MAYO CLINIC

REVIEW

# The Role of Glucagon in the Pathophysiology and Treatment of Type 2 Diabetes

Sofie Hædersdal, MD; Asger Lund, MD, PhD; Filip K. Knop, MD, PhD; and Tina Vilsbøll, MD, DMSc

## Abstract

Type 2 diabetes is a disease involving both inadequate insulin levels and increased glucagon levels. While glucagon and insulin work together to achieve optimal plasma glucose concentrations in healthy individuals, the usual regulatory balance between these 2 critical pancreatic hormones is awry in patients with diabetes. Although clinical discussion often focuses on the role of insulin, glucagon is equally important in understanding type 2 diabetes. Furthermore, an awareness of the role of glucagon is essential to appreciate differences in the mechanisms of action of various classes of glucose-lowering therapies. Newer drug classes such as dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists improve glycemic control, in part, by affecting glucagon levels. This review provides an overview of the effect of glucose-lowering therapies on glucagon on the basis of an extensive PubMed literature search to identify clinical studies of glucose-lowering therapies in type 2 diabetes that included assessment of glucagon. Clinical practice currently benefits from available therapies that impact the glucagon regulatory pathway. As clinicians look to the future, improved treatment strategies are likely to emerge that will either use currently available therapies whose mechanisms of action complement each other or take advantage of new therapies based on an improved understanding of glucagon pathophysiology.

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The opposing actions of insulin and glucagon were demonstrated nearly a century ago.[1,2] Today, the role of glucagon is recognized as important in glucose homeostasis and diabetes pathophysiology.[3-6] Glucagon, a 29-amino acid peptide hormone, is counterregulatory to insulin, stimulating hepatic glucose production, thereby increasing plasma glucose levels.[7] Glucagon also stimulates ketogenesis, thus working in tandem with insulin to maintain a normal "fuel balance."[8,9] Simply put, insulin acts as a glucose-depositing and anabolic hormone, whereas glucagon is glucose mobilizing and catabolic.[8,10]

During the past decade, the use of medications that modulate glucagon levels has gradually increased in the treatment of patients with type 2 diabetes (T2D). Dipeptidyl peptidase-4 inhibitors (DPP-4is) and glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs), which both suppress glucagon secretion, have received increasing attention as add-on therapies for patients with T2D.[11,12] Other glucose-lowering drug classes also affect glucagon secretion (either positively or negatively), including sulfonylureas, exogenous insulin, amylin mimetics, and sodium-glucose cotransporter 2 inhibitors (SGLT2is).

Although plasma glucagon levels are not used in a clinical stratification of diabetic treatment, health care providers may gain clinical insight from understanding how glucagon levels can be pharmacologically controlled in patients with T2D. Of particular interest are the abilities of glucose-lowering drugs to preserve a normal counterregulatory glucagon response in hypoglycemic conditions and, thus, avoid hypoglycemic adverse events. Moreover, as will be discussed, potential benefits can be gained from emerging glucagon-modulating therapeutic strategies.

To explore the relationship between glucagon and T2D, we performed a literature review of glucagon and diabetes, including glucagon in normal physiology and the pathophysiology of T2D. We also made an extensive effort to identify studies that assessed the effect

From the Center for Diabetes Research, Gentofte Hospital, University of Copenhagen, Hellerup, Denmark (S.H., A.L., F.K.K., T.V.); Steno Diabetes Center Copenhagen, University of Copenhagen, Gentofte, Denmark (T.V.); Faculty of Health and Medical Sciences, Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark (F.K.K., T.V.); and Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark (F.K.K.).

## ARTICLE HIGHLIGHTS

- Under normal physiological conditions, glucagon, which is secreted by pancreatic alpha cells, works alongside insulin to regulate plasma glucose levels, including an increase in hepatic glucose production and release of glucose into circulation during hypoglycemia.
- The pathophysiology of type 2 diabetes includes aberrant secretion of glucagon, resulting in elevated glucagon concentrations in both the fasting state and after a meal.
- Some glucose-lowering drug classes, including dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists, decrease glucagon secretion, resulting in amelioration of the inappropriately high glucagon concentrations characteristic of type 2 diabetes and improvement of the insulin:glucagon ratio.
- As clinicians consider treatment strategies for patients with type 2 diabetes, knowledge of the effect of glucose-lowering therapies on glucagon can inform treatment choices.

on glucagon of glucose-lowering drugs within the most commonly used drug classes in current clinical practice. We performed a 2-stage literature search for sulfonylureas, pioglitazone, pramlintide, DPP4-is, GLP-1RAs, and SGLT2is: (1) search of the PubMed database for names of the glucose-lowering drugs and the terms "diabetes" and "glucagon" in the title or abstract (restricted to English-language articles and clinical trials in humans with no date restriction); and (2) assessment of each large, phase 3 clinical trial identified in articles describing each drug's clinical development program to identify studies in which glucagon levels were measured. For metformin and insulin, a less extensive literature search was conducted that relied primarily on mention of glucagon results in other publications. Although this is neither a systemic nor comprehensive review of all clinical studies with results related to glucagon, the literature search did identify an extensive number of relevant studies.

## DISCOVERY OF GLUCAGON AND ITS IMPORTANCE

Glucagon, a peptide hormone,[13] was identified and named in 1923 when 2 chemists experimenting with "aqueous extracts of pancreas" found a substance that had a hyperglycemic effect in dogs whose pancreas was removed and in normal rabbits.[2] Despite the initial confusion about whether glucagon was merely a contaminant during purification of insulin,[1,5] researchers recognized by the 1950s that glucagon was secreted from pancreatic alpha cells,[14] thus establishing the existence of 2 distinct pancreatic hormones,[15,16] both responsive to plasma glucose levels.[16] In 1975, Unger and Orci[9] proposed a "bihormonal hypothesis" of diabetes on the basis of evidence that the metabolic effects of T2D result from absolute or relative hyperglucagonemia, as well as absolute or relative insulin deficiency.[9] The authors further suggested that controlling glucagon secretion could potentially improve the treatment of diabetes.[9]

A substantial body of evidence suggests that hyperglucagonemia contributes to the hyperglycemic state of patients with T2D.[17-20] Although the mechanisms behind diabetic hyperglucagonemia and to what extent it affects the T2D state remain to be elucidated, studies with transgenic mice provide insight into the role of glucagon and its receptor. Transgenic mice lacking the glucagon receptor do not develop diabetes, even after nearly-complete beta-cell destruction.[21,22] However, this finding has not been confirmed by other groups.[23] Furthermore, transgenic mice with defective leptin receptors develop the phenotype of severe T2D, whereas transgenic mice defective in both glucagon and leptin receptors do not.[24] Adenoviral reintroduction of the glucagon receptor in these leptin receptor− and glucagon receptor−deficient mice resulted in severe hyperinsulinemia and hyperglycemia.[24]

## ROLE OF GLUCAGON IN HEALTHY INDIVIDUALS

Normal glucose homeostasis depends largely on balanced secretion of glucagon and insulin from pancreatic alpha and beta cells, respectively, in a tightly regulated, multiloop feedback system (Figure).[7,25] Following a meal, high plasma glucose levels (hyperglycemia) stimulate the pancreas to release insulin. Insulin promotes glucose uptake and use by insulin-dependent tissues, stimulates formation of glycogen from glucose (glycogenesis) in the liver and muscle, and suppresses glucagon secretion.[7,25] When plasma glucose levels fall too low