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[Perspective] Exploring the Synergistic Approach of Dual GLP-1 Agonist with Degludec Basal Insulin for Type 1 Diabetes Treatment for Albumin-InsulinProducing Cells Expression

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Abstract

This manuscript explores various aspects related to the use of dual GLP-1 agonist with degludec basal insulin as a potential treatment approach for type 1 diabetes. The background section highlights the destruction of beta cells in type 1 diabetes and the emergence of GLP-1 agonists as a promising option for managing obesity and type 2 diabetes. The authors discuss a retrospective analysis of the efficacy of semaglutide, a GLP-1 agonist, in patients with newly diagnosed type 1 diabetes. The results show the elimination of prandial and basal insulin, increased C-peptide levels, and improved glycemic control. However, the study's retrospective nature and lack of a control group emphasize the need for larger prospective trials. The interpretation section highlights the potential of GLP-1 agonists in protecting residual beta cells, stimulating cell proliferation, and reprogramming liver cells into insulin-producing cells. Moreover, modifying GLP-1 agonists with albumin ligands shows promise in extending their half-life and enhancing their anti-diabetic effects. The perspective section provides a comprehensive overview of the synergistic approach, considering the pharmacokinetic properties of degludec, the plasticity of adult human hepatic tissue, and the benefits of modified GLP-1 derivatives. The conclusion emphasizes the need for further research to explore the full potential of this approach in type 1 diabetes treatment. The manuscript is planned to undergo clinical trials in 2024, registered as 'Amr Ahmed, Maher M. Akl, Semaglutide GLP1 Agonists with Degludec Basal-bolus Insulin in Early Type 1 Diabetes to Basal-bolus' with **ClinicalTrials.gov Identifier NCT06057077**.

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1. Background

Type 1 diabetes is characterized by the destruction of beta cells, which necessitates the use of daily basal-bolus insulin as the primary treatment option. However, the emergence of drugs such as glucagon-like peptide 1 (GLP-1) agonists has brought new hope for the management of obesity and type 2 diabetes mellitus.[1] Notably, the United States Food and Drug Administration (FDA) has approved the use of GLP-1 agonists for adolescents as young as 12 years old, making it a promising choice for various indications, including combating obesity at an early age.[2] While the prolonged and stable effects of degludec (Deg), a basal insulin, are primarily attributed to its mechanism of action involving binding to albumin, it is crucial to consider the factors contributing to its stability and extended duration of effects.[3]

In this manuscript, we aim to address a letter to the editor titled**"Semaglutide in Early Type 1 Diabetes"** ***by Paresh Dandona, M.D., Ph.D., and Ajay Chaudhur, M.D., published in The New England Journal of Medicine on September 7, 2023.*** The authors conducted a retrospective analysis to evaluate the efficacy of semaglutide, a GLP-1 agonist, in patients with newly diagnosed type 1 diabetes.

Their study included 10 patients aged between 21 and 39 who initiated semaglutide treatment within 3 months of their type 1 diabetes diagnosis. The patients were followed up for 12 months, and metabolic outcomes were analyzed. Some patients presented with diabetic ketoacidosis at the time of diagnosis, while others exhibited symptoms such as polyuria, polydipsia, and weight loss. Additionally, most patients had antibodies against glutamic acid decarboxylase. Semaglutide was administered initially at a weekly dose of 0.125 mg, and the dose of prandial insulin was gradually reduced while the semaglutide dose was increased. Within 3 months, prandial insulin was completely eliminated in all patients, and within 6 months, basal insulin was eliminated in 7 patients. Throughout the 12-month follow-up period, the mean glycated hemoglobin level decreased to 5.7-5.9%, the fasting C-peptide level increased, and the time spent in the target glucose range improved. The authors compared their findings with control groups from four studies involving patients with early type 1 diabetes who were receiving insulin therapy. The results revealed that initiating semaglutide soon after the diagnosis of type 1 diabetes was associated with the elimination of prandial and basal insulin, increased C-peptide levels,

and improved glycemic control. However, as this was a retrospective analysis and lacked a control group from their own study, the authors emphasized the need for prospective, randomized clinical trials with larger sample sizes to further investigate this approach. Despite its limitations, this small case series suggests the potential of semaglutide as a treatment option in early type 1 diabetes. The objective of this manuscript is to support and interpret this approach and propose an alternative approach that may be more effective.[4]

2. Interpretation and Commentary on the Manuscript "Semaglutide in Early Type 1 Diabetes" by Paresh Dandona, M.D., Ph.D., and Ajay Chaudhur, M.D., published in The New England Journal of Medicine on September 7, 2023.

Comment 1: The presence of anti-GAD antibodies in most cases of type 1 diabetes suggests an autoimmune etiology. Early intervention with GLP-1 agonists may potentially protect residual beta cells and reverse the autoimmune response. It is suggested that GLP-1 agonists like semaglutide may discourage the release of these antibodies, leading to the reversal of beta cell dysfunction. The reversible binding of degludec to albumin allows for the release of insulin in the target tissue, resulting in glucose-lowering effects. Further investigations, such as measuring anti-GAD and anti-IA2 antibodies after stopping insulin, can provide valuable insights into the validity of this theory.[5]

Comment 2: GLP-1 receptors are found in pancreatic islets, acini, and ducts. GLP-1 agonist therapy has been observed to stimulate proliferation in acinar and duct cells containing endocrine stem cells. Additionally, previous studies have suggested that pancreatic exocrine duct cells have the potential to differentiate into insulin-producing beta cells during embryogenesis but not after birth. The direct reprogramming of liver cells into insulin-producing cells offers another approach for cell replacement therapy.

The plasticity of adult human hepatic tissue and its ability to acquire pancreatic characteristics have been demonstrated in vitro. These findings highlight the potential of utilizing adult hepatic tissue for regenerative medicine approaches.[6]

Comment 3: Modifying GLP-1 receptor agonists with albumin ligands specific for human serum albumin (HSA) has shown promise in extending the half-life of GLP-1 and enhancing its anti-diabetic effects. Rhein-C12-GLP-1, a derivative modified with Rhein, has demonstrated improved glucose tolerance and significant hypoglycemic effects in animal models. This modification could potentially increase the action time of GLP-1 and make it a viable option for the treatment of type 2 diabetes mellitus and as a long-acting anorectic agent. Further studies are needed to fully evaluate the potential of this modification, including molecular docking studies, pharmacokinetic assays, and pharmacology assays.[7]

3. Perspective

The information provided suggests a comprehensive and interconnected perspective on the potential treatment of type 1 diabetes through the synergistic approach of dual GLP-1 agonist with degludec basal insulin. Type 1 diabetes is

characterized by the destruction of beta cells, resulting in the need for daily basal-bolus insulin as the primary treatment option. However, the emergence of GLP-1 agonists offers new hope for the treatment of obesity and type 2 diabetes. These agonists have been approved by the FDA for adolescents as young as 12 years old, making them a promising choice for various indications, including combating obesity at an early age. The stability and prolonged effects of degludec basal insulin are attributed to its mechanism of action, which involves reversible binding to albumin. This allows for the release of more than 99% of the drug in the target tissue, exerting glucose-lowering effects. Notably, changes in albumin concentrations are unlikely to impact the pharmacokinetic properties of degludec due to the high levels of serum albumin. The bound insulin decreases at night, leading to increased free insulin levels and maintaining a constant association constant (Ka). This may result in a stronger effect of degludec at night, potentially causing nocturnal hypoglycemia.[8]

Another intriguing approach discussed is the direct reprogramming of liver cells into insulin-producing cells, which could be a viable option for cell replacement therapy in diabetes. Experimental studies have shown that human liver cells possess significant cellular plasticity and can acquire mesenchymal-like characteristics.[9] Insulin-producing cells were primarily generated in cells enriched for adult hepatic markers that coexpress albumin and mesenchymal markers. These findings suggest that adult human hepatic tissue retains a considerable level of developmental plasticity, which could be harnessed for regenerative medicine approaches.[10] Furthermore, modifying GLP-1 receptor agonists with albumin ligands specific for human serum albumin (HSA) has proven to be an effective strategy for extending the half-life of GLP-1. This modification enhances the anti-diabetic profile of GLP-1, resulting in improved glucose tolerance and significant hypoglycemic effects.[11] Rhein-C12-GLP-1, a derivative modified with Rhein, has shown promising hypoglycemic effects in animal models, surpassing the action time of the backbone peptide Arg34-GLP-1(7–37)-OH.[12] It holds potential for the treatment of type 2 diabetes mellitus and could be developed as a long-acting anorectic agent. However, further evaluations, including molecular docking studies, pharmacokinetic assays, and pharmacology assays, are necessary to fully assess its potential.

4. Conclusion

The proposed theory of beta cell regeneration in type 1 diabetes through the synergistic approach of dual GLP-1 agonist with degludec basal insulin offers a comprehensive and interconnected perspective. It takes into account the pharmacokinetic properties of degludec, the potential plasticity of adult human hepatic tissue, and the promising outcomes of GLP-1 derivatives modified with albumin ligands. Further research and investigations are warranted to explore the full potential of this approach for the treatment of type 1 diabetes.

The present hypothesis has been registered for undergoing clinical trials in 2024 under the title 'Amr Ahmed, Maher M. Akl, Semaglutide GLP1 Agonists With Degludec Basal-bolus Insulin in Early Type 1 Diabetes to Basal-bolus.' Additionally, the ClinicalTrials.gov Identifier for this study is **NCT06057077**.

Statements and Declarations

The authors declare that there are no conflicts of interest.

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