes to address oxidative stress and proinflammation or for high body mass index[1,2].

At type 1 diabetes diagnosis, 60% of β cells are destroyed (insulitis and possible enteroviruses), 30% are in fetal dedifferentiation with synchronization changes, and the remaining 10% are stressed to secrete more insulin similar to type 2 diabetes. In addition, the predisposing factors for type 1 diabetes are similar to type 2 diabetes. Furthermore, mixed phenotypes with autoantibodies and insulin resistance have been observed, and 9.3% of patients with type 2 diabetes showed islet autoantibodies[3,4]. Therefore, diabetes mellitus is better viewed as a palette disease model where multiple defects can occur throughout the pathophysiological cascade resulting in different phenotypes.

RELEVANCE OF GLP-1 AGONISTS

The similarity between type 1 and type 2 diabetes paves the way for GLP-1 agonists as prophylaxis in type 1 diabetes to restore and prevent β cell damage[5]. Similarly, there is a strong rationale for the use of GLP-1 agonists among patients with type 1 diabetes due to glucose lowering independent of insulin secretion, weight reduction, and cardiac and renal protection.

CURRENT GAPS IN TREATMENT

Despite great advances in insulin therapy and delivery and glucose monitoring, the majority of patients with type 1 diabetes (80%) fail to achieve their glycemic target. In addition, the association between insulin use and weight gain and hypoglycemia decreases the patient's confidence in insulin therapy and nonadherence. Therefore, there is much interest in the potential role of GLP-1 agonists as adjuvant therapy in type 1 diabetes[6,7].

The action of GLP-1 agonists is complex (increase insulin secretion, decrease glucagon release, decrease appetite, and slow gastric emptying with a net effect of weight reduction and glycemic control)[8]. GLP-1 agonists were shown to decrease insulin dose, reduce body weight, and decrease glycated hemoglobin in patients with type 1 diabetes. The greatest benefit was observed in overweight patients with detectable C-peptide, and patients who were at risk of insulin-induced hypoglycemia. Importantly, GLP-1 agonists were well-tolerated with non-significant hypoglycemia, and the effects varied depending on the GLP-1 agonist used[9-11]. Another important effect is immunomodulation and the effects on regulatory T cells, as GLP-1 agonists activate the adenosine monophosphate kinase pathway. Therefore, it could play an important role in type 1 diabetes prevention and β cell preservation[12]. Interestingly, GLP-1 agonists also regulate/have negative effects on adenosine monophosphate kinase pathways explaining their negative effects on glucagon response[13].

β cell destruction is not unique for insulin loss, amylin is also deficient, and an interesting finding is the synergistic effects of pramlintide (an amylin analog) and semaglutide in weight reduction, glycemic control, and reduced insulin dose among patients with type 1 diabetes[14]. The overlap of GLP-1 agonists and amylin in the area postrema of the brain with the key energy-controlling areas (the central amygdala, nucleus tractus solitarius, hypothalamus) could explain these synergistic effects. In addition, parabrachial nucleus signaling reduces the food reward, decreases gastric emptying, and induces satiety[15]. Importantly, this review provides new insights into the role of gut microbiota and the need for personalized GLP-1 agonist therapy in type 1 diabetes.

GENERAL COMMENTS ON JIN ET AL'S SIGNIFICANT FINDINGS

Firstly, the authors included male C57BL/6J mice which is not the case in the real world and male-only mice might impact the findings. Type 1 diabetes is the only autoimmune disease with a male predominance as puberty decreases the incidence of type 1 diabetes in girls[16]. Gender differences are significant in diabetes research, and these differences in the incidence of type 1 diabetes are explained by hormonal factors and fluctuations in body weight. Pregnancy and menopause can unmask preexisting metabolic abnormalities including diabetes[17,18]. In addition, females are more likely to acquire the disease at a younger age and are more autoantibody (multiple antibodies) positive[19,20]. Furthermore, body mass index and body composition differ across genders[21]. Therefore, the course of the disease in males and females is not the same.

Secondly: The type of GLP-1 agonists was not stated in the study. GLP-1 agonists are produced from Gila monster venom or human GLP-1 active fragment, and they differ in potency, half-life, immunogenicity, and tolerability[22,23]. Therefore, in the study by Jin *et al*[24], important findings cannot be generalized to the whole class of GLP-1 agonists and new formulations are continuously being developed. Thirdly: Failure in the glucagonic response was not tested before the introduction of the GLP-1 agonist, and due to this a cause and effect is difficult to conclude. On the other hand, the findings are very significant to the field of diabetology and point to the role of the gastrointestinal tract in particular the interaction between the gut microbiota and GLP-1 agonists.

GLUCAGONOSTATIC POTENCY TO MEALS, STRESS, AND EXERCISE AMONG PATIENTS WITH DIABETES

The predisposition and β cell profile of type 1 and type 2 diabetes could be similar. However, glucagonostatic potency is different in patients with type 1 diabetes compared to type 2 diabetes and healthy controls. A randomized controlled trial examined the dose-responsive suppression of glucagon with GLP-1 agonists and glucose and showed that patients with type 1 diabetes were not sensitive to the glucagonostatic effects of glucose and GLP-1 agonists[23]. The above results imply that the response to various stimuli in type 1 diabetes is different to type 2 diabetes and normal individuals. The suppression of glucagon with glucose and GLP-1 agonists observed in type 2 diabetes and healthy subjects without diabetes is not found in type 1 diabetes indicating suboptimal effects.

Jin *et al*[24] touched on an important issue in diabetology and found that excessive intestinal GLP-1 is strongly associated with impaired counterregulatory responses to hypoglycemia, and overactivation of the sympathoadrenal reflex leads to sympathetic, adrenal, and glucagon counter-regulation during recurrent hypoglycemia[24]. The findings by Jin *et al*[24] support previous *in vivo* and human studies that showed an absent and irreversible glucagon response to hypoglycemia. In addition, responsiveness to other stimuli including lipids, proteins, and exercise was intact[25,26]. The association of glucagon unresponsiveness with β cell function and the duration of type 1 diabetes is controversial, as Siafarikas *et al*[27] found an association, while Sherr and colleagues[28] showed no association between glucagon responsiveness and residual β cells. The results of Jin *et al*[24] showed that failure of glucagon response can occur early in the course of type 1 diabetes. The mechanism underlying glucagon unresponsiveness in Jin *et al*[24] could be in the islets of Langerhans or the gastrointestinal tract. Similarly, Banarer *et al*[29] and Karimian *et al*[30] concluded that the action is paracrine and within the islets. The study by Jin *et al*[24] is unique in that it is the first to confirm Lund and colleagues[31] speculation of perhaps extra pancreatic glucagon (gut) based on their findings of 29-amino acid glucagon in the circulation of totally pancreatectomized patients.

The above findings of the gastrointestinal effects of GLP-1 agonists are important as previous studies showed that GLP-1 agonists decreased the motility index and shortened large bowel transit time with positive effects on the enteric nervous system[32].

AMINO ACID METABOLISM IN PATIENTS WITH TYPE 1 DIABETES

We are in the new era of diabetes as a comprehensive nutrition disorder involving glucose and amino acids. Ito *et al*[33] showed that dysregulated glucagon contributed significantly to postprandial hyperglycemia among patients with type 1 diabetes regardless of residual β-cell functions. A characteristic pattern of amino acids with reduced glutamate was shown among patients with type 1 diabetes in contrast to healthy controls and patients with type 2 diabetes, suggesting a crucial role of the remaining α cells in amino acid metabolism[34]. GLP-1 agonists increase β cell survival and increase insulin secretion among patients with type 2 diabetes and in the early stages of type 1 diabetes. An important factor is the suppression of inappropriate glucagon secretion by pancreatic α cells[9]. The majority of β cells are lost at the diagnosis of type 1 diabetes, unlike type 2 diabetes in which insulin resistance is predominant. Thus, GLP-1 agonists are appropriate in the early stages of type 1 diabetes, and when weight reduction is needed[35,36].

THE INTERACTION BETWEEN GLP-1 AGONISTS AND THE GUT MICROBIOTA

GLP-1 agonists exert a direct action (extra-receptor) on intraepithelial lymphocytes to regulate gut microbiota population and diversity[37]. In addition, gut microbiota was found to influence GLP-1 agonists secretion, rhythm, and function[38].

The above interaction was shown to suppress inflammation in the gut and other systems broadening the use of GLP-1 agonists to involve many conditions associated with type 1 and type 2 diabetes including colitis and metabolic-associated fatty liver disease.

The gut microbiota plays an important role in bile acid metabolism, gastrointestinal motility, short fatty acid synthesis, and intestinal permeability. Similarly, the activation of farnesoid X receptors in enteroendocrine cells by bile acids stimulates GLP-1 agonist secretion. The above cross-talk between GLP-1 agonists and the gut microbiota influence the rhythm and function of GLP-1 agonists, while GLP-1 antagonists shape the disrupted gut microbiome in patients with diabetes[38,39]. The interaction between GLP-1 agonists and gut microbiota could partially explain the difference in GLP-1 agonist's effects on insulin resistance and blood glucose.

PRACTICAL SOLUTIONS

Selecting the appropriate GLP-1 agonist and monitoring for specific side effects to avoid hypoglycemia is vital. Semaglutide introduced early in the course of type 1 diabetes was found to increase the C-peptide, reduce insulin requirement, and decrease glycated hemoglobin. Impressively, all the studied patients ceased meal insulin, and the majority ceased basal insulin after three and six months of semaglutide therapy, respectively[40]. The above hopeful path contrasts the therapeutic conundrum observed with liraglutide as the patients presented with both hypoglycemia and hyperglycemia during the 52-week therapy period[41]. Nassar *et al*[42] highlighted the importance of early risk stratification, prevention, and early GLP-1 agonist therapy to improve quality of life and prevent vascular complications.

CONCLUSION

The hopeful path of GLP-1 agonist use among patients with type 1 diabetes needs to be viewed in the light of the significant gut-induced glucagon dysregulation, and hypoglycemia unawareness. The selective involvement of the glucagon pathway and intact reaction to protein and exercise among patients with type 1 diabetes in contrast to type 2 diabetes is important and further research is needed. The role of GLP-1 agonists in gut nervous system regulation raises an important issue particularly in patients with peripheral and autonomic neuropathy. The use of GLP-1 agonists should be individualized and further research is needed on the optimal dosing regimens, long-term effects, and understanding individual variations in response to GLP-1 agonists including tachyphylaxis and hypoglycemia. Such research could allow dose adjustments to reinforce the benefits and minimize unwanted adverse effects.

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