Review Article

Glucagon-Related Advancements in Diabetes Therapy

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Abstract

Traditionally, treatment for type 2 diabetes (T2D) centered on the failure of insulin secretion from the beta cells of the pancreas and insulin resistance. Though effective in certain respects, these treatments are marred by multiple undesirable side effects. The discovery of the incretin defect and the role of glucagon in T2D shifted the focus to therapies that addressed not only the beta cell defect but also the alpha cell defect in the pancreas. Therapies addressing these defects, simultaneously, have switched the entire focus of T2D therapy by not only improving glycemic control but also reducing the risk of hypoglycemia and weight gain and improving outcomes. These newer modalities of treatment started off with dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists (GLP1-RAs), and now further treatments in the form of twincretins (GLP1/GIP dual agonists) and triple agonists (GLP1/GIP/glucagon agonists) are unraveling. This article provides a summary of the evidence available with these newer antidiabetics, which address the glucagon defect in T2D.

Keywords: Diabetes, glucagon, treatment

Introduction

Traditional strategies for blood glucose lowering in patients with type 2 diabetes (T2D) target improving the insulin secretory capacity of the pancreas and reducing insulin resistance. These strategies led to the discovery of agents like sulfonylureas, glinides, metformin, pioglitazone, etc. These drugs caused a glucose-independent augmentation of insulin release and improved glycemic control but were sadly associated with deleterious side effects like hypoglycemia and weight gain. Thus, there was always a search for agents that reduce hyperglycemia without the side effects described above.

The incretin effect had been proposed in the 1900s and was formally proved in the 1960s with alpha cells and the role of *glucagon* in regulating postprandial sugar coming into focus.[1,2] The suppressed first-phase insulin response after a meal, reflective of an incretin defect is responsible for the post-meal spikes commonly encountered in T2D patients.[3] Gastric inhibitory polypeptide (GIP) and *glucagon*-like peptide-1 (GLP-1) are a couple of gut hormones regulating the incretin axis. While the sensitivity of the β cells to the former is lost completely, the circulatory concentration of the latter as well as its impact on both the alpha and the beta cells are preserved.[4] *Glucagon* which till not so long ago had been reserved as only an antidote for insulin-induced hypoglycemia, came into focus, as research on the incretin axis and the *glucagon* connect led to the discovery of dipeptidyl peptidase-4 inhibitors (DPP-4is) and glucagon-like peptide-1 receptor agonists (GLP1-RAs) as therapeutic agents targeting both the alpha and beta cells resulting in a glucose-dependent reduction in hyperglycemia, depending not only on insulin secretion but *glucagon* release too. These drugs promise improved metabolic control without the troublesome side effects associated with the older molecules.

Received: 02-October-2023, **Revised:** 15-October-2023, **Accepted:** 03-October-2023, **Published:** 14-November-2023

Access this article online

Quick Response Code:

Website: https://journals.lww.com/JODB

DOI: 10.4103/jod.jod_96_23

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How to cite this article: Sinha B, Ghosal S, Mukhopadhyay S, Hussain A, Mohan AR, Schwarz P, *et al*. Glucagon-related advancements in diabetes therapy. J Diabetol 2023;14:S16-8.

Dipeptidyl peptidase-4 (DPP4) inhibitors

DPP-4is typically works by inhibiting the enzyme DPP-4 responsible for degradation of the circulatory incretin gut hormones.[5] This leads to an increase in the active component of the circulatory GLP-1 hormone resulting in lowering of fasting and post-meal hyperglycemia. The 2023 American Diabetes Association (ADA) consensus statement classifies DPP-4is in the intermediate glucose-lowering category.[6] This inference was based on a network meta-analysis conducted by Tsapas *et al.*[7] The mean HbA1C reduction was -0.60% (95% confidence interval [CI] -0.75% to -0.46%) in the drug naïve group and –0.51% (95% CI –0.63% to –0.40%) in the backdrop of metformin. The risk of hypoglycemia is minimal with DPP4i. Although pleiotropic benefits on lipids, adiponectin, vascular inflammatory markers were documented DPP-4is had at best a neutral effect on MACE and its individual components.[8]

From an Indian perspective, Sinha and Ghosal[9] documented an impressive glucose-lowering capability of DPP-4is along with a positive impact on the disposition index, in contrast to North Asian counterparts.

Glucagon-like peptide-1 receptor agonists

Endogenous GLP-1 has a very short half-life (2 min).[10] The GLP1-RAs available for clinical use have been modified structurally either from the human backbone structure or synthetically from Exendin-4 rendering them much more potent compared to a DPP-4i.[11] This is due to larger levels of circulatory GLP-1 levels, resulting in longer interaction with GLP1 receptors-inducing β-cell glucose-dependent insulin release as well as effective suppression of *glucagon* secretion from alpha cells.[12] As a result, as expected the ADA 2023 consensus statement categorizes GLP1-RAs under the high to very high glucose-lowering efficacy section.[6] As monotherapy, a -1.48% (95% CI -2.15% to -0.81%) reduction in HbA1C and –1.33 (95% CI –1.50% to –1.16%) reduction can be expected from injectable semaglutide.[7] In addition to impressive glycemic control, weight and systolic blood pressure reduction are the added benefits.[13] The impact of GLP1-RAs on metabolic and inflammatory vascular markers translates into impressive cardiovascular benefits.[9] The additional organ-specific indications ascribed to GLP1-RAs by modern guidelines span from obesity to nonalcoholic fatty liver disease.[6] They also hold promise in the management of polycystic ovarian syndrome and Alzheimer's disease.

GLP1/GIP dual agonists

GLP1 and GIP are both gut hormones that increase insulin secretion from the pancreatic beta cells. GIP reduces *glucagon* secretion in normoglycemia but increases *glucagon* in the presence of hypoglycemia in normal subjects. However, GIP does not impact *glucagon* release in T2D. GLP1-RA reduces body weight by delaying gastric emptying, but GIP seems to be reducing body weight by its direct effect on the hypothalamus. GIP also acts peripherally, rationalizing fat deposition in muscles and adipose tissue, thereby reducing insulin resistance. Thus, GLP1-RA and GIP act synergistically and complementarily with improved glycemia and more robust weight loss than GLP1-RA alone.[14,15] This has been borne out quite clearly in the SURPASS clinical trial program with tirzapetide, the only dual agonist or "twincretin" available for clinical use and recommended by the ADA/EASD as a treatment for T2D and obesity.[16]

In the SURPASS trials, tirzepatide showed a dose-dependent reduction in HbA1C that was significantly greater than all comparators, including placebo, basal insulin, and semaglutide, irrespective of background glucose-lowering therapy. Tirzapetide resulted in a dose-dependent weight loss; in fact, the lowest dose of tirzapetide (5 mg) resulted in 1.68 kg more weight loss than 1 mg of semaglutide. Obviously, weight loss was of significantly higher magnitude when compared to basal insulin. Tirzepatide showed cardiovascular safety and a positive impact on renal function in the SURPASS trials. Tolerability was similar to GLP1-RA with no increased risk of hypoglycemia.[16]

SURPASS-CVOT[17] a novel cardiovascular outcome trial compares tirzepatide versus dulaglutide a pure GLP-1RA that demonstrated superiority versus placebo in the REWIND trial, instead of the traditionally availed placebo. This study will be completed in 2024.

GLP-1/GIP/glucagon agonists (triagonists)

Triagonists are single peptides with agonist activity at the GIP, GLP-1, and *glucagon* receptors. In animal studies, retatrutide, the triagonist that is most studied, has shown more potent action at human GIP receptors compared to its potency at the human *glucagon* and GLP-1 receptors. In preclinical models, retatrutide treatment reduced food intake and also increased energy expenditure, an effect attributable to *glucagon* receptor agonism.[18] In a phase 1, multiple-ascending dose study in people with T2D, retatrutide showed robust reductions in glucose and bodyweight.[19]

In a recently published phase 2 study, retatrutide showed a significant and robust HbA1C reduction when compared to placebo, as well as dulaglutide 1.5 mg weekly. In fact, at a maximal dose of 12 mg retatrutide treatment resulted in an impressive 2.16% reduction of HbA1C at week 36. Treatment with retatrutide resulted in 16.94% weight loss from baseline. Approximately 40% of patients treated with a maximal dose of retatrutide attained a weight loss of greater than 20%. Retatrutide improved insulin sensitivity as well as increased serum insulin and C peptide levels. *Glucagon* levels were reduced with retatrutide.[20] Safety profile of retatrutide was similar to GLP1-RA as well as dual agonists.

Conclusion

Glucagon-based therapies have already revolutionized the management of T2D by conferring its dual benefit

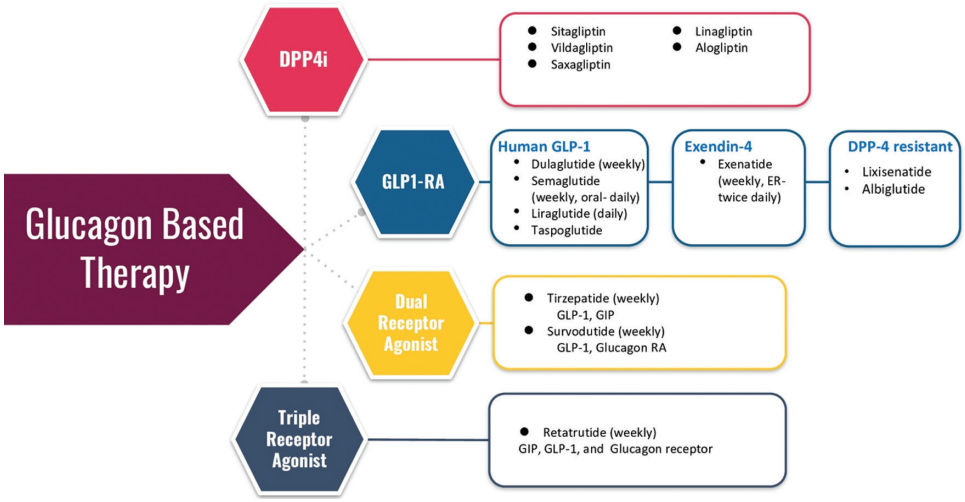

Figure 1: A snapshot of the different glucagon-based therapies with a few examples of each

on metabolic and organ-protective aspects. Future drug developments, as well as novel areas of target, are based on targeting *glucagon*. This narrative review gave a snapshot of a few aspects of *glucagon*-based strategies [Figure 1].

Patients' consent form and ethical approval

Not applicable.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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