

Assessing Islet Function Using Two-hour Postprandial C-peptide in Type 2 Diabetes Mellitus

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ABSTRACT

Objective: This study aims to investigate the role of two-hour postprandial C-peptide C-peptide (2HPC-P) for assessing islet β -cell function in Type 2 diabetes mellitus (T2DM).

Methods: A total of 326 T2DM patients were enrolled into this clinical study. The correlations were analysed between 2HPC-P, 2HPC-P increment, and 2HPC-P/fasting C-peptide (FC-P) with the area under the C-peptide curve (AUC-C) after a 100 g bread challenge. Of these patients, 87 newly diagnosed T2DM patients were divided into two Groups, Group I (2HPC-P/FC-P ≥ 3 , n = 43) and Group II (2HPC-P/FC-P < 3, n = 44), and performed insulin pump-intensive therapy for two weeks, followed by follow-up for three months.

Results: The positive correlations were found between the 2HPC-P, 2HPC-P increment and 2HPC-P/FC-P with AUC-C ($r = 0.97, 0.88$ and 0.77 , respectively, $p < 0.05$). After the insulin pump-intensive therapy, the HOMA2 IR values showed no significantly difference (2.50 ± 0.69 vs 2.23 ± 1.36 , $p > 0.05$), while HOMA2 B% was significantly higher (145.9 ± 56.2 vs 26.9 ± 22.4 , $p < 0.01$) than the basic values in newly diagnosed T2DM in total. During the follow-up, more patients in Group I underwent remission than in Group II (20/43 vs 5/44).

Conclusions: Two-hour postprandial C-peptide and its derivative indicators could effectively assess islet β -cell function.

Keywords: C-peptide, intensive therapy, islet functions, Type 2 diabetes mellitus

Evaluación de la función del islote usando péptido C postprandial de dos horas en la diabetes mellitus tipo 2

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RESUMEN

Objetivo: Este estudio tiene como objetivo investigar el papel del péptido C postprandial de dos horas (2HPC-P) en la evaluación de la función de las células β del islote en la diabetes mellitus tipo 2 (DM2).

Métodos: Un total de 326 pacientes de DM2 fueron inscritos en este estudio clínico. Se analizaron las correlaciones entre 2HPC-P, el incremento de 2HPC-P, y 2HPC-P/péptido C en ayunas (PCA) con el área bajo la curva del péptido C (AUC-C) tras un desafío de 100 g de pan. De estos pacientes, 87 recientemente diagnosticados con DM2 fueron divididos en

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dos grupos, grupo I ($2\text{HPC-P/PCA} \geq 3$, $n = 43$) y el grupo II ($2\text{HPC-P/PCA} < 3$, $n = 44$), y, realizaron un tratamiento intensivo con bomba de insulina durante dos semanas, con un seguimiento de tres meses.

Resultados: Las correlaciones positivas se encontraron entre en el 2HPC-P , el incremento de 2HPC-P , y 2HPC-P/PCA con AUC-C ($r = 0.97$, 0.88 y 0.77 , respectivamente, $p < 0.05$). Después de la terapia intensiva con bomba de insulina, los valores del modelo homeostático para evaluar la resistencia a la insulina (HOMA2 IR) no mostraron diferencias significativas (2.50 ± 0.69 vs 2.23 ± 1.36 , $p > 0.05$), mientras que los valores de HOMA2 B\% fueron significativamente más altos (145.9 ± 56.2 vs 26.9 ± 22.4 , $p < 0.01$) que los valores básicos en el DM2 recientemente diagnosticado en total. Durante el seguimiento, más pacientes en el grupo I fueron objeto de remisión que los pacientes en el grupo II ($20/43$ vs $5/44$).

Conclusiones: El péptido C postprandial de dos horas y sus indicadores derivados pudieron evaluar con eficacia la función de las células β del islote.

Palabras clave: Péptido C, terapia intensiva, funciones del islote, diabetes mellitus tipo 2

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INTRODUCTION

Islet β -cell dysfunction is key to the onset of diabetes (1). To treat diabetes, the most appropriate solution for blood glucose control should be determined based on the patient condition, particularly the status of islet β -cell function (2). The assessment of islet β -cell function typically involves insulin as the measurement parameter. The islet molecules secrete insulin and C-peptide. Some studies have shown that C-peptide can be used to guide the clinical treatment of diabetes (3, 4) and postprandial C-peptide could reflect the patient's islet reserve function (5). Short-term intensive insulin therapy could induce remission in some newly diagnosed Type 2 diabetes mellitus (T2DM) patients (6–10); however, not all patients are suitable for intensive treatment, and its clinical application still lacks effective indicators. The present study aimed at exploring the role of two-hour postprandial C-peptide (2HPC-P) for assessing islet β -cell function in T2DM in order to guide treatment selection for patients with newly diagnosed T2DM.

SUBJECTS AND METHODS

Type 2 diabetes mellitus patients ($n = 326$) with complete clinical information who were diagnosed and treated in the Department of Endocrinology at the Affiliated Hospital of Nantong University between May 2006 and April 2012 were selected to undergo a C-peptide releasing test using 100 g of bread. Type 2 diabetes mellitus was diagnosed using the 1999 Diabetes Classification Criteria of the World Health Organization (WHO) Expert

Committee, and patients with Type 1 diabetes mellitus, ketoacidosis, severe infection, severe kidney disease, cardiac dysfunction, pregnancy, or thyroid dysfunction were excluded. This study was conducted in accordance with the Declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Nantong University. Written informed consent was obtained from all participants.

C-peptide releasing test

The patients fasted for more than eight hours before the blood specimens were collected by cubital vein catheterization. Starting at 7:30 am, after oral administration of 100 g of bread, 4 mL blood samples were collected from the cubital vein at 0, 30, 60, 90, 120, 150, and 180 minutes, the blood samples were immediately centrifuged to obtain the serum for the analyses.

Grouping and treatment

Based on the ratio of 2HPC-P to fasting C-peptide (2HPC-P/FC-P), 87 patients with newly diagnosed T2DM were divided into Group I ($2\text{HPC-P/FC-P} \geq 3$, $n = 43$) or Group II ($2\text{HPC-P/FC-P} < 3$, $n = 44$). The insulin pump-intensive therapy was administered for two weeks, with a target fasting blood glucose (FBG) of 4.4–6.1 mmol/L and two-hour postprandial plasma glucose of 4.4–8.0 mmol/L. Protamine-biosynthesized human insulin 30R (Novolin 30R, Novo Nordisk) was used as maintenance treatment after discharge; the patients attended regular outpatient reviews, and the blood glucose control solution was adjusted according

to the blood glucose level. Follow-up was performed for three months.

Measurement methods

Serum C-peptide was measured by magnetic separation enzyme-linked immunosorbent assay, with the BIOZYME Type I (1107–103606) endocrine-quantitative determination system (Cardiff CF14 5DX, UK) and the reagents were purchased from Beijing Bioekon Co Ltd (Beijing, China). Blood glucose was measured using the glucose oxidase method.

Statistical analysis

The data were analysed using SPSS 17.0 (SPSS Inc, Chicago, IL, USA). The data are expressed as mean \pm standard deviation. The area under the curve was calculated using the trapezoidal area formula. Homeostatic Model Assessment-2 (HOMA2) index software (HOMA2 Calculator v2.2, Diabetes Trials Unit, University of Oxford, Oxford, England) was used to calculate the insulin resistance index (HOMA2 IR) and insulin secretion index (HOMA2 B%). Correlations were determined using the Pearson correlation analysis. Pairwise comparisons were conducted using *t*-tests and the α level was set at 0.05.

RESULTS

The 326 T2DM patients included 144 men (44.2%) and 182 women (55.8%) with a disease duration of 0–324 months; additional details are shown in Table 1.

The 87 newly diagnosed T2DM patients (58 males, 29 females) had the following characteristics: mean age, 58.1 ± 14.7 years; FBG, 13.0 ± 4.9 mmol/L; two-hour postprandial blood glucose (2HPBG), 19.4 ± 8.5 mmol/L; BMI, 24.7 ± 3.8 kg/m²; waist circumference (WC), 89.5 ± 10.5 cm and glycated haemoglobin (HbA_{1c}), $11.4 \pm 2.5\%$. The data by groups are shown in Table 2; there were no significant differences between the two groups in any of the variables ($p > 0.05$).

Correlation analysis

The Pearson correlation analysis, which was conducted with all of the T2DM patients, indicated that the significant correlations with AUC-C were 2HPC-P ($r = 0.97$, $p < 0.05$), 2HPC-P increment ($r = 0.88$, $p < 0.05$) and 2HPC-P/FC-P ($r = 0.77$, $p < 0.05$).

Blood glucose control after the intensive treatment

After the intensive insulin therapy, both FBP and postprandial blood glucose were well controlled in the newly diagnosed T2DM patients, with an overall achievement rate of the standard values of 60.9% (53/87). Homeostatic Model Assessment-2 B% increased significantly after the treatment ($p < 0.01$), while HOMA2 IR did not change significantly ($p > 0.05$). There were also no significant

Table 1: Clinical data of 326 Type 2 diabetes mellitus patients ($\bar{x} \pm s$)

Item	Unit	Result
Age	years	57.9 \pm 13.3
Disease duration	months	82.0 \pm 82.1
BMI	Kg/m ²	24.6 \pm 3.9
FBG	mmol/L	10.2 \pm 4.5
2HPBG	mmol/L	14.7 \pm 5.4
HbA _{1c}	%	10.0 \pm 7.3
Total cholesterol	mmol/L	4.88 \pm 1.45
Triglyceride	mmol/L	1.98 \pm 2.17
Fasting C-peptide	ng/mL	1.22 \pm 0.75
30 min C-peptide	ng/mL	1.57 \pm 1.04
60 min C-peptide	ng/mL	2.29 \pm 1.61
90 min C-peptide	ng/mL	2.97 \pm 1.95
120 min C-peptide	ng/mL	3.43 \pm 2.16
150 min C-peptide	ng/mL	3.57 \pm 2.24
180 min C-peptide	ng/mL	3.57 \pm 2.09
2H PC-P increment	ng/mL	2.21 \pm 1.73
2 HPC-P/FC-P		3.1 \pm 1.5
AUC-C	(ng/mL) \times min	486.95 \pm 292.13

BMI: body mass index; FBG: fasting blood glucose; 2HPBG: 2-hour plasma blood glucose; HbA_{1c}: heamoglobin A_{1c}; 2H PC-P: two-hour postprandial C-peptide; 2H PC-P/ FC-P: two-hour postprandial C-peptide/ fasting C-peptide; AUC-C: area under the C-peptide curve; min: minute

Table 2: Grouping data of 87 newly diagnosed Type 2 diabetes mellitus patients

Group	Gender (F/M)	Age (years)	FBG (mmol/L)	2HPBG (mmol/L)	BMI (Kg/m ²)	WC (cm)	HbA _{1c} (%)
Group I (n = 43)	13/30	57.8 \pm 15.1	13.4 \pm 5.1	19.5 \pm 8.7	24.5 \pm 3.9	90.7 \pm 10.8	11.5 \pm 2.5
Group II (n = 44)	16/28	58.7 \pm 14.5	12.8 \pm 4.7	20.2 \pm 8.2	25.0 \pm 3.6	89.1 \pm 10.5	11.3 \pm 2.4

2HPBG: 2-hour plasma blood glucose; FBG: fasting blood glucose; BMI: body mass index; WC: waist circumference; HbA_{1c}: heamoglobin A_{1c}

changes in body mass index and waist circumference (WC) after the treatment ($p > 0.05$) [Table 3].

After the three-month intensive treatment in newly diagnosed T2DM patients, the ratio that achieved the standard blood glucose control values was 44.2% (19/43) of Group I and 36.4% (16/44) of Group 2, and this difference between the groups was not significant ($p > 0.05$). There were 20 patients (46.5%) in Group I (20/43) and five patients (11.4%) in Group II (5/44) who were able to stop the use of all antidiabetic drugs and achieve good results simply through lifestyle interventions to control blood sugar. The common feature of these patients who achieved good control of blood glucose simply through lifestyle interventions was a relatively high basic C-peptide concentration (> 2.0 ng/mL). Group I had nine patients that used insulin ≥ 20 u daily (20.9%), while Group II had 21 patients (47.7%). The common feature of these patients was a relatively low basic C-peptide concentration (< 0.5 ng/L). Furthermore, 10 patients in Group I only needed one oral hypoglycaemic drug and four patients required the combination of two antidiabetic drugs; in Group II, it was six patients and 12 patients, respectively.

DISCUSSION

The results of the present study suggest that 2HPC-P and its derivative indicators could effectively assess islet β -cell function in T2DM, thus guiding the choice of clinical treatment. Owing to the slow clearance rate of C-peptide, the liver exhibits a low rate of C-peptide uptake rate and C-peptide in the peripheral blood is not likely impacted by the exogenous insulin; therefore, it could much more accurately reflect islet β -cell function (11).

C-peptide was initially thought to be biologically inactive and was only used in combination with insulin to assess islet β -cell function; however, clinical studies have shown that C-peptide has important physiological functions (12). C-peptide could regulate islet β -cell function (13). A reduction in fasting C-peptide level has been significantly correlated with damage of thick myelinated nerve fibres; therefore, C-peptide has a protective

effect on nerves (14). Fasting and postprandial 2HPC-P values are considered protective factors for diabetic nephropathy and diabetic retinopathy, and a reduction in these values might cause and exacerbate T2DM-related microvascular disease (15).

The oral glucose tolerance test + C-peptide releasing test are common clinical methods to assess islet β -cell function (16). The glucose load might increase the changes in postprandial insulin resistance indicators; because some patients might not tolerate the oral glucose solution, a bread-based glucose load is more accepted clinically. The area under the C-peptide curve is a much more accurate assessment indicator (17).

With diabetes progression, islet β -cell dysfunction gradually increases (1, 18). Protection of damaged islet β -cell function has become one of the primary goals of clinical treatments (19). Exercise and some oral hypoglycaemic agents might delay T2DM-related β -cell dysfunction (20–24). Short-term intensive insulin therapy could protect and even partially reverse T2DM-related islet β -cell function (6, 7), and this beneficial effect could be maintained for a period of time after the intensive treatment; the length of this maintenance period is related to the patients' residual islet β -cell reserve function before the intensive treatment (8, 9). Newly diagnosed T2DM patients lose approximately 50% of β -cell function, on average, and the islet β -cell reserve function also decreases, which results in a non-significant increase of C-peptide after a glucose load (1).

The duration of diabetes has some effect on islet β -cell function; however, because of the small sample size, stratification based on disease duration could not be performed in the present study. In clinical practice, fasting and two-hour postprandial blood glucose, as well as serum C-peptide, should be routinely monitored in T2DM patients to guide clinical treatment.

Conflict of interest

All of the authors declare that they have no conflicts of interest regarding this paper

Table 3: Blood glucose, Homa2 index, body mass index and waist circumference of the newly diagnosed Type 2 diabetes mellitus patients before and after the intensive treatment

	FBG (mmol/L)	2HPBG (mmol/L)	B%	IR	BMI (kg/m ²)	WC (cm)
Baseline	13.0 ± 3.9	19.4 ± 6.5	26.9 ± 22.4	2.23 ± 1.36	24.7 ± 3.8	89.5 ± 10.5
After the treatment	5.7 ± 1.1*	7.5 ± 0.9*	145.9 ± 56.2*	2.50 ± 0.69	24.5 ± 3.5	89.0 ± 9.8

*Compared with the baseline, $p < 0.01$

2HPBG: 2-hour plasma blood glucose; FBG: fasting blood glucose; BMI: body mass index; WC: waist circumference

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