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Original Article

The relationship between postprandial C peptide-glucose ratio, beta-cell function and treatment success in type 2 diabetes mellitus

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ABSTRACT

Objectives: This study aims to investigate the relationship between postprandial C-peptide-to-glucose ratio (PCGR), β-cell function and successful glycemic glycemic control in type 2 diabetes mellitus (DM) and determine the efficacy and feasibility of the PCGR index in the individualization of diabetes treatment.

Materials and methods: This prospective study included a total of 49 patients (17 males, 32 females; mean age: 56±10 years; range, 32 to 75 years) under follow-up in Istanbul Medeniyet University Göztepe Training and Research Hospital Department of Internal Medicine with the diagnosis of type 2 DM between June and December 2016. Patients receiving insulin or insulin secretagogues were excluded. Data including age, sex, weight, height, waist circumference, hip circumference, date of DM diagnosis, serum hemoglobin A1c (HbA1c), and creatinine levels were recorded. All patients underwent a mixed meal test and their fasting blood glucose, C-peptide, postprandial glucose, and C-peptide levels were measured and recorded. Patients with a serum HbA1c level of 7% or lower were considered to have good glycemic control while patients with a serum HbA1c level of higher than 7% were considered to have uncontrolled diabetes. The relationship between C-peptide index (CPI), PCGR index, and parameters related to glycemia and β cell function was investigated.

Results: Mean diabetes duration was 6.6±6 years and mean serum HbA1c level was 7.9±1.8%. There was a weak correlation between CPI and Homeostasis Model Assessment-β (HOMA-β), a moderate correlation between fasting C-peptide, delta C-peptide, and HOMA-β, and a strong correlation between fasting C-peptide, postprandial C-peptide, PCGR, and HOMA-β ($p<0.05$, $p<0.05$, $p<0.001$, respectively). There was a moderate negative correlation between postprandial C-peptide, delta C-peptide, fasting C-peptide-to-glucose ratio (FCGR), and serum HbA1c level ($p<0.05$). There was no correlation between fasting C-peptide and serum HbA1c level while there was a strong negative correlation between PCGR and serum HbA1c level ($p<0.001$). Comparison of the patient groups with and without glycemic control revealed that mean PCGR was significantly higher in the former group than the latter ($p<0.001$).

Conclusion: We conclude that PCGR is significantly associated with glycemic control and variability. Our data suggest that PCGR is a useful index indicating β-cell function, and it can be used in the individualization of DM treatment.

Keywords: C-peptide, diabetes mellitus, homeostasis model assessment, postprandial C-peptide-to-glucose ratio.

Type 2 diabetes mellitus (DM) is a disease characterized by insulin resistance and reduced insulin secretion.[1] It is widely accepted that β-cell function should be considered during the initiation or modification of its treatment.[2,3] It is known that pancreatic β-cell function deteriorates as the disease progresses. The United Kingdom Prospective Diabetes Study (UKPDS) and Belfast Diet Study showed that the primary reason for persistent hyperglycemia and failure of treatment in diabetic patients was the loss in β-cell function.[4,5] Therefore, measurement of the variations in insulin secretion and analysis of β-cell function is essential in selecting the optimal

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treatment method.[6] The C-peptide, which is secreted from the secretory granules of pancreatic β-cells simultaneously with insulin, is the most important marker of β-cell function. Unlike other markers, it can be used for evaluating β-cell function even in patients on insulin treatment. Recently, it was suggested that postprandial C-peptide-glucose ratio (PCGR) measured following oral glucose intake could be a better marker than the markers such as Homeostasis Model Assessment-beta (HOMA-β) which relies on fasting blood levels in the assessment of β-cell reserve.[7,8] It was also recommended that PCGR could be used as a marker for measuring β-cell function during both treatment and follow-up of type 2 DM patients. In this study, we aimed to investigate the relationship between PCGR, β-cell function, and treatment outcomes and determine the efficacy of PCGR index in the individualization of treatment in patients with type 2 DM.

MATERIALS AND METHODS

This single center, prospective study included a total of 49 patients (17 males, 32 females; mean age: 56±10 years; range, 32 to 75 years) under follow-up in Istanbul Medeniyet University, Göztepe Training and Research Hospital Department of Internal Medicine with the diagnosis of type 2 DM between June and December 2016. Type 2 DM patients who were older than 20, who were under follow-up for at least six months and had a body mass index (BMI) of 28 kg/m^2 or higher and a glomerular filtration rate (GFR) of 60 mL/min or higher were included in the study. All patients were on at least one anti-diabetic medication. A written informed consent was obtained from each patient. The study protocol was approved by the Medeniyet University Goztepe Training and Research Hospital Ethics Committee (Date and number of approval: 14.06.2016/0134). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patients who were on medications such as sulfonylurea, glynids, dipeptidyl peptidase 4 inhibitors (DPP4-i), insulin or steroids, those who have severe liver or kidney disease were excluded. Data including sex, age, diabetes duration, waist circumference, hip circumference, height, weight, BMI, serum hemoglobin A1c (HbA1c), fasting blood C-peptide level, fasting blood glucose level, urea, and creatinine levels were recorded. The waist-hip ratio (WHR) of each patient was calculated. A WHR of 0.95 or lower was considered normal for male patients while a WHR of 0.85 or lower was considered normal for female patients.

All patients underwent a mixed meal test after blood sampling. During mixed meal test, patients were fed with Ensure liquid enteral nutrition supplement (Abbott, Illinois, USA) which contains 500 kcal (17.5 g fat [31.5%], 68 g carbohydrate [54.6%] and 17.5 g protein [14%]) per 200 mL serving. Blood C-peptide and glucose levels were measured at minutes 0 and 90. The HOMA-β, postprandial C-peptide, delta C-peptide, PCGR, C-peptide index (CPI) values were measured.[9] The correlations between HOMA-β, PCGR and CPI were analyzed. The threshold level for serum HbA1c was accepted as 7%; patients with a serum HbA1c level of 7% or lower were considered to have good glycemic control while those with a serum HbA1c level of higher than 7% were considered to have

Table 1. Clinical and demographic characteristics of the study patients (n=49)

	n	%	Mean±SD
Age (year)			56±10
Sex			
Male	17	34.7	
Female	32	65.3	
Weight (kg)			83±16
Sex			
Male			85±16
Female			81±16
BMI (kg/m^2)			32±5
Sex			
Male			31±4
Female			33±5
Waist circumference (cm)			101±12
Sex			
Male			99±8
Female			101±13
Waist-hip ratio			0.96±0.07
Duration of diabetes (year)			6.6±6
HbA1c (%) mean			7.9±1.8
Creatinine (mg/dL)			0.8±0.1
Fasting plasma glucose (mg/dL)			153±43
Postprandial plasma glucose (mg/dL)			211±68

SD: Standard deviation; BMI: Body mass index; HbA1c: Hemoglobin A1c.

uncontrolled diabetes. Relationships between fasting blood C-peptide, postprandial C-peptide, delta C-peptide, PCGR, CPI, HOMA-β, and treatment success were analyzed.

Patients with normal WHRs were compared with the patients who had high WHRs regarding fasting C-peptide, postprandial C-peptide, fasting C-peptide-to-glucose ratio (FCGR), and PCGR. Also, patients with a diabetes duration of more than five years were compared with those with a follow-up period of shorter than five years concerning the same parameters.

Delta C-peptide was calculated by taking the difference between C-peptide measured at min 90 and min 0. The formula 'fasting insulin (μIU/mL)×20/fasting blood glucose (mmol/L) - 3,5' was used for the calculation of HOMA-β. The C-peptide index was calculated by using the formula '(90th min C-peptide - C-peptide measured at min 0)/(90th min glucose level - glucose level measured at min 0)'. The formula '(postprandial 90th min C-peptide [ng/mL]/ postprandial 90th min glucose level) [mg/dL] ×100' was used for PCGR calculation.

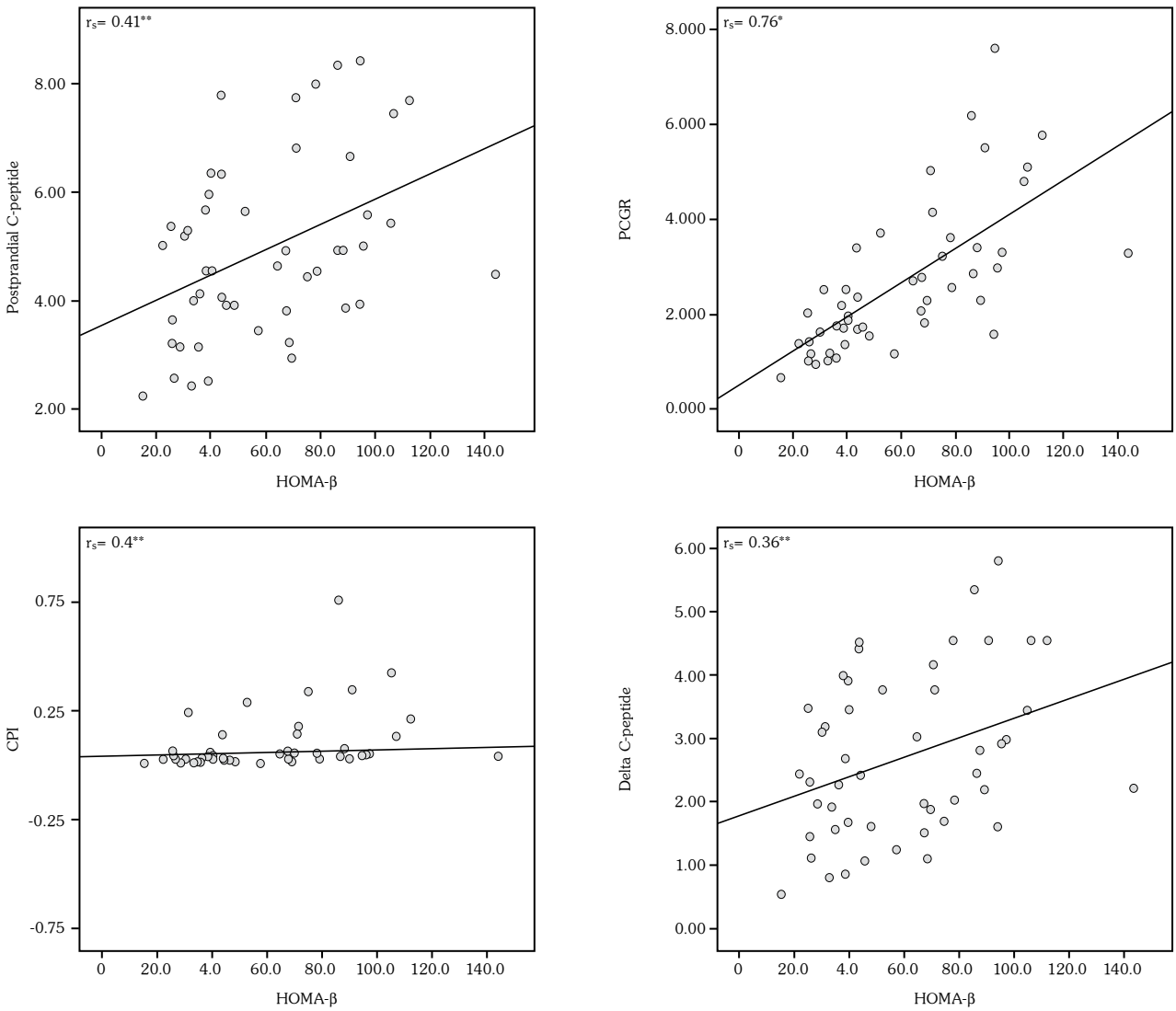

Figure 1. HOMA-β with PCGR, postprandial C-peptide, CPI, delta C-peptide correlations.

* p<0.001; ** p<0.05; HOMA-β: Beta cell function homeostasis model assessment; CPI: C-peptid index; PCGR: postprandial C-peptide glucose ratio.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation. The chi-square test was used for the analysis of categorical data. The Student's t-test was used for the analysis of parametric continuous data while the Mann-Whitney U test was used for analyzing the non-parametric continuous data. The suitability of the data to normal distribution was checked using the Shapiro-Wilk test. The Analysis of Variance (ANOVA) test was used for the comparison of three groups with normally distributed homogeneous data and the Tukey's test was used for post hoc comparisons. The Kruskal Wallis test was used for the analysis of non-normally distributed and heterogeneous data. Pearson and Spearman correlation tests were implemented for the correlation analyses. A *p*-value of <0.05 was considered statistically significant.

RESULTS

The mean diabetes duration of the patients was 6.6±6 years. The mean serum HbA1c level

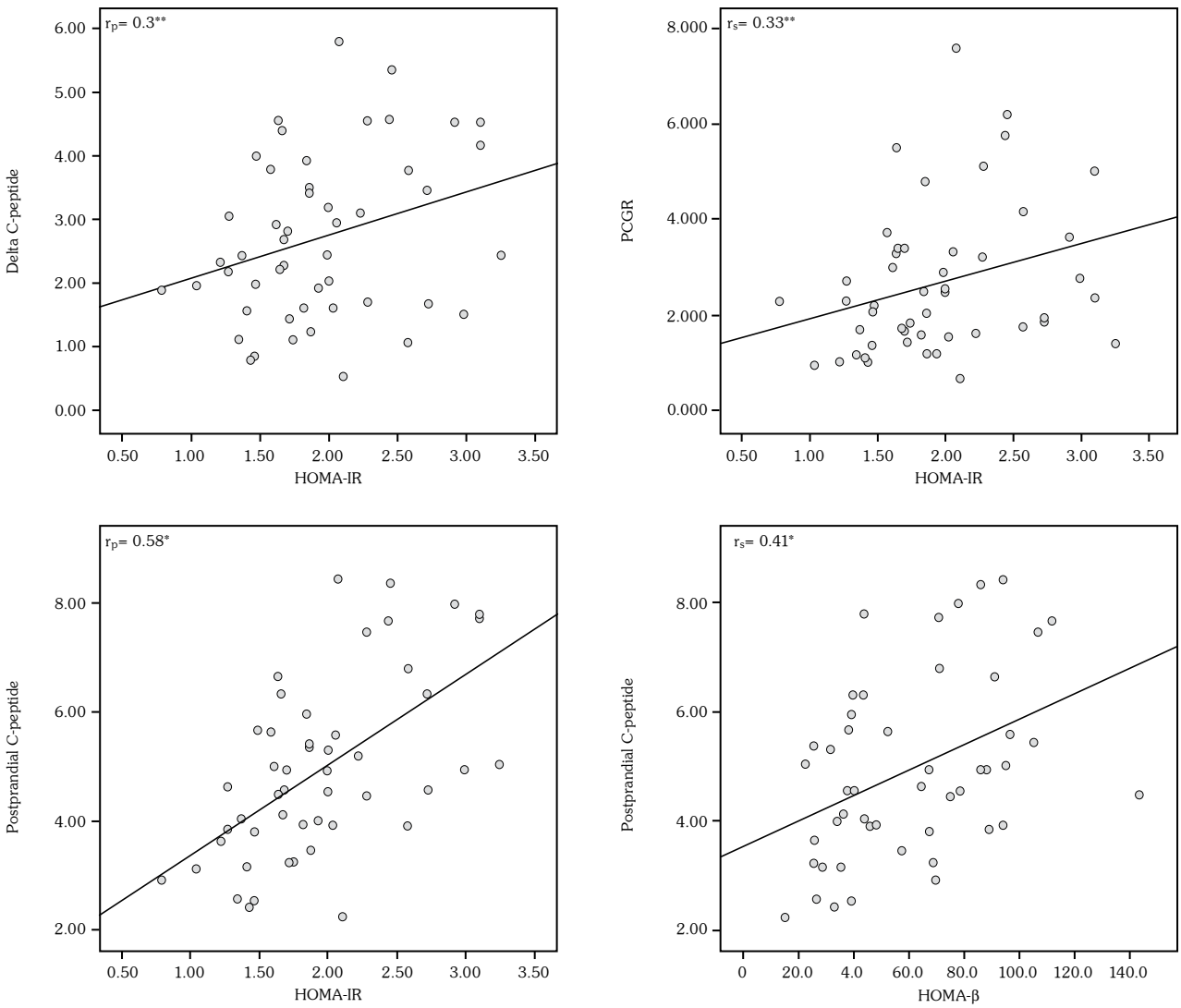

Figure 2. HOMA-IR with delta C-peptide, PCGR, postprandial C-peptide correlations.

* p<0.001; ** p<0.05; HOMA-IR: Homeostasis model assessment of insulin resistance; HOMA-β: Beta cell function homeostasis model assessment; PCGR: postprandial C-peptide glucose ratio.

Table 2. Comparative correlation analysis of indexes showing glycemic status

	FCP	PCP	DCP	FCGR	PCGR	CPI	HOMA-β
FCP	-	0.7*	0.43**	0.764*	0.577*	0.313**	0.490*
PCP	-	-	0.94*	0.581*	0.801*	0.544*	0.414**
DCP	-	-	-	0.430**	0.753*	0.537*	0.360**
FCGR	-	-	-	-	0.792*	0.420**	0.917*
PCGR	-	-	-	-	-	0.721*	0.762*
CPI	-	-	-	-	-	-	0..40**
HOMA-β	-	-	-	-	-	-	-
HbA1c	0.22***	-0.29**	-0.29**	-0.63*	-0.7*	-0.57*	-0.75*

FCP: Fasting C-peptide; PCP: Postprandial C-peptide; DCP: Delta C-peptide; FCGR: Fasting C peptide-glucose ratio; PCGR: Postprandial C peptide-glucose ratio; CPI: C-peptide index; HOMA-β: Beta cell function homeostasis model assessment; * p<0.001; ** p<0.05; *** p>0.05.

was 7.9±1.8%. The mean fasting blood glucose level was 153±43 mg/dL and postprandial 90th min blood glucose level measured after mixed meal test was 211±68 mg/dL. The clinical and demographic data of the patients in the study are given in Table 1.

The correlation analysis revealed that there was a strong correlation between PCGR and HOMA-β (p<0.001). On the other hand, there was a moderate correlation between postprandial C-peptide and HOMA-β (p<0.05). There were weak correlations between CPI, delta C-peptide and HOMA-β (p<0.05). The relevant scatter plots are shown in Figure 1.

There was a strong correlation between Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) and postprandial C-peptide levels (p<0.001). On the other hand, there were weak correlations between HOMA-IR and PCGR, delta C-peptide levels (p<0.005). The relevant scatter plots are shown in Figure 2.

Analyses of the correlations between the glycemia-related parameters revealed that there was no significant correlation between fasting C-peptide levels and serum HbA1c levels while there were borderline significant negative correlations between postprandial C-peptide, delta C-peptide and serum HbA1c levels (p<0.05). There was a moderate negative correlation between FCGR and serum HbA1c. However, there was a significant negative correlation between PCGR and serum HbA1c (p<0.001). Results of the correlation analysis are given in Table 2.

There was no difference between the patients with normal and high WHRs concerning fasting C-peptide, postprandial C-peptide, FCGR, and PCGR levels (p>0.05) (Table 3).

Comparisons between patients with more and less than five years of DM follow-up showed that there was no difference between the groups regarding fasting C-peptide, postprandial C-peptide, FCGR, and PCGR levels (p>0.05) (Table 4).

Table 3. Comparison of fasting C-peptide, postprandial C-peptide, FCGR and PCGR according to WHR

	Normal WHR	High WHR	
	Mean±SD	Mean±SD	*p*
Fasting C-peptide (ng/mL)	2.2±0.7	2.3±0.6	0.66
Postprandial C-peptide (ng/mL)	4.7±2	5±1.6	0.581
FCGR	1.5±0.7	1.6±0.6	0.66
PCGR	2.6±2.2	2.8±1.4	0.310

FCGR: Fasting C-peptide-glucose ratio; PCGR: Postprandial C-peptide-glucose ratio; WHR: Waist-hip ratio; SD: Standard deviation.

Table 4. Comparison of fasting C-peptide, postprandial C-peptide, FCGR and PCGR according to duration of diabetes

Duration of diabetes	≤5 years	>5 years	
	Mean±SD	Mean±SD	*p*
Açlık C-peptid (ng/mL)	2.2±0.6	2.3±0.6	0.475
Postprandial C-peptide (ng/mL)	5±1.7	4.7±1.5	0.377
FCGR	1.7±0.6	1.4±0.6	0.186
PCGR	2.9±1.7	2.2±1.2	0.113

FCGR: Fasting C-peptide-glucose ratio; PCGR: Postprandial C-peptide-glucose ratio; WHR: Waist-hip ratio; SD: Standard deviation.

Table 5. Comparison of patients with good and poor glycemic control

	Patients with good glycemic control			Patients with poor glycemic control			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			58±11			54±10	0.240
Sex							0.440
Male	6			11			
Female	15			17			
Waist-hip ratio, count (%)	17	80		22	79		0.905
BMI (kg/m^2)			32±5			32±5	0.936
Duration of diabetes, (year)			4±3.6			8±7.6	0.007
Fasting glucose (mg/dL)			119±20			178±38	<0.001
Postprandial glucose (mg/dL)			153±28			255±55	0.002
Fasting C-peptide (ng/mL)			2.4±0.6			2.1±0.6	0.07
Postprandial C-peptide (ng/mL)			5.6±1.5			4.5±1.6	0.02
CPI			0.09±0.4			0.05±0.05	0.567
PCGR			3.7±1.5			1.8±0.9	<0.001
FCGR			2.02±0.5			1.23±0.4	<0.001

SD: Standard deviation; BMI: Body mass index; CPI: C-peptide index; PCGR: Postprandial C peptide-glucose ratio; FCGR: Fasting C peptide-glucose ratio.

Comparisons between the 21 patients with good glycemic control (i.e., serum HbA1c ≤7) and 28 patients with poor glycemic control (i.e., serum HbA1c >7) revealed that mean patient age was 58±11 in the former group and 54±10 in the latter. There was a high WHR in 80% (n=17) of the patients with good glycemic control and 79% (n=22) of the patients with poor glycemic control. Mean BMI was 32±5 kg/m^2 in both groups. The mean fasting blood glucose level was 119±20 mg/dL and the mean postprandial glucose level was 153±28 mg/dL in the former group. In the latter group however, the mean fasting blood glucose level was 178±38 mg/dL and the mean postprandial blood glucose level was 255±55 mg/dL (Table 5).

There was no significant difference between the patient group with good glycemic control and poor glycemic control regarding fasting C-peptide levels and CPI. The PCGR index was significantly higher in the former group (p<0.001). Also, there was a significant difference concerning mean postprandial C-peptide and FCGR (p<0.05). There was a stronger association between PCGR index and glycemia-related parameters compared to the association between other indices and these parameters (Table 5).

DISCUSSION

Oral glucose tolerance test (OGTT) and HOMA-β index are widely used for assessing β-cell function and insulin secretion capacity.[10,11]

However, HOMA-β is an index that can solely be used in fasting state and in patients who are not on insulin treatment. These features are considered as the disadvantages of this index. It was suggested that postprandial C-peptide-based indices could reflect the β-cell function in patients on insulin or oral antidiabetic treatments.[12,13] They can also be used as a guide while making decisions such as initiating or ceasing insulin treatment and predicting the progression of DM. Some studies showed that postprandial measurements were superior to fasting state measurements in estimating the progression of DM.[14] In our study, we investigated the association of PCGR index - a postprandial C-peptide-based index - with the other indices and compared the patients who responded well to diabetes treatment with those who did not respond well to diabetes treatment regarding this index.

Our analysis found strong correlations between PCGR, HOMA-β and other indices showing β-cell function. Also, we determined that PCGR and HOMA-β had a significant negative correlation with serum HbA1c. On the other hand, there was a weak correlation between CPI - an index that controversially shows the β-cell function - and HOMA-β. There was a moderate-weak correlation between fasting C-peptide, postprandial C-peptide, delta C-peptide and HOMA-β. However, there was a strong correlation between PCGR and HOMA-β.

Similarly, Lee et al.[9] found a stronger correlation between HOMA-β and PCGR than other indices. In the same study, the researchers determined a strong negative correlation between HOMA-β, PCGR, fasting blood glucose, postprandial glucose and serum HbA1c. They also stated that PCGR could be a more accurate and practical index than HOMA-β in indicating insulin secretion capacity. In our study, although there was a significant negative correlation between PCGR and HgA1c, we did not find PCGR to be superior to HOMA-β. However, there was no correlation between fasting C-peptide and serum HgA1c and a weak-moderate negative correlation between postprandial C-peptide, delta C-peptide and FCGR.

Recently it was shown that PCGR index is inversely correlated with glycemic control and glycemic variability regardless of the antidiabetic treatment used.[15-17] Similarly, we determined that PCGR was significantly associated with glycemic control. We also found that PCGR was superior to fasting C-peptide, postprandial C-peptide, delta C-peptide and FCGR in indicating insulin secretion capacity. We suggest that PCGR is at least as effective as HOMA-β in showing insulin secretion capacity and it could be useful in the management of DM patients since it can be used in patients on insulin treatment.

Currently, there is an ongoing debate in the literature regarding the use of PCGR and other indices for assessing β-cell reserve in the management of patients with type 2 DM.[18] Some recent studies showed that PCGR is a better predictor of β-cell function than FCGR and urinary C-peptide levels and it could predict the disease progression and insulin treatment requirements better than these markers.[18,19] It was also reported that the PCGR value decreased with the progression of DM.[9] Also, some other studies showed that postprandial C-peptide-based indices could predict the optimal time for insulin dose reduction or insulin treatment cessation.[12] In another study, it was reported that the PCGR index could predict transition to liraglutide monotherapy in diabetic patients.[20] In our study, we determined that PCGR index was higher in the patient group with good glycemic control than the patient group with poor glycemic control. We detected that PCGR decreased and glycemic control deteriorated as DM duration increased. Altogether, these findings indicate that PCGR index could be used for predicting insulin treatment requirement, it could be used to predict DM progression and it could be used as a guide in establishing treatment strategies, as it has a strong association with DM progression.

The limitation of our study is that it is a retrospective, single-center study conducted on a small sample size with a relatively short-term follow-up, and its results cannot be readily generalized. Also, PCGR was determined with a mixed meal test instead of a glucagon stimulation test because the former is a more practical and less invasive test method than the latter.[21,22]

We conclude that PCGR was at least as effective as HOMA-β and superior to fasting C-peptide, postprandial C-peptide, delta C-peptide and FCGR in measuring insulin

secretion capacity. Also, we found that PCGR had a strong inverse correlation with glycemic control and glycemic variability. We suggest that PCGR can be used as an effective and simple index to assess β-cell function; it can assist in the individualization of DM treatment and selection of antidiabetic treatment methods. Nevertheless, our results should be confirmed by multi-center studies conducted in relatively larger patient populations.

Declaration of conflicting interests

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