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Glucagon Response to Glucose Challenge in Patients with Idiopathic Postprandial Syndrome

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Background: Postprandial syndrome is characterized by hunger, weakness, and anxiety neurosis after meals. Although abnormal glucagon response is a suggested mechanism, inaccuracies in conventional glucagon measurement methods have prevented precise analysis. Recently, a more reliable dual-antibody sandwich enzyme-linked immunosorbent assay for glucagon was developed.

Methods: We conducted a 75-g oral glucose tolerance test (OGTT) extending to 4 hours in 14 patients with idiopathic postprandial syndrome. In addition to blood glucose and insulin, glucagon concentration was measured with the novel method and analyzed retrospectively.

Results: Median (lower quartile, upper quartile) age and body-mass index were 40 years (30, 49) and 24.9 (23.1, 26.2), respectively. The OGTT revealed that one patient had a diabetic pattern, and two were glucose intolerant. Fasting insulin was 7.6 μU/mL (6.8, 8.8) and reached 73.7 μU/mL (54.3, 82.6) at 30 min. Insulin remained elevated until 180 min. Fasting glucagon was 21.1 pg/mL (16.1, 33.8), reached a nadir of 6.9 (3.5, 10.3) at 60 min, one-third the baseline level, and remained suppressed until 180 min. We observed two types of glucagon dynamics: a lower fasting glucagon with further suppression and a normal or higher fasting glucagon with a subsequent large decrease.

Conclusions: These data suggest that glucagon suppression is greater in patients with idiopathic postprandial syndrome than in previously studied healthy subjects. The present data will contribute to our understanding and future research of this syndrome. (J Nippon Med Sch 2022; 89: 102–107)

Key words: glucagon, postprandial syndrome, hypoglycemia

Introduction

Postprandial syndrome is characterized by hunger, weakness, palpitations, and anxiety neurosis, usually at 2 to 4 hours after a meal[1,2]. Although hypoglycemia has been suggested as the cause of these symptoms, hypoglycemia below 55 mg/dL (defined as hypoglycemia in persons without diabetes)[3] does not always co-exist with these features of postprandial syndrome[4,5]. Nonetheless, patients exhibiting postprandial syndrome and relatively low blood glucose levels are occasionally referred to endocrine specialists for evaluation of suspected hypoglycemic disorders, including insulinoma.

To identify abnormalities in glucose homeostasis in patients with symptoms of postprandial syndrome, we conduct a 75-g oral glucose tolerance test (OGTT) extending to 4 hours. For analysis of OGTT samples, we measure blood glucose and immunoreactive insulin (IRI), as well we glucagon, concentrations. Until recently, glucagon assessment was unreliable because of inaccuracies in commercially available radioimmunoassays. A dual-antibody sandwich enzyme-linked immunosorbent assay (ELISA) has resolved this issue[6]. Herein, we used this new ELISA to retrospectively analyze plasma glucagon levels during prolonged OGTT in patients with postprandial syndrome.

Methods

This study was designed in accordance with the princi-

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Table 1 The patients characteristics

Characteristics		Characteristics	
Male: Female	3:11	HDL chol (mg/dL)	65.0 (56.5, 70.5)
Age	40 (30, 49)	LDL chol (mg/dL)	113.0 (85.0, 145.0)
BMI	24.9 (23.1, 26.2)	ALT (IU/L)	19.0 (15.3, 20.8)
HbA1c (%)	5.3 (5.2, 5.5)	AST (IU/L)	18.0 (16.0, 22.3)
Systolic BP (mm Hg)	122 (114, 126)	γGTP (IU/L)	19.0 (17.0, 27.0)
Diastolic BP (mm Hg)	76 (69, 85)	Cr (mg/dL)	0.68 (0.62, 0.79)
TSH (μIU/mL)	1.99 (1.70, 2.58)	eGFR (mL/min)	82.1 (71.1, 90.3)
Free T4 (ng/dL)	1.34 (1.20, 1.50)	Na (mEq/L)	141.0 (140.0, 141.8)
Triglyceride (mg/dL)	105.0 (63.5, 149.8)	K (mEq/L)	4.1 (4.0, 4.4)

Data represent numbers or medians (lower quartile, upper quartile).
BMI; body mass index, HbA1c; glycosylated hemoglobin, BP; blood pressure, TSH; thyroid stimulating hormone, T4; thyroxine, HDL chol; high-density lipoprotein cholesterol, LDL chol; Low-density lipoprotein cholesterol, ALT; alanine aminotransferase, AST; aspartate aminotransferase, γGTP; γ-glutamyl transpeptidase, Cr; creatinine, eGFR; estimated glomerular filtration rate

ples of the Declaration of Helsinki, and all study procedures were approved by the Ethics Committee of the Nihon University Itabashi Hospital (RK-200609-7). The protocol of this study was published on the web page of the Ethics Committee, and all study subjects were provided an opportunity to opt out.

We included 17 patients who visited Nihon University Itabashi Hospital because of symptoms of so-called postprandial syndrome associated with postprandial hypoglycemia during the period between October 2017 and October 2020. Sex, age, body-mass index (BMI), smoking habit, systolic and diastolic blood pressures, diabetes status, anti-hypertension drug use, statin use, and biochemical variables, including lipid metabolism, uric acid, and HbA1c, were evaluated in all subjects. Biochemical variables were measured after an overnight fast. Total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, uric acid, creatinine, and HbA1c were measured with an automatic analyzer. Oral glucose tolerance tests were performed for all patients. Blood was drawn at 0, 30, 60, 90, 120, 180, and 240 min. Glucagon was measured using a sandwich ELISA (Mercodia AB, Uppsala, Sweden). Measurements below the lower limit of detection (3.5 pg/mL) were recorded as 3.5 pg/mL. Data are presented as median plus lower quartile (Q1) and upper quartile (Q3) values. Differences were assessed by using Welch's *t*-test.

Results

The postprandial symptoms experienced by the 17 patients included hunger, sweating, palpitations, and weakness. Some but not all patients had ambient blood glucose levels of 45-70 mg/dL. One patient had previously received a diagnosis of polycystic ovary syndrome (PCOS), and insulinoma was later detected in another woman. In addition, glucagon data were missing for one female patient. Thus, data from 14 patients with idiopathic postprandial syndrome were analyzed. The patient characteristics are shown in **Table 1**. Only three patients were male. Three of the women had neurosis or depression and had been prescribed anti-depressants. Laboratory examinations yielded essentially normal results.

Homeostatic model assessment of insulin resistance (HOMA-IR) and of β-cell function (HOMA-beta) were calculated by using data at fasting during the OGTT. HOMA-IR was 1.78 (1.58, 1.93) and HOMA-beta was 88.5 (78.1, 103.1), indicating that the subjects were slightly insulin resistant but had normal or exaggerated insulin secretory capacities.

Glucose, IRI, and plasma glucagon dynamics during OGTT are presented in **Figure 1**. One patient exhibited a diabetic pattern, and two were glucose intolerant. Three patients had glucose levels below 70 mg/dL during the tests. The median (Q1, Q3) fasting IRI was 7.6 μU/mL (6.8, 8.8) and reached 73.7 μU/mL (54.3, 82.6) at 30 min. Insulin remained elevated until 180 min. Fasting glucagon peaked at 21.1 pg/mL (16.1, 33.8), immediately fell thereafter and reached, at 60 min, a nadir of 6.9 pg/mL (3.5, 10.3), one-third of the baseline value. Glucagon levels remained suppressed until 180 min and returned to the baseline at 240 min.

We then classified the subjects as those with a blood glucose level that decreased to a level below their fasting

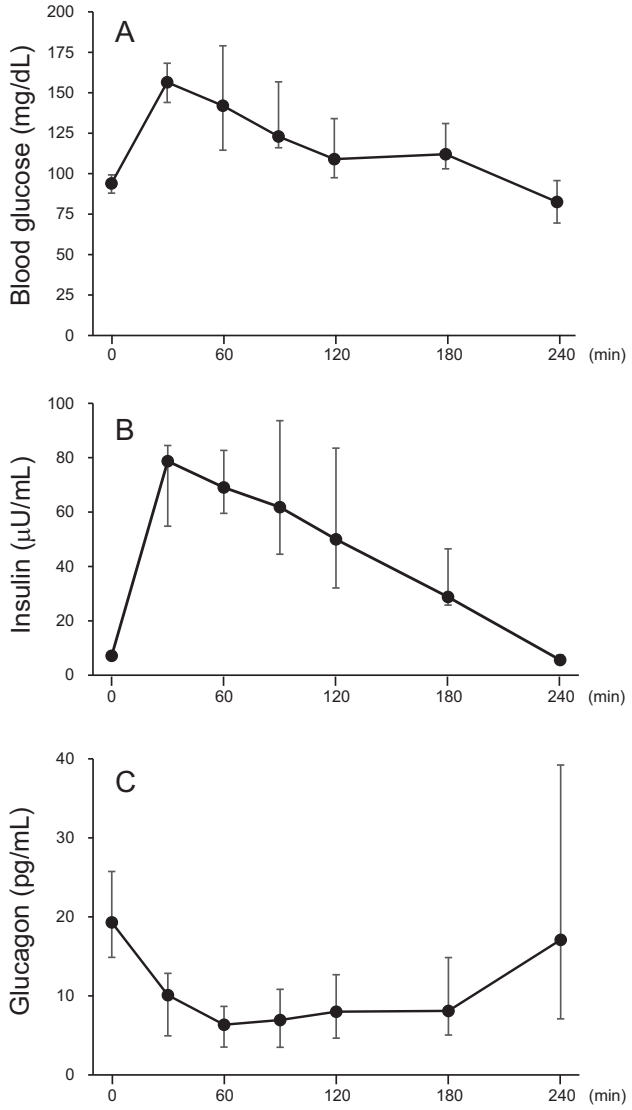

Fig. 1 Blood glucose (A), insulin (B), and glucagon (C) levels during OGTT in patients with postprandial syndrome. Data are medians; error bars represent quartile ranges.

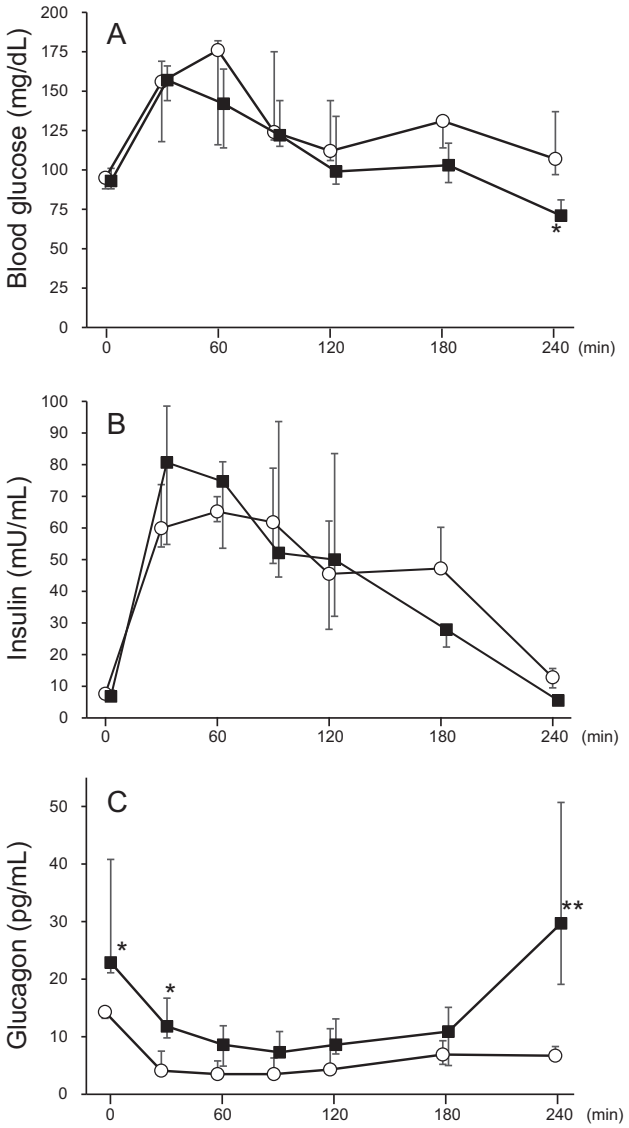

Fig. 2 Blood glucose (A), insulin (B), and glucagon (C) levels during OGTT in patients with postprandial syndrome whose blood glucose decreased to a level below their fasting levels (filled squares) and in those whose glucose remained above their fasting levels (open circles) during OGTT. Data are medians; error bars represent quartile ranges. *p<0.05, **p<0.01

level during OGTT (group D [dropped], n = 9) and those who maintained a blood glucose level above their fasting value (group ND [not dropped], n = 5). Clinical characteristics did not significantly differ between these groups, except for serum total cholesterol level (median: 174 mg/dL in group D and 226 mg/dL in group ND; P = 0.04). Unsurprisingly, blood glucose levels tended to be lower in group D than in group ND from 60 to 180 min and were significantly lower at 240 min (**Fig. 2**). Although insulin levels were similar, glucagon levels clearly differed between the two groups. The fasting plasma glucagon concentration in group D was twice that in group ND (**Fig. 2**). Glucagon was suppressed by more than threefold in both groups, but recovered only in the D group at 240 min.

For reference, OGTT results are presented for the patients with insulinoma (**Fig. 3A-C**) and PCOS (**Fig. 3D-F**). The insulinoma patient was a woman in her 40s with a BMI of 24.7 and an HbA1c of 4.7. The results of other laboratory tests were normal. During OGTT, insulin levels did not fully decline after 120 min, and blood glucose decreased to 60 and 45 mg/dL at 180 and 240 min, respectively. Glucagon levels appeared to be properly suppressed but did not recover at 120 min and remained so until 180 min. The patient with PCOS (a woman in her late 30s with a BMI of 33.4 and an HbA1c of 5.8) had se-

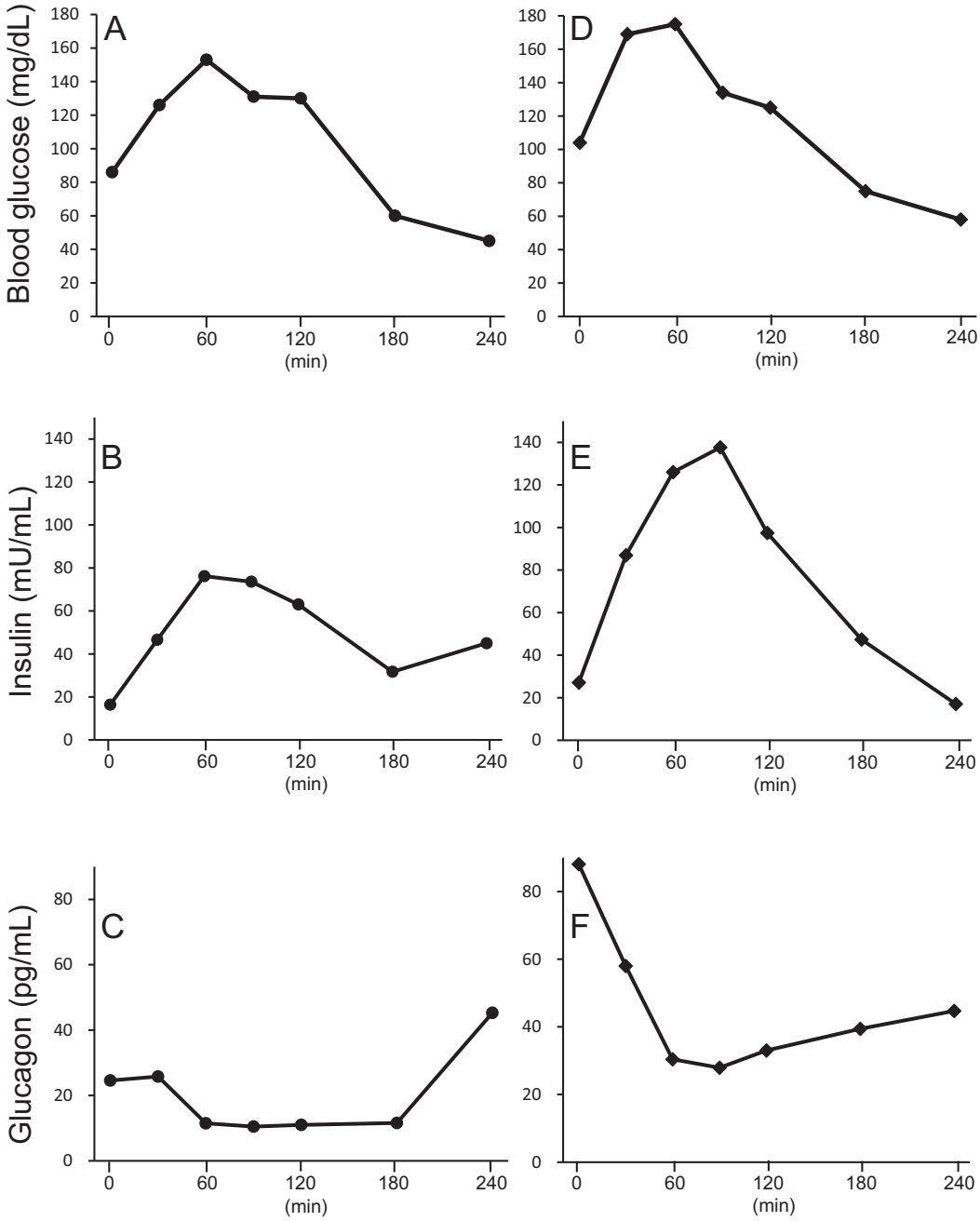

Fig. 3 Blood glucose (A), insulin (B), and glucagon (C) levels during OGTT in a patient with insulinoma. Blood glucose (D), insulin (E), and glucagon (F) levels in a PCOS patient.

vere insulin resistance (HOMA-IR of 6.96), and fasting insulin and glucagon levels were very high. After glucose challenge, insulin secretion was delayed and the peak was at 90 min. Glucagon secretion greatly decreased, by 60 pg/mL. Blood glucose decreased to 58 mg/dL at 240 min, at which time the patient reported dizziness.

Discussion

This study is the first to report plasma glucagon levels measured with the recently developed ELISA in patients with idiopathic postprandial syndrome. Minimization of cross-reactivity to other proglucagon products allowed us to evaluate dynamic changes in glucagon responses after glucose challenge. We found that glucagon levels were promptly suppressed, decreasing to one third of fasting levels, and that this decrease persisted until 180 min in patients with postprandial syndrome.

Because this study was retrospective and the data were obtained during routine medical practice, we do not have corresponding data from healthy persons. Therefore, we used data for Japanese from recent studies as a reference[7–9]. Glucagon responses were measured using the

same ELISA in two of these prior studies[7,8]. Glucose excursions in patients with postprandial syndrome were essentially normal. Although insulin secretion was rapid, it appeared to be higher than in healthy persons and did not diminish even at 180 min, which resembles the pattern seen in patients with prediabetes[9]. Indeed, HOMA-IR analysis showed mild insulin resistance. Glucagon secretion was rapidly suppressed, as in healthy persons[8]. However, while glucagon secretion reportedly recovered at 180 min in healthy persons, suppression persisted until 180 min in our patients with postprandial syndrome. In addition, plasma glucagon was suppressed by nearly 70% in our patients, while in healthy persons glucagon was reportedly suppressed by approximately 50%[8]. These data suggest that patients with idiopathic postprandial syndrome have abnormalities in insulin and glucagon secretion.

When patients were divided into two groups based on whether or not glucose had dropped below fasting levels during prolonged OGTT, we observed two types of glucagon dynamics. In patients who did not exhibit a glycemic decrease, fasting glucagon levels were slightly lower and strongly suppressed to below the lower limit. In patients with a glycemic decrease, fasting glucagon was normal or higher than normal, reaching the levels seen in patients with type 2 diabetes[8]. Glucose challenge greatly reduced glucagon concentrations to below one third of fasting values. We speculate that in patients with relative fasting hyperglucagonemia, the contribution of hepatic glucose output to maintaining fasting glycemic levels might be high, and that once glucagon secretion is suppressed, patients may be prone to hypoglycemia. However, the effect of exaggerated glucagon secretion of pancreatic α-cells on insulin secretion of β-cells and blood glucose levels was unclear in our study subjects. We speculate that patients in group D included those who might develop type 2 diabetes and that they have excess glucagon secretion because of pancreatic α-cell insulin resistance[10]. Further, sandwich ELISA used for glucagon measurement in our study might experience cross-reactivity with gastrointestinal glucagon-related peptides[11].

The present findings suggest that glucagon suppression is stronger in patients with idiopathic postprandial syndrome than in previously reported healthy persons. The mechanism underlying this abnormality is not clear. Insulin resistance and hyperinsulinemia might be causes, since insulin could be an intra-islet regulator of glucagon secretion[12]. In this regard, OGTT data from PCOS patients are informative. Higher insulin secretion in PCOS might increase suppression of glucagon secretion. Although symptoms of postprandial syndrome resemble those of hypoglycemia, the syndrome is not always associated with hypoglycemia. Dynamic changes in blood glucagon may cause these symptoms directly, since glucagon acts on diverse physiological functions, including gastrointestinal tract motility and satiety regulation[13]. We hope that the present data will improve understanding of this syndrome and glucagon pathohysiology.

Because islet hormone secretion in patients with idiopathic postprandial syndrome is abnormal, but not severely so, timely follow-up is recommended. In addition, although symptoms of postprandial syndrome are often considered psychological, they could be early manifestations of insulinoma, as in our patient.

Conflict of Interest: The authors declare no conflicts of interest.

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