Commentary
Volume 10:01, 2025

Journal of Diabetic Complications & Medicine

ISSN:2475-3211

Open Access

Altered Glucagon Regulation by Insulin Under Chronic Hyperglycemic Conditions in Healthy Humans

Neosns Fredein*

Department of Radiation Oncology, The Catholic University of Korea, Seoul 06591, Republic of Korea

Introduction

Glucose homeostasis is maintained through a delicate balance of hormones, with insulin and glucagon playing pivotal, opposing roles. Insulin lowers blood glucose by promoting uptake into tissues, while glucagon raises glucose by stimulating hepatic glucose production. This hormonal balance ensures stable energy availability across physiological states. While much of diabetes research focuses on insulin deficiency or resistance, increasing attention is being paid to the dysregulation of glucagon secretion—particularly how insulin affects it under varying glucose conditions. Chronic hyperglycemia, even within physiological limits in healthy individuals, may have subtle yet significant effects on hormone regulation. This article explores how chronic, physiological hyperglycemia alters insulin's ability to suppress glucagon in healthy humans and its implications for early dysregulation and metabolic disease progression [1].

Description

In a healthy individual, insulin is secreted by pancreatic β-cells in response to rising blood glucose levels, such as after a carbohydrate-rich meal. Insulin exerts multiple effects: enhancing glucose uptake in muscle and fat tissues, promoting glycogen synthesis in the liver, and inhibiting lipolysis and gluconeogenesis. Concurrently, insulin also suppresses glucagon secretion from neighboring α-cells in the pancreatic islets—a mechanism that prevents the liver from releasing more glucose when it is already abundant. Glucagon, secreted during fasting or hypoglycemic states, increases blood glucose levels by stimulating glycogenolysis and gluconeogenesis in the liver. Its secretion is normally inhibited when glucose and insulin levels are high. However, under certain physiological or pathological conditions, this inhibitory control may weaken or become dysfunctional.

Chronic hyperglycemia refers to sustained elevations in blood glucose levels. In healthy individuals, this state can be induced experimentally through prolonged glucose infusion or high-carbohydrate feeding protocols. Unlike in diabetic patients, glucose levels in these individuals typically remain within the upper end of the normal range, but still represent a persistent elevation compared to baseline. Though these glucose levels do not immediately result in clinical symptoms or diagnosis of diabetes, chronic exposure may begin to alter hormonal dynamics at a subtle level. It is within this context that the regulation of glucagon by insulin begins to show signs of impairment—even in the absence of overt metabolic disease. Several controlled studies have demonstrated that during chronic physiological hyperglycemia, insulin's effectiveness in suppressing glucagon secretion declines. In glucose clamp experiments where healthy subjects are maintained at mildly elevated glucose levels for several hours or days, insulin infusion no longer suppresses glucagon to the same extent as under normal glycemic conditions.This impaired suppression suggests that α-cells become less responsive to insulin signaling in a hyperglycemic environment. The mechanism is multifactorial and likely involves a combination of reduced insulin receptor sensitivity on α-cells, alterations in intra-islet signaling, and changes in paracrine communication from β-cells.

The pancreatic islets are highly integrated micro-organs where cells communicate closely through paracrine signaling. β-cells secrete insulin, which diffuses locally to suppress glucagon release from α-cells. This intra-islet communication is essential for tight regulation of glucose levels. Chronic hyperglycemia may disrupt this local crosstalk by impairing insulin signaling at the α-cell membrane. Studies show that insulin receptors are present on α-cells, and activation of these receptors under normal conditions reduces glucagon secretion. When hyperglycemia is sustained, this signaling pathway may be downregulated due to receptor desensitization or post-receptor defects. As a result, insulin's paracrine inhibition on α-cells is weakened, and glucagon secretion becomes dysregulated [2].

The inability of insulin to properly suppress glucagon under hyperglycemic conditions may have profound implications for long-term metabolic health. While a healthy individual can compensate for transient hormonal fluctuations, chronic dysregulation may set the stage for metabolic inefficiency and disease progression. Inappropriately elevated glucagon contributes to increased hepatic glucose output, counteracting the glucose-lowering effects of insulin. This creates a self-perpetuating cycle: high glucose levels impair insulin's suppression of glucagon, which in turn exacerbates hyperglycemia. Although subtle in healthy individuals, such mechanisms may represent the earliest stages of beta- and alpha-cell dysfunction—a hallmark of prediabetes and type 2 diabetes. Furthermore, this imbalance can burden pancreatic β-cells, which are forced to produce more insulin to offset the hepatic glucose output driven by glucagon. Over time, this excessive demand can accelerate β-cell exhaustion and progression to overt diabetes [5].

Conclusion

While insulin is rightly recognized as a central regulator of glucose metabolism, glucagon plays an equally critical and often underappreciated role. In healthy individuals subjected to chronic physiological hyperglycemia, insulin's ability to suppress glucagon secretion becomes impaired. This subtle hormonal shift reflects early islet dysfunction and may precede more overt markers of metabolic disease. Recognizing and addressing this altered regulation offers a valuable opportunity for early intervention in the trajectory toward diabetes. Further research into α-cell biology, intra-islet signaling, and glucagon resistance will be crucial in developing more comprehensive strategies for maintaining glucose homeostasis and preventing metabolic disease.

Acknowledgement

None.

***Address for Correspondence:** Genica Frewe, Department of Radiation Oncology, The Catholic University of Korea, Seoul 06591, Republic of Korea ; E-mail: fredein@edu.kr*

Received: 23 January, 2025, Manuscript No. jdcm-25-168164; **Editor Assigned:** 25 January, 2025, PreQC No. P-168164; **Reviewed:** 08 February, 2025, QC No. Q-168164; **Revised:** 13 February, 2025, Manuscript No. R-168164; **Published:** 20 February, 2025, DOI: 10.37421/2475-3211.2025.10.295

Conflict of Interest

None.

References

1. Chuang, Jen-Chieh, Ichiro Sakata, Daisuke Kohno and Mario Perello, et al. "Ghrelin directly stimulates glucagon secretion from pancreatic α-cells." *J Mol Endocrinol* 25 (2011): 1600-1611.

2. Andersen, Soren Kaeseler, Jakob Gjedsted, Christian Christiansen and Else Tønnesen. "The roles of insulin and hyperglycemia in sepsis pathogenesis." *J Leukoc Biol* 75 (2004): 413-421.

3. Okamoto, Haruka, Katie Cavino, Erqian Na and Elizabeth Krumm, et al. "Glucagon receptor inhibition normalizes blood glucose in severe insulin-resistant mice." *Proc Natl Acad Sci* 114 (2017): 2753-2758.

How to cite this article: Fredein, Neosns. "Altered Glucagon Regulation by Insulin Under Chronic Hyperglycemic Conditions in Healthy Humans." *J Diabetic Complications Med* 10 (2025): 295.