High glucagon-to-C-peptide ratio and inadequate glucose control in type 2 diabetic patients

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Abstract

Objective: Unbalanced glucagon and insulin secretion may contribute to glucose fluctuations and inadequate glucose control in type 2 diabetic patients. This study aimed to investigate the relationship between the glucagon-to-C-peptide ratio and glycemic control.

Methods: From January 2017 to December 2018, a total of 1128 type 2 diabetic patients were recruited. The fasting and postprandial glucagon-to-C-peptide ratios were calculated following a 75-g oral glucose tolerance test (OGTT). Subjects were divided into quartiles based on their fasting and postprandial glucagon-to-C-peptide ratios. Statistical analysis was then carried out.

Results: HbA₁c levels were significantly and positively correlated with fasting (r = 0.333, p < 0.001) and postprandial glucagon-C-peptide-ratio (r = 0.373, p < 0.001). The proportion of patients with uncontrolled hyperglycemia significantly increased from 76.2% to 83.0%, 89.4% and 94.7% from the first to second, third and fourth quartiles of the fasting glucagon-C-peptide ratio and increased from 73.4% to 80.9%, 93.3% and 95.7% from the first to second, third and fourth quartiles of the postprandial glucagon-C-peptide ratio, respectively. After adjusting for potential influences, the mean difference (95% CI) in HbA₁c between the patients in the lowest
and highest quartiles of the fasting glucagon-C-peptide ratio was 1.925 (1.512, 2.338) %, and the mean difference in HbA1c between the patients in the lowest and highest quartiles of the prandial glucagon-C-peptide ratio was 2.401 (1.981, 2.820) %. After adjusting for possible metabolic risks by multiple logistic regression analysis, the corresponding odds ratios (ORs) for uncontrolled hyperglucose of the second, third and fourth quartiles versus the first quartile of fasting glucagon-C-peptide ratio were 1.331 (95% CI 0.829–2.136), 2.818 (1.647–4.823) and 7.268 (3.573–14.784), respectively. When compared with the first quartile of the postprandial glucagon-C-peptide ratio, the corresponding ORs for uncontrolled hyperglucose of the second, third and fourth quartiles were 1.752 (95% CI 1.100–2.793), 6.304 (3.348–11.560) and 15.998 (7.353–34.805), respectively.

**Conclusions:** For type 2 diabetic patients, an increased glucagon-to-C-peptide ratio is associated with an increased risk of uncontrolled hyperglucose.

**Key words:** glucagon-C-peptide-ratio; type 2 diabetes; OGTT; postprandial glucose; glycosylated hemoglobin A1c

**Background**

Insulin secretion dysfunction and insulin resistance are the major factors contributing to the development and progression of type 2 diabetes [1]. In addition to insulin, abnormal glucagon secretion is also an important etiology of type 2 diabetes [2]. Glucagon is secreted by pancreatic alpha cells and then binds to its receptor to promote hepatic gluconeogenesis in situations such as hypoglycemia, hypovolemia, prolonged fasting and cold environments [3]. In most type 2 diabetic patients, glucagon levels rise at rest and continue to rise within the first hour of the oral glucose tolerance test (OGTT) or after intake of a carbohydrate-rich diet [4]. Thus, hyperglucagon has been increasingly recognized as a vital therapeutic target for patients with type 2 diabetes in recent years. A hypoglycemic effect is achieved by inhibiting glucagon secretion [5].

Since both insulin and glucagon play important roles in the development and progression of type 2 diabetes, assessing the two indicators is critical for type 2 diabetic patients. Because insulin can highly affect glucagon secretion and the imbalance between the two hormones has been clearly revealed, it makes sense to consider glucagon relative to insulin as a glucagon-to-insulin ratio (GI ratio) and glucagon-to-C-peptide ratio rather than separately detecting absolute values of glucagon and insulin [6]. Emerging data have shed light on the fact that the GI ratio is a determinant of hyperglycemia in patients with type 2 diabetes [7]. A Korean study including subjects native to insulin treatment demonstrated that a high postprandial GI ratio was positively associated with glycosylated hemoglobin A1c (HbA1c) [8]. Similarly, in patients with pancreatic cancer, a high GI ratio after a 75-g oral glucose challenge was a surrogate marker of uncontrolled hyperglycemia [9]. A Chinese cross-sectional study found that a high glucagon-to-C-peptide ratio was associated with diabetic nephropathy in patients with type 2 diabetes, and the underlying mechanism might be that a high glucagon-to-C-peptide ratio reflected overall pancreatic islet dysfunction [10]. Therefore, relative hyperglucagon may indicate uncontrolled hyperglucose in type 2 diabetic patients. However, no study has focused
on the association between relative hyperglucagon and glucose control in Chinese type 2 diabetic patients with or without insulin antidiabetic therapy.

In this study, we evaluated the association between an increase in glucagon relative to insulin and metabolic indexes (HbA1c, postprandial glucose, lipid and so on) in Chinese type 2 diabetic patients. We also assessed the contribution of relative hyperglucagon to uncontrolled glucose. To rule out the influences of insulin use, this study adopted the glucagon-C-peptide ratio as an indicator of relative hyperglucagon instead of the GI ratio.

Methods

Study design and participants

This study was a cross-sectional study, and a total of 1128 type 2 diabetic patients were recruited for this study at the Second Affiliated Hospital of Nantong University between January 2017 and December 2018. Patients with type 2 diabetes diagnosed based on the statement of the American Diabetes Association were eligible for inclusion \[^{[11]}\]. The exclusion criteria were as follows: (1) type 1 diabetes; (2) previous drug uses that affect glycemic metabolism, i.e., steroids; (3) previous and current malignant tumors; (4) chronic hepatitis and renal failure; and (5) acute diabetic complications, i.e., diabetic ketoacidosis. All subjects agreed to participate in this study, and their consent form was obtained upon enrollment in this study. The study was approved by the medical research ethics committee of Second Affiliated Hospital of Nantong University.

Basic data collection

A questionnaire including parameters on age, sex, weight, height, blood pressure, illness and medical therapy history was conducted among all patients by experienced physicians upon enrollment. Body mass index (BMI) was calculated as the weight/height squared. A standard mercury sphygmomanometer was used to measure blood pressure, and the average of three recordings was recorded.

OGTT procedures and calculation

An OGTT (75-g glucose) was performed after an overnight fast. Plasma glucose, serum insulin, C-peptide and glucagon at fasting (0) and 30, 60, 120 and 180 min (FPG, PG30, PG60, PG120, PG180, respectively) were determined. The glucagon-C-peptide ratio was calculated as the ratio of glucagon to C-peptide. $\text{AUC}_{\text{glu}}$ was measured by area under the glucose curve.

Laboratory examination

We also collected fasting blood samples to measure laboratory parameters. Through standard laboratory procedures, insulin, C-peptide, glucagon, glucose, HbA1c concentration, alanine transaminase (ALT), aspartate aminotransferase (AST), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), total cholesterol (TC), triglycerides (TG), creatinine (Cr), blood urea nitrogen (BUN) and serum uric acid (UA) were determined.

Statistical analyses

Clinical variables are shown for all participants and for the quartiles of fasting and postprandial glucagon-C-peptide ratio. Normally distributed continuous variables, skewed continuous variables and categorical variables are described as the mean ± SD,
median (25 and 75% interquartile range) and frequency (percentage), respectively. Skewed distributed variables were diabetic duration, BMI, ALT, AST, TG, TC, HDL-c, LDL-c, Cr, UA, HbA1c, PG60, PG120, PG180, glucagon-C-peptide ratio 0 and glucagon-C-peptide ratio 120. We conducted one-way analysis of variance (ANOVA) or the Kruskal–Wallis test as appropriate to compare differences in continuous data among the four subgroups based on glucagon-C-peptide ratio 0 and glucagon-C-peptide ratio 120 quartiles and the chi-square test for comparing categorical data. Spearman’s correlation test was applied to analyze the correlation between the glucagon-C-peptide ratio, postprandial glucose, AUC_{glu}, HbA1c, and other metabolic parameters. Furthermore, a multiple logistic regression analysis was applied to explore the associations between the second, third, and fourth quartiles (Q2, Q3 and Q4) of the glucagon-C-peptide ratio and uncontrolled hyperglucose (identified as HbA1c more than 7.0%) relative to the first quartile (Q1) based on the odds ratio (OR) and 95% confidence interval (95% CI). Data analyses were performed using SPSS statistical software 18.0 (IBM SPSS Inc., USA). A value of p < 0.05 was considered to be statistically significant.

Results

Clinical characteristics of the participants

The clinical characteristics of the total participants and four subgroups according to the fasting and postprandial glucagon-C-peptide ratios are presented in Tables 1 and 2, respectively. HbA1c and the corresponding proportion of patients with uncontrolled hyperglucose significantly increased from Q1 to Q4 according to both fasting and postprandial glucagon-C-peptide ratios. As the fasting and postprandial glucagon-C-peptide-ratio quartiles increased, diabetic duration, values of HDL-c, PG120, PG180 and AUC_{glu} significantly increased, whereas the ratio of males, BMI, DBP, ALT, AST, TG, Cr, serum UA levels decreased. Age, TG, LDL-c and BUN did not show differences among the fasting and postprandial glucagon-C-peptide-ratio quartiles. Comparisons of hypoglycemic treatments showed that the frequency of insulin treatment increased along with both fasting and postprandial glucagon-C-peptide-ratio quartiles increased, whereas the frequency of DPP-4 inhibitor treatment decreased only as the postprandial glucagon-C-peptide-ratio quartiles increased.

Relationship between glucagon-C-peptide-ratio, postloading glucose, AUC_{glu}, HbA1c, and other metabolic parameters

Correlations between metabolic parameters and fasting or postprandial glucagon-C-peptide ratios were analyzed. Diabetic duration, HDL-c, PG120, PG180 and AUC_{glu} were positively correlated with both fasting and postprandial glucagon-C-peptide-ratio, whereas BMI, DBP, ALT, AST, TG, Cr, serum UA and HbA1c levels showed negative correlations. (Table 3).

Mean differences in HbA1c between quartiles of glucagon-C-peptide-ratio

The glucagon-C-peptide ratio was significantly correlated with HbA1c as determined by univariate analysis. We further constructed multivariable linear regression models to investigate mean differences (95% CI) in HbA1c between both fasting and postprandial glucagon-C-peptide-ratio quartiles. Comparisons of patients
in the lowest and highest quartiles of fasting glucagon-C-peptide-ratio showed that the mean difference in HbA1c was 1.982 (1.635, 2.329) %. After adjusting for potential influences, the adjusted mean difference in HbA1c between the patients in the lowest and highest quartiles of fasting glucagon-C-peptide-ratio was 1.925 (1.512, 2.338) %. Similarly, compared with patients in the lowest quartile of prandial glucagon-C-peptide-ratio, HbA1c of patients in the highest quartile of prandial glucagon-C-peptide-ratio increased by an average of 2.272(1.930, 2.615) % and 2.401(1.981, 2.820) % when adjusting for potential influences (table 4).

**Odd ratios (ORs) of uncontrolled hyperglucose according to glucagon-C-peptide-ratio quartiles**

Table 5 also shows the ORs of uncontrolled hyperglucose according to the fasting and postprandial glucagon-C-peptide-ratio quartiles. Compared with participants in Q1 of fasting glucagon-C-peptide-ratio, the ORs of uncontrolled hyperglucose for Q2, Q3 and Q4 of fasting glucagon-C-peptide-ratio were 1.519 (95% CI 1.004–2.299), 2.618 (1.640–4.178) and 5.547 (3.081–9.986), respectively. After adjustment in the multiple logistic regression, the corresponding ORs of uncontrolled hyperglucose for Q2, Q3 and Q4 of the fasting glucagon-C-peptide ratio versus Q1 were 1.331 (0.829–2.136), 2.818 (1.647-4.823) and 7.268 (3.573-14.784), respectively. Similar results were observed for the ORs of uncontrolled hyperglucose in the four subgroups according to the postprandial glucagon-C-peptide-ratio quartiles. Compared with participants in Q1 of the postprandial glucagon-C-peptide ratio, the ORs of uncontrolled hyperglucose for Q2, Q3 and Q4 of the fasting glucagon-C-peptide ratio were 1.530 (95% CI 1.028-2.276), 5.015 (2.936–8.566) and 8.152 (4.317-15.394), respectively. After adjustment in the multiple logistic regression, the corresponding ORs of uncontrolled hyperglucose for Q2, Q3 and Q4 of the postprandial glucagon-C-peptide ratio versus Q1 were 1.752 (1.100–2.793), 6.304 (3.438-11.560) and 15.998 (7.353-34.805), respectively.

**Discussion**

In the present study, we analyzed the associations between the glucagon-C-peptide ratio and glycemic indices in a large cohort of type 2 diabetic patients. The advantages of this study are as follows: first, a high fasting and postprandial glucagon-C-peptide ratio might be a significant contributor to increased postprandial glucose and HbA1c; second, relative hyperglucagon possibly contributes to lipid and UA metabolite homeostasis; third, compared with patients in the first fasting and postprandial glucagon-C-peptide-ratio quartile, those in the second, third and fourth glucagon-C-peptide-ratio quartiles were associated with increased HbA1c and increased risk for uncontrolled hyperglucose. A high glucagon-C-peptide ratio may partly contribute to inadequate glucose control.

There is ample evidence that poor glycemic control is associated with diabetic complications, and good glycemic control can avoid the incidence of these complications. Although there are many indicators for evaluating glycemic control, HbA1c is still the most appropriate indicator for evaluating long-term glycemic control. As a surrogate marker of glycemic control in the previous 8-12 weeks, a high HbA1c concentration may predict an increased risk of cardiovascular disease and
mortality in type 2 diabetic patients [15]. The American Diabetes Association recommended that HbA1c <7% was a suitable target for glucose control among nonpregnant patients [16]. Therefore, in this study, HbA1c was chosen as the evaluation index of glycemic control, and HbA1c greater than 7.0% was defined as poor glycemic control.

In this study, we demonstrated that both fasting and postprandial glucagon-C-peptide ratios were positively associated with HbA1c and postprandial glucose, and a high glucagon-C-peptide ratio might predict that the risk of poor glucose control increased significantly. A Korean study, similar to this study, demonstrated that a high postprandial GI ratio, rather than fasting GI ratio, was positively associated with uncontrolled hyperglucose in patients naive to insulin use [8]. The underlying mechanism by which the glucagon-C-peptide ratio can predict glucose control may be that the glucagon-C-peptide ratio reflects overall pancreatic islet dysfunction [10]. In addition, the glucagon-C-peptide ratio may be a potential indicator of the degree of beta- to alpha-cell transdifferentiation. Beta-cell transdifferentiation is defined as losing its phenotype, converting to an entirely new islet endocrine-like cell and expressing a second hormone [17]. The process of beta-cell transdifferentiation into other cell types is likely to account for the dysfunction of beta-cells in diabetes. Therein, beta- to alpha-cell transdifferentiation is the most normal phenomenon [18].

As a result, both fasting and postprandial glucagon-C-peptide ratios are able to predict glucose control. This study showed a significant positive association between the glucagon-C-peptide ratio and postprandial glucose. Previous studies revealed that in type 2 diabetic patients, fasting and postprandial glucose contributed equally to HbA1c [19]. Therefore, relative hyperglucagon possibly leads to postprandial hyperglycemia, which eventually leads to increased HbA1c and uncontrolled hyperglucose.

Glucagon functions by binding to the glucagon receptor, which is a special G-protein-coupled receptor that is expressed in a variety of tissues. In addition to regulating glucose levels, glucagon also plays a role in regulating protein and lipid metabolism [20]. Glucagon can maintain lipid homeostasis by promoting lipid mobilization, and inhibition of glucagon may result in adverse lipid deposition in the liver [21]. A Korean cross-sectional study found that lower glucagon relative insulin was independently associated with nonalcoholic fatty liver disease (NAFLD) in type 2 diabetic patients [22]. Similar results were observed in this study, in which the glucagon-C-peptide ratio was independently negatively associated with TG, ALT and AST but positively associated with HDL-c. Therefore, a lower glucagon-C-peptide ratio potentially contributes to the occurrence of hyperlipidemia and NAFLD in patients with type 2 diabetes. We also observed a negative correlation between the glucagon-C-peptide ratio and UA levels in type 2 diabetic patients. This correlation exists due to the fact that insulin can augment renal UA reabsorption [23], and glucagon can promote urea and electrolyte excretion [24]. Accordingly, when applying hypoglycemic agents that can affect the glucagon-C-peptide ratio, plasma lipid and UA levels should be monitored simultaneously.

In addition to regulating metabolic homeostasis, glucagon relative to insulin can also affect the secretion of hepatokines [25]. The most studied hepatokines are
follistatin [26] and fibroblast growth factor-21 (FGF21) [27]. Follistatin is linked to reproductive physiology, since follistatin inhibits the secretion of follicles by binding activin in the pituitary [28]. Other studies have proven that follistatin has multiple roles in promoting muscle growth [29] and stimulating beta-cell survival by inhibiting beta-to alpha-cell transdifferentiation [30]. FGF21 is thought to increase insulin sensitivity [26] and promote weight loss [31]. Both follistatin and FGF21 are especially sensitive to changes in the ratio between plasma glucagon and insulin [25]. It seems that follistatin and FGF21 are regulated by glucagon relative to insulin and ultimately influence glucose metabolism.

Several limitations of our study should be pointed out. First, on account of the common problem of cross-sectionalal studies, this study could not explain the causal relationship between the glucagon-C-peptide ratio and HbA1c. Second, some antidiabetic drugs, such as DPP-4 inhibitors and GLP-1 analogs, have been proven to exert functions in lowering the glucagon-C-peptide ratio. However, in our study, we failed to verify the association between the glucagon-C-peptide ratio and these drugs due to the low usage rates of these drugs. Third, all the subjects enrolled in this study were Chinese, which limits the wide applicability of our study. Further research should be conducted to validate the results of our study and to address the above limitations.

In summary, a high glucagon-C-peptide ratio is an indicator of increased risk of uncontrolled hyperglucose in type 2 diabetic patients. If a type 2 diabetic patient has a high glucagon-C-peptide ratio, clinicians should pay more attention to postprandial glucose. When using drugs that may affect the glucagon-C-peptide ratio, attention should be devoted to the possible impacts on plasma lipids, UA and hepatokines.

Abbreviations
OGTT: oral glucose tolerance test, ORs: odds ratios, GI ratio: glucagon-to-insulin ratio, HbA1c: hemoglobin A1c, BMI: body mass index, ALT: alanine transaminase, AST: aspartate aminotransferase, LDL-c: low-density lipoprotein cholesterol, HDL-c: high-density lipoprotein cholesterol, TC: total cholesterol, TG: triglycerides, Cr: creatinine, BUN: blood urea nitrogen, UA: uric acid, ANOVA: analysis of variance, FGF-21: fibroblast growth factor-21.

Authors’ contributions
CL and XG participated in the design of the study, data collection, analysis of the data, and drafting of the manuscript. JS and XW conceived of the study, participated in its design and revised the manuscript. WL and DZ participated in the analysis of the data and revised the manuscript. WL and FX participated in data collection. All authors read and approved the final manuscript.

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**Competing interests**
The authors declare that they have no competing interests.

**Availability of data and materials**
The current data are available to all interested researchers upon reasonable request. Requests for access to data should be made to the principal investigators of the study.

**Consent for publication**
Not applicable.

**Ethics approval and consent to participate**
The study was approved by the institutional review board of Affiliated Hospital 2 of Nantong University and First People’s Hospital of Nantong City, and written informed consent was obtained from all participants.

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