

The Role of Glucagon in Glycemic Variability in Type 1 Diabetes: A Narrative Review

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Abstract: Type 1 diabetes mellitus (T1DM) is a progressive disease as a result of the severe destruction of islet β -cell function, which leads to high glucose variability in patients. However, α -cell function is also compromised in patients with T1DM, characterized by aberrant fasting and postprandial glucagon secretion. According to recent studies, this aberrant glucagon secretion plays an increasing role in hyperglycemia, insulin-induced hypoglycemia and exercise-associated hypoglycemia in patients with T1DM. With application of continuous glucose monitoring system, dozens of metrics enable the assessment of glycemic variability, which is an integral component of glycemic control for patients with T1DM. There is growing evidences to illustrate the contribution of glucagon secretion to the glycemic variability in patients with T1DM, which may promote the development of new treatment strategies aiming to mitigate glycemic variability associated with aberrant glucagon secretion.

Keywords: type 1 diabetes, glucagon secretion, continuous glucose monitoring, hyperglycemia, hypoglycemia, glycemic variability

Key Summary Points

Why carry out this study?

Aberrant glucagon secretion also contributes to T1DM.

The contribution of glucagon secretion to glycemic variability in patients with T1DM has not been clarified.

What is learned from the study?

In addition to β -cell dysfunction, aberrant glucagon secretion also contributes to glycemic variability in type 1 diabetes.

Glucagon suppression or inactivation may underlie potential therapeutic advantages over insulin monotherapy.

Introduction

Type 1 diabetes mellitus (T1DM) is a chronic, immune-mediated disease on account of the destruction of islet β -cell that leads to insulin deficiency.^{1–3} Multiple genetic and environmental factors are involved in the development of β -cell-targeted autoimmune processes and β -cell dysfunction.⁴ However, α -cell function and gene expression are also compromised in T1DM.⁵ Dysfunction of α -cell can aggravate hyperglycemia caused by abnormally elevated glucagon and hypoglycemia resulting from insufficient glucagon due to failure of counter regulation,⁶ such as impaired glucagon secretion making patients with T1DM more prone to

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insulin-induced hypoglycemia and postprandial hyperglycemia associated with hyperglucagonemia.^{7,8}

Glucagon is a proglucagon-derived peptide hormone secreted from pancreatic islet α -cell in response to hypoglycemia,⁹ as well as has a reaction to nutrients, hormones, neurotransmitters, and drugs.^{10,11} Glucagon, as a glucose-regulating hormone, can counteract excessive insulin action and play an important role in maintaining blood glucose homeostasis.^{10–12} In healthy individuals, physiological glucagon levels are in the range of 20–40 pg/mL in fasting state, which is twice as much as that in prandial state.^{6,13,14} In contrast, individuals with T1DM are characterized by postprandial hyperglucagonemia and inadequate glucagon secretion during hypoglycemia. The bi-hormonal hypothesis of diabetes was first proposed by Roger Unger,¹⁵ arguing that diabetes is as much caused by glucagon excess as insulin deficiency, and its association with T1DM has been known for nearly half a century.^{16,17} In recent years, studies surrounding the glucagon receptor in rodents with T1DM have demonstrated that glucagon plays an important part in regulating glucose homeostasis,^{18–21} which gives support to clinical observations discussed in the following.

Glycemic variability (GV) is an integral component of glycemic control in patients with T1DM,^{22,23} which can represent the presence of excess glycemic excursions and, consequently, the risk of hyperglycemia or hypoglycemia.^{24,25} With application of continuous glucose monitoring system (CGMs) since the late 1990s, dozens of metrics enable estimation of GV in patients with T1DM.^{26–28} Some studies showed that GV was associated with diabetic complications in T1DM,^{29–32} but this remained controversial^{33–38} and needed to be elucidated by further prospective studies on a large group of diabetes patients using CGM. Besides, it was reported that GV influenced the quality of life in patients with T1DM.^{39–41} Recent studies proposed GV in T1DM is not only due to the insulin deficiency, but also due in part to the aberrant dynamics of glucagon secretion.

Papers published up to December 2020 in the PubMed database were reviewed using the terms “glucagon”, “type 1 diabetes”, “hypoglycemia”, “hyperglycemia” and “glycemic variability”. The references of pertinent articles were also handsearched for relevant papers. Only papers published in English were considered.

Glucagon Secretion in T1DM

It is generally acknowledged that the aberrant glucagon secretion dramatically affects glucose control in patients

with T1DM,^{6,42} even at the special stage, the partial remission (PR) phase generally called “the honeymoon”, which is characterized by transient β -cell function recovery and better glycemic control accompanied by lower insulin requirement.⁴³ PR after diagnosis of T1DM were more prone to have lower glucagon secretion than non-remission.⁴⁴ The aberrant glucagon secretion in fasting and postprandial state is a complex phenomenon that plays a pivotal role in aggregating hyperglycemia and hypoglycemia in patients with T1DM.

Fasting Glucagon Secretion in T1DM

By comparison of serial sampling data, it was found that there was significant elevation of fasting glucagon in patients with T1DM,⁴⁵ which was in line with the results of non-insulin treatment type 2 diabetes mellitus (T2DM)⁴⁶ and T1DM with different disease durations.⁴⁷ However, other researchers found that fasting glucagon concentrations in new onset T1DM remained within the health control reference range over 12 months.^{48,49} There are multiple interpretations for these incompletely consistent results, such as differences in subjects, insulin resistance and detection methods,^{50–53} but certainly not all. The inhibition of glucagon secretion by insulin is the core mechanisms involved in the regulation of glucagon secretion.^{54,55} It's understandable, then, that elevated fasting glucagon is associated with disease durations in T1DM, which is conditional on rates of decrease in β -cell function.⁵⁶ Besides, earlier study in T1DM patients without residual β -cell function clearly demonstrated that exogenous insulin can restrain responses to other glucagon secretagogues.⁵⁷ As expected, exogenous insulin infusion was shown to suppress glucagon secretion.^{58,59} Based on these data, it can be observed that exogenous insulin does not fully normalize glucagon secretion in poorly controlled T1DM patients. On the contrary, in insulin-treated and relatively well-controlled T1DM patients, fasting glucagon levels tend to be within normal range, suggesting that hyperglucagonemia may not be detected if only sampling in fasting state.

Postprandial Glucagon Secretion in T1DM

The postprandial hyperglucagonemia plays a role in initiation and maintenance of postprandial hyperglycemia in T1DM even including LADA (latent autoimmune diabetes in adults) and T2DM.^{60–62} The early study showed

postprandial plasma glucagon level increased 160% in five years follow-up period after diagnosis of T1DM, which was negatively associated with postprandial C-peptide, an index to evaluate the residual β -cell function.⁶³ Further study also showed that residual β -cell function had potential impact on postprandial glucagon in some individuals with long-standing T1DM.⁶⁴ Recent study in T1DM with more than 3 years duration suggested that patients with high postprandial glucose tended to have high postprandial plasma glucagon,⁶⁵ which may exacerbate glycemic control gradually. Therefore, it is clear that the trend of gradual aggravation in postprandial hyperglucagonemia in line with the progressive reduction in β -cell function. Intriguingly, the aberrant increase in postprandial glucagon showed no inversion when euglycemia was achieved prior to oral glucose test in patients with T1DM,⁶⁶ which demonstrated the postprandial hyperglucagonemia in T1DM irrespective of ambient glycemia. Besides, the secretion of glucagon is inhibited during hyperglycemia by paracrine mechanisms of insulin, zinc, and GABA secreted by β -cell.^{67–69} When the postprandial glucose level increases, β -cell is stimulated simultaneously. As alteration of β -cell function, individuals with T1DM have no power to completely inhibit glucagon secretion.^{70,71} It might result in the postprandial hyperglucagonemia, which is consistent with the U-shaped dose-response curve for glucose-regulated glucagon secretion obtained in animal experiment.⁷² These findings illustrate that postprandial hyperglycemia induces glucagon secretion, which in turn exacerbates postprandial hyperglucagonemia. Of course, it triggers a vicious circle.

Glucagon Secretion and Hyperglycemia in T1DM

Previous studies have clearly shown that aberrant hypersecretion of glucagon plays a key role in inducing hyperglycemia in patients with T1DM.⁷³ The early study⁷⁴ reported postprandial glucagon increased by 17% and C-peptide decreased by half from baseline levels in the first year after diagnosis. Further studies on C-peptide-negative T1DM patients suggested that plasma glucagon concentration might be higher in hyperglycemic patients,^{65,75} which was consistent with the study between total pancreatectomy and T1DM with a complete lack of endogenous insulin.⁷⁶ There is some evidence that the impact of glucagon response on early postprandial glucose excursion is independent of residual β -cell function in type

1 diabetes.⁷⁷ In summary, there is growing evidences that, aberrant hyperglucagonemia, under the condition of relative insulin deficiency, is one of the main pathogenesis of hyperglycemia in patients with T1DM.

Another interesting phenomenon was that patients with T1DM manifested hyperglucagonemia when suffering from diabetic ketoacidosis,¹⁶ which contributed not only to their pronounced hyperglycemia but also to their hyperketonemia. Glucagon increases hepatic glucose and ketone production, in the case of insulin deficiency.⁷³ The somatostatin, the first glucagon-suppressing agent,⁷⁸ reduced plasma β -hydroxybutyrate and glucose level in patients after temporary withdrawal of insulin with T1DM.⁷⁹ Because these T1DM patients almost certainly lost considerable β -cell function, it was rational to attribute the hypoglycemic effect of somatostatin to its inhibition of glucagon secretion.⁵⁴ Besides, administration of somatostatin analog also allowed some patients to achieve better glycemic control⁸⁰ and the suppression of glucagon secretion might increase insulin sensitivity at the same time.^{81,82}

Glucagon Secretion and Hypoglycemia in T1DM

The risk of hypoglycemia in individuals with T1DM is high: about 12% of the patients experience severe hypoglycemia with loss of consciousness per year.⁸³ Insulin-induced hypoglycemia is customarily the result of the interaction between excessive exogenous insulin and aberrant glucagon secretion in T1DM. This kind of hypoglycemia is main complication of T1DM and is estimated to account for 4% of all-cause mortality in patients with T1DM.⁸⁴ The early study suggested that the glucagon response to hypoglycemia was lost as early as the first month after diagnosis of T1DM,⁸⁵ which was consistent with the finding that aberrant glucagon secretion during hypoglycemia was commonly observed after the first year, in youth with T1DM.⁸⁶ The glucagon response to hypoglycemia in patients with T1DM is relevant to the duration of diabetes and can be deprived early in the disease. The physiological mechanism for the speedy deprivation of the glucagon response to hypoglycemia is certainly multifactorial. Most important of these is likely the decrease of insulin secretion and the aberrant counter-regulation of glucagon secretion during hypoglycemia. However, this counter regulation follows the recognition of hypoglycemia by the autonomic nervous system. Early studies

suggested that marked loss of islet sympathetic nerves as well as diabetic autonomic neuropathy could destroy the recognition function of hypoglycemia in patients with T1DM.^{87,88} Intriguingly, a recent study in adults with T1DM reported that impaired awareness of hypoglycemia was not associated with autonomic dysfunction or peripheral neuropathy.⁸⁹ For these reasons, the aberrant glucagon secretion is one of the key components in pathophysiology of insulin-induced hypoglycemia, although the exact mechanisms *in vivo* remain to be identified.

Exercise is a fundamental component of diabetes management. Current guidelines recommend that individuals with T1DM can benefit from physical activity, and exercise should be recommended to all.⁹⁰ However, the complexity of exercise-associated management has become a major impediment to attainment of regular exercise at recommended levels for many patients with T1DM. Although both mean peak glucagon levels and the AUC (area under the curve) glucagon had little difference between individuals with T1DM and health controls during exercise,⁹¹ the episodes of hypoglycemia would influence glucagon secretion. Therefore, the addition of glucagon might have great potential to reduce hypoglycemia during exercise. Low-dose glucagon was more effective in preventing exercise-induced hypoglycemia than the reduction of insulin dosage and might result in less post-intervention hyperglycemia than carbohydrate supplement.⁹² The artificial pancreas, combining storage and delivery of insulin and glucagon with CGM,⁹³ is a highly effective and safe approach for treating T1DM.^{94,95} The dual-hormone artificial pancreas has a better practicality in glycemic control during exercise than the single-hormone artificial pancreas in patients with T1DM.⁹⁶

Glucagon Secretion and Glycemic Variability in T1DM

GV is an integral component of glycemic control in patients with T1DM, closely associated with insulin deficiency as well as aberrant glucagon secretion during glycemic changes, such as a deficient glucagon response to hypoglycemia and a relative hyperglucagonemia during hyperglycemia. These aberrant glucagon secretions might be related to GV in patients with T1DM, which is a serious clinical problem and a major consideration when evaluating quality of glycemic control. GV increases progressively from prediabetes to advanced

T2DM and is much higher in T1DM.^{97,98} Besides, the increased availability of CGM offers dozens of metrics for variability and enables measurement and observation of GV within a day and intraday, a more rigorous and valuable approach to evaluate glycemic control in daily life.⁹⁸ Therefore, to illustrate the contribution of glucagon secretion to GV in patients with T1DM may promote the development of new treatment strategies, could eventually mitigate GV associated with aberrant glucagon secretion.⁹⁹

Glucagon Secretion and Glycemic Variability Calculated by CGM

In a study exploring the relationship between aberrant glucagon secretion and GV in T1DM with different disease duration,⁴⁷ the correlation between fasting glucagon levels and SD (standard deviation of glucose) and MAGE (mean amplitude of glycemic excursions) was demonstrated. As mentioned above, in insulin-treated and relatively well-controlled T1DM patients, fasting glucagon levels are prone to be within normal range. Fasting glucagon may reflect the status of glycemic control and is potentially used as an index to predict GV. Further study showed positive correlations between some parameters of GV and arginine-stimulated postprandial glucagon secretion response in T1DM without any endogenous insulin.⁷⁵ In this study, patients with higher AUC glucagon tended to have higher SD and MAGE. In addition, recent research also showed positive associations between measurement of GV and AUC glucagon undergoing arginine stimulation tests and AUC glucagon was significantly correlated with the SD.¹⁰⁰ Moreover, other measurements of GV such as MODD (absolute means of daily differences) and LBGI (low blood glucose index) were also reported to be significantly correlated with AUC glucagon in T1DM.⁴⁷ So far, from the above researches it can be seen that fasting glucagon, postprandial glucagon and AUC of glucagon are all closely related to GV. Furthermore, it was reported that metrics of GV were predictors of aberrant glucagon secretion. CV (coefficient of variation) and CONGA (continuous overall net glycemic action) were correlated with change in glucagon concentration during the progressive fall in plasma glucose and might be predictors of impaired glucagon responses to insulin-induced hypoglycemia in patients with T1DM.¹⁰¹

According to the above research findings in patients with T1DM, dysfunction of β -cell responsiveness to

hyperglycemia as well as α -cell responsiveness to hypoglycemia likely resulted in higher GV demonstrated by CGM, and the contribution of aberrant glucagon secretion was indeed not negligible.

Glucagon Suppression or Inactivation and Glucose Variability Migration

The aforementioned findings suggest that glucagon suppression or inactivation may underlie potential therapeutic advantages over insulin monotherapy.¹⁰² The adjunctive treatment of GLP-1 analogue liraglutide to insulin therapy was effective in well-controlled T1DM characterized by reduction in glycemic excursions and insulin dose.¹⁰³ Besides, the addition of pramlintide created a more efficient capacity to suppress the postprandial glucagon secretion than liraglutide.¹⁰⁴ Similarly, compared with baseline and control patients, there was a significant decrease of arginine-stimulated glucagon secretion with a concomitant reduction of the MAGE and CV in exenatide-treated patients, although it had no effect on glucagon during hypoglycemia.¹⁰⁵ However, the DPP-4 inhibitor vildagliptin combined with insulin in T1DM retained glucagon counter-regulation during hypoglycemia while improved glycemic excursion due to, at least in part, the inhibition on postprandial glucagon secretion.¹⁰⁶ Another study has also shown reduction in AUC glucagon and changes in GV and insulin requirement in the linagliptin group, although not statistically significant, after all it was a small size study.¹⁰⁷ Moreover, the addition of glucagon might also have great potential to improve glycemic control. For example, the improved mean glycemia and reduced hypoglycemia with the dual-hormone artificial pancreas relative to insulin pump therapy in preadolescent children was reported in T1DM.⁹² Besides, patients with T1DM displayed absolute glucagon concentrations and a decrease in glucagon levels across the night comparable to those observed in the healthy control subjects.¹⁰⁸ The application of dual-hormone artificial pancreas systems also provided better overnight glucose control than conventional therapy with T1DM.¹⁰⁹

Discussion

Glucagon is a critical regulator of glucose homeostasis¹¹⁰ and the aberrant glucagon secretion in patients with T1DM is heterogeneous that is not fixed over the course of disease and poor glycemic control would flow from these changes, even in patients with tight glycemic control.^{6,42} The effect

of aberrant glucagon secretion includes hyperglycemia owing to paradoxical increase in glucagon, postprandial hyperglucagonemia in particular, and hypoglycemia induced by inadequate glucagon secretion. Emerging therapies designed to improve aberrant glucagon secretion are promising to mitigate GV.

The challenge, of course, is to interpret the available research results of glucagon concentration in patients with T1DM on account of the use of different assays.⁶ RIA kits use polyclonal antibodies against the glucagon C-terminal region, which will cross-react with proglucagon, truncated forms of glucagon and other fragments also containing this C-terminal region.¹⁴ Subsequently, with the advent of double-sandwich ELISA kits, these monoclonal antibodies against both the C- and N-terminal regions of glucagon allow for greater accuracy and have power to detect small changes with little cross-reactivity to other fragments. Therefore, the aberrant glucagon secretion in patients with T1DM needs to be revised based on previous results obtained from RIA kits.¹³ Next, one of multiple possible reasons for discrepant results between studies on glucagon secretion is probably due to the stimuli of various amino acid composition in the different tests, such as MMTT, oral glucose, arginine stimulation, etc. Thus, there is an urgent need to establish the method of standardization of glucagon assay, and it is important to select the methods to stimulate and detect glucagon scientifically and rationally.

What's more, T1DM is a progressive disease, and a more in-depth research of aberrant glucagon secretion at different stages of T1DM has been hindered by the incapability of early diagnosis before overt decline of insulin secretion and hyperglycemia. Therefore, prospective multicenter studies with large sample size are needed in different stages, especially prediabetes and first-degree relatives of T1DM, to confirm the present findings.

Compliance with Ethics Guideline

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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