C-peptide as a marker to assess pancreatic beta cell function in Iraqi patients with type 2 diabetes

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Abstract

The aim of this study was to determine the best marker to assess pancreatic beta cell function from fasting and postprandial C-peptide, fasting and postprandial C-peptide index, to assess effect of duration of diabetes and BMI on beta cell function in patients with type 2 diabetes. The study groups consist of 63 Iraqi patients (26 male and 37 female) with type 2 diabetes and 20 healthy (10 male and 10 female) matched as a control group. Blood samples were drawn from all patients at fasting and then after 2hrs from breakfast. Fasting and postprandial serum C-peptide levels and concentrations of glucose had been determined. Insulin and other biochemical indicators were measured. Those patients were stratified according to time since diagnosis, then subdivided according to BMI: within healthy weight (18.5– 24.9kg/m^2), overweight (25–29.9kg/m^2) and obese (>30kg/m^2).

There was a significant negative correlation between C-peptide indices and duration of diabetes (P<0.001, r=-0.445 in fasting state vs. P<0.001, r=-0.561 in postprandial state) and a significant positive correlation between C-peptide indices and BMI (P=0.003, r=0.363 in fasting state vs. P<0.001, r=0.626 in postprandial state). Also, a significant positive correlation between C-peptide indices and disposition index (P=0.001, r=0.416 in fasting state vs. P<0.001, r=0.694 in postprandial state). Area under the receiver operating characteristic curve (AUC) of postprandial C-peptide index might have been the better one (0.896 vs. 0.779 in fasting state). Postprandial C-peptide index has the best value which mirrors the maximal beta cell function (sensitivity=80.6%, specificity=87.5% vs. sensitivity=71%, specificity=75% in fasting index). In conclusion, postprandial C-peptide index is a good marker to assess beta cell function and it is significantly associated with disposition index. Beta cell function (insulin secretion) is conversely related to duration of T2DM and higher BMI association with higher insulin secretion during early period but after longer period insulin secretion decreased.

Keywords: Type 2 diabetes, C-peptide index, duration of diabetes, BMI, Beta cell function.

Introduction

Type 2 diabetes mellitus is recognized by obesity and insulin resistance and a deficit of beta cells is added a core problem between in this type of diabetes[1]. The incidence of diabetes is continuously increasing, in Iraq the prevalence of diabetes was 13.9% in 2015[2]. The number of people with diabetes in the world was estimated to 424.9 million in 2017 and is expected to rise to 628.6 million in 2045[3].

Beta cell deficit will be a common pathogenetic characteristic of both types of diabetes. Therefore, evaluation for beta cell function will be fundamental in each form of diabetes[4]. Importantly, there is a beta cell deficiency in patients with kind 2 diabetes, as well as this deficiency has been shown to worsen with the time of diabetes. Those outcomes of the United Kingdom Prospective Diabetes Study (UKPDS) reveal that pancreatic β-cell work (% β) was evaluated by Homeostasis Model Assessment (HOMA) in patients.[5]

A and B chains of insulin connected by 31 amino acid peptide are called C-peptide[6,7]. Insulin secreted from pancreatic beta cells might be partly cleared inside the liver before coming into the peripheral circulate[8,9]. The concentration insulin calculated in peripheral blood cannot represent the whole quantity of insulin secreted by using the pancreas. On the opposite, C-peptide secreted together with insulin in equimolar quantities is not cleared in the liver. The peripheral plasma C-peptide focuses mirror endogenous insulin secretion greater precisely than serum insulin[10,11]. The half-life of C-peptide level in blood is longer than insulin level in it (30 vs. 4 min)[12,13]. Furthermore, C-peptide is able to assess beta cellular function even in patients who take insulin therapy[14].

The C-peptide index (a proportion of serum C-peptide to plasma glucose concentrations) is use to assess beta cell function[15]. Compared with fasting C-peptide level, postprandial C-peptide level is greater capable of appearing the maximum insulin secretory capacity, specifically in patients with diabetes[4]. The aim of this study is to determine the best marker to assess pancreatic beta cell function from fasting and postprandial C-peptide, fasting and postprandial C-peptide index and to assess effect of duration of diabetes and BMI on beta cell function in patients with T2DM.

Material and Methods

Study groups: Sixty-three Iraqi patients with type 2 diabetes (26 male and 37 female) and twenty control (10 male and 10 female) attending to Imamein Kadhimein Medical City with

age from 35-60 were enrolled in the study. Formal consent from health community and subjects was taken. The date of diagnosis for patients was determined from their medical record, medical history, diagnostic criteria based on the American Diabetes Association (ADA) (FBG≥ 126 mg/dL, postprandial plasma glucose≥200 and HbA1C≥6.5%)[14]. The purpose of enrolled control subjects is to compare postprandial value of C-peptide for them with diabetic patients. We excluded patients having age less than 35 and more than 60. C-peptide is excreted by the kidneys, so we excluded patients with renal disability, because renal disability impacts on C-peptide level[15]. We also excluded patients with chronic liver disease, chronic pancreatic disease, pregnancy, patients who were taking insulin therapy and patients with type 1 diabetes.

The patients had been divided according to the time next diagnosis and subdivided according to the BMI: underweight (<18.5kg/m^2), normal (18.5– 24.9kg/m^2), overweight (25–29.9kg/m^2) and obesity (>30kg/m^2)[16]. Age and BMI (mean ± S.D.) were 50.68 ± 5.72 years and 28.37 ± 4.62 kg/m^2 respectively. Years from diagnosis were 4.25± 2.81; HbA1c when attended to the hospital was 8.33 ± 2.28. The number of patients treated with Sulfonylurea, Sulfonylurea plus Metformin were 27 and 36 respectively.

Methods: Blood samples were drawn after overnight fasting to determine glucose concentrations, serum insulin levels, C-peptide levels, lipids profile including triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol. Then after 2hs from breakfast, blood samples were drawn to determine glucose concentrations and C-peptide levels. Fasting and postprandial Plasma glucose were measured by a glucose oxidase method. Fasting and postprandial serum c-peptide level was measured by (Demeditec Diagnostic company, Germany) ELISA kit. Fasting and postprandial C-peptide indices were studied as follows: fasting or postprandial serum c-peptide (ng/mL) / fasting or postprandial plasma glucose (mg/dL) × 100, respectively.[19] The disposition index (DI) was calculated as result to (insulin sensitivity(HOMA-S) × insulin secretion).[20]

Statistical analysis: Data were reported as means ± standard deviation. A student's t-test was used for comparison of significance between two groups. A paired-samples t-test was used for comparison of significance between pre and post 2hr breakfast in the same group, with a P value less than 0.05 indicating statistically significant difference. The correlation between pre index, postprandial index and duration of diabetes was detected using the Pearson correlation analysis. To compare which kinds of c-peptide index have the best ability to appear the function in pancreatic beta cells in T2DM, we used the receiver operating characteristic curve (ROC). IBM SPSS software package version 22.0 was used for data statistical analysis.

Results and Discussion

To evaluate the correlation between beta cell function and time next diagnosis, the patients had been divided according to the time next diagnosis (group I: 1-4 years, group II: 5-10 years), There was a significant increase in fasting and postprandial concentration of glucose in group II than group I (220.88±75.81 vs. 163.19±52.78 at fasting state, 313.78±74.25 vs. 227.58±66.38 at post prandial state), the mean of HbA1c increase in group II but the difference was not significant (8.55 ±2.4 (%) in group II vs. 8.1±2.17(%) in group I). There was a significant decrease in group II in BMI, fasting and postprandial concentration of c-peptide, fasting and postprandial of c-peptide index, all anthropometric and biochemical characteristics of the participant in both groups were illustrated in table 1.

On comparison of C-peptide concentration and index between pre and post (2hr) breakfast by paired t-test, we found highly significant difference increase in postprandial C-peptide and C-peptide index than fasting C-peptide and C-peptide index (2.68 ±0.49, 1.1±0.44 vs. 0.6±0.2, 0.36±0.19) suggesting beta cell still work and secreted insulin in patients involved, but there was a significant difference decrease in group II (5-10 years after diagnosis) in postprandial C-peptide and postprandial C-peptide index than in group I (1-4 years after diagnosis) (the mean value 2.39±0.34, 0.81±0.23 in group II vs. 2.97±0.45, 1.4±0.4 in group I) (Table 2) suggesting a gradual decrease to β cell function next diagnosis of T2DM (5-10 years) ongoing diabetics.

A significant negative correlation of C-peptide indices and time next diagnosis was found among them, the greatest negative correlation with time next diagnosis was apparent in postprandial C-peptide index ($r = -0.561$, $p < 0.001$). BMI is positively correlated together with β cell function estimated by serum C-peptide and C-peptide index (Table 3). The study groups were sub divided according to BMI: group I containing healthy weight (24.46 ±0.32 kg/m^2) and obese (33.67±3.39 kg/m^2) and group II containing healthy weight (23.45±1.83 kg/m^2) and overweight (28.07±1.39 kg/m^2). There was a highly significant difference in C-peptide index measurement between groups, larger values of C-peptide and C-peptide index were observed in high-BMI patients compared with low-BMI patients in group I. In this group there was a significant increase in postprandial c-peptide index in obese than in healthy weight subjects (1.64±0.25 vs. 0.96 ±0.18, P<0.001), (Table 4).

To compare which kinds of c-peptide index have the best ability to appear the function in pancreatic beta cells through the duration of diabetes, we performed area under the receiver operating characteristic curve (ROC). In ROC curve analysis, we found that postprandial c-peptide index has the very best diagnostic value to predict dysfunction in pancreatic β cells as compared to the other markers (Figure 1), (AUC =0.896, sensitivity =80.6%, specificity =87.5%). Other results were in table 5. In this cross-sectional study beta cell function decreases with duration of T2DM (measured by pre and postprandial C-peptide). C-peptide is extensively agreeable as a sign of β cellular function[17,18].

Upon comparison, the concentration of C-peptide and C-peptide index between pre and post (2hr) breakfast by paired t-test, we found a highly significant increase in postprandial C-peptide and C-peptide index than in fasting C-peptide and C-peptide index (2.68 ±0.49(ng/mL)and 1.1±0.44 in postprandial state vs. 0.6±0.2(ng/mL)and 0.36±0.19 in fast state). These results confirm beta cell still work and secreted insulin in patients involved in this study, but there was a significant difference decrease in group II (5-10 years after diagnosis) in postprandial C-peptide and postprandial C-peptide index than in group I (1-4 years after diagnosis) (the mean value are 2.39±0.34(ng/mL)and 0.81±0.23 in group II vs. 2.97±0.45(ng/mL)and 1.4±0.4 in group I) (Table 2), implying the increment in beta cell workload makes overwork on beta cells.

Beta cells can also become dysfunctional. We found a significant negative correlation among C-peptide indices and time after diagnosis in Iraqi patients with T2DM (Table 3) which closely resembles result by United Kingdom Prospective Diabetes Study. The United Kingdom Prospective Diabetes Study (UKPDS) showed that β cellular function measured by way homeostasis model assessment (HOMA) between patients including newly diagnosed T2DM was approximately 50% of that within normal subjects and then continued to reduce approximately 5% per year and reduced approximately 25% in 5 years; UKPDS has additionally shown glycemic control within those patients progressively deteriorated with time regardless of treatment; furthermore this deterioration about glycemic control was mainly because of a decrease in β cellular function[5].

Saisho et al[19] reported that postprandial C-peptide index is negatively correlated with the period of type 2 diabetes mellitus. Also, Funakoshi et al[23] observed that period of diabetes was negatively correlated with C-peptide level in patients with T2DM.

In our study we found a significant difference in BMI, the mean of BMI increase in group I than group II (30.40+5.23 (kg/m^2) vs. 26.33+2.75(kg/m^2)). Our results are similar to that obtained by Matsuba et al[24] who reported that mean of BMI of newly diagnosed T2DM patients has increment over the last decade. Insulin secretion by β cell increment within the face of obesity causes workload in β cell[25,26]. Saisho et al[4] suggest that decline in C-peptide level with duration of diabetes might have been greater in high BMI subjects than in low BMI subjects; suggesting that obesity might quicken those decrease for beta cellular function with duration in subjects including T2DM.

Also, in our study there was a significant positive correlation between fasting and postprandial C-peptide indices with BMI and postprandial C-peptide index has the highest value between them to reflect the maximal beta cellular function (Table 3). Funakoshi et al[23] found that BMI was positively correlated with serum C-peptide level in patients with T2DM.

We divided each group according to BMI into subgroup, (Table 4), we noticed higher values of BMI association with higher values of endogenous insulin secretion (C-peptide and index) during early period (1-4 years) but after longer period (5-10) C-peptide and index decrease. A previous study suggests that one possible reason behind this phenomenon is that the compensatory beta cell mass increase with obesity is progressively lessened through long –time period diabetic exposure.

Funakoshi et al[23] have reported that large values of C-peptide (endogenous insulin secretion) in high-BMI patients as compared for low-BMI patients had been observed in groups with fewer years from diagnosis, so they suggest that the impact of BMI on beta cell secretory function is more distinguished in disease of shorter duration.

In our study, there is a negative correlation among C-peptide indices and HbA1c in patients with T2DM. Patients with lower postprandial C-peptide index showed higher HbA1c (group II) as comparison with patients with higher postprandial C-peptide index (group I) (Table 3), that means C-peptide is no less important than HbA1c in diagnosis dysfunction in beta cells. Saisho et al[14] suggested poorer glycemic control in patients with T2DM and lower postprandial C-peptide index although the treatment. Indeed, postprandial C-peptide index became negatively correlated with HbA1c next two years[27].

On other hand, in our study we found Postprandial C-peptide index is a good marker to assess beta cell function as compared with fasting C-peptide index, fasting and postprandial C-peptide, this finding is consistent with other researchers studies, Zhang et al[25] found that postprandial C-peptide index is more related to β-cell function. Saisho et al[14] have reported the insulin need for the management of T2DM is more closely related to postprandial C-peptide index than with fasting C-peptide index. Kim et al[28] found that postprandial C-peptide index was more closely related to future development of diabetes than fasting c-peptide index.

Lee et al[29] have reported that postprandial C-peptide index was more useful for predicting treatment strategies such as oral anti diabetic agents and insulin therapy than other C-peptide indices. Other researchers additionally appeared that in comparison with fasting C-peptide index and HOMA-β, postprandial C-peptide index showed the greatest correlation with beta cellular mass in surgical pancreatic specimens from those suffering from diabetes.[30]

In our study we found a significant difference in DI, the mean of DI decrease in group II than group I (2.66 ± 0.61 vs. 2.03 ± 0.64) (Table 1). We suggest a decrease in the mean value of DI may be due to lack of insulin secretion and insulin sensitivity over time.

Holder et al[31] reported that participants showed a decrease in the disposition index regardless of obesity, indicating

insufficient compensation of insulin secretion by beta cells in the context of insulin resistance. In addition, this indicator showed predicting deterioration of glucose metabolism during the time of diabetes in adults and children. This may be due to defects in the secretion of beta cells.[32]

In our study we also found a positive correlation between C-peptide indices and DI in patients with T2DM, both postprandial CPI and fasting CPI were correlated independently with DI, but postprandial CPI was the most closely related to DI than fasting CPI (r=0.694 ، P <0.001) (Table 3). Our results are consistent with the results of Zhang et al[20] who are found that the postprandial CPI is most closely associated with DI. Therefore, the DI assessment, which is measured of relative cell function for insulin sensitivity, is critical to describe the risk and progression of diabetes. Sjaarda et al[33] explained the importance of assessing insulin secretion and insulin sensitivity at the same time. A (DI) indicator is proposed to measure beta cell function, which is critical to describe the risk and progress of diabetes.

Conclusion

Postprandial C-peptide index is a best marker to assess beta cell function as compared with fasting C-peptide index, fasting and postprandial C-peptide. The Disposition index is significantly associated with Postprandial CPI, so it provides a beneficial measure of beta cell function. Beta cell function (insulin secretion) is conversely related to duration of T2DM. Higher BMI association is with higher insulin secretion during early period but after longer period, insulin secretion was decreased. Provide a better knowledge of the degree and rate of deterioration of beta cell function at the early stage of the disease provides an additional tool to help manage diabetes.

Table 1
Clinical and biochemical characteristics of patients

	Total	Group 1 Mean ±SD	Group 2 Mean ±SD	P value
N	63	31	32	
Gender(M/F)	26M/37F	11M/20F	15M/17F	
Age	50.68±5.72	50.26±6.03	51.09±5.48	0.567
BMI (kg/m^2)	28.33±4.61	30.40±5.23	26.33±2.75	<0.001
FPG (mg/dL)	192.50±71.18	163.19±52.78	220.88±75.81	0.001
Fasting CP (ng/mL)	0.60±0.20	0.70±0.24	0.50±0.09	<0.001
Fasting CPI	0.36±0.19	0.45±0.21	0.27±0.12	<0.001
Postprandial PG (mg/dL)	271.37±82.32	227.58±66.38	313.78±74.25	<0.001
Postprandial CP (ng/mL)	2.68±0.49	2.97±0.45	2.39±0.34	<0.001
Postprandial CPI	1.1±0.44	1.40±0.40	0.81±0.23	<0.001
HbA1c (%)	8.33± 2.28	8.1±2.17	8.55±2.4	0.438

BMI=Body mass index, FPG=Fasting plasma glucose, CP=C-peptide, CPI=C-peptide index, PG=Plasma glucose, HbA1c=Hemoglobin A1c.

Table 2
Comparison of C-peptide concentration and index between pre and post (2hr) breakfast by Paired t –test

Parameter	Pre Mean ± SD	Post Mean ± SD	P value
C-peptide (ng/mL)	0.6±0.2	2.68±0.49	< 0.001
C-peptide index	0.36±0.19	1.1±0.44	< 0.001
C-peptide (1-4) duration(ng/mL)	0.71±0.24	2.97±0.45	<0.001
C-peptide (5-10) duration (ng/mL)	0.50±0.09	2.39±0.34	<0.001
C-peptide Index (1-4) duration	0.45±0.21	1.4±0.4	<0.001
C-peptide Index (5-10) duration	0.27±0.12	0.81±0.23	<0.001

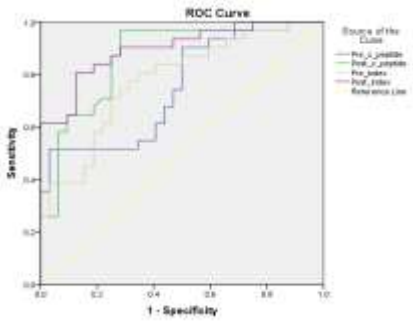

Figure 1: Receiver operating characteristic curves of markers of assessment beta cell function: fasting and postprandial c-peptide and index

Table 3
Correlations between pre and postprandial C-peptide index with duration of diabetes, BMI and HbA1c

Negative correlations between pre and postprandial index with duration of diabetes		
parameter	R value	P value
Pre index	-0.445	<0.001**
Postprandial index	-0.561	<0.001**
Positive correlations between pre and postprandial index with BMI		
Pre index	0.363	0.003**
Postprandial index	0.626	<0.001**
Positive correlations between fasting and postprandial index with DI		
Pre index	0.416	0.001**
Postprandial index	0.694	<0.001**
Negative correlations between pre and postprandial index with HbA1c		
Pre index	-0.132	0.301
Postprandial index	-0.148	0.247

*Statistically significant at $p \leqslant 0.05$. **highly significant at $p \leqslant 0.01$. BMI: body mass index, DI: disposition index, Hba1c: hemoglobin A1c.

Table 4
divided each group into subgroup according to body mass index (BMI)

Parameter	**Low BMI Mean± SD**	**High BMI Mean ± SD**	**P value**
Group I (1-4 duration of diabetes): subdivided into healthy weight and obese			
	BMI 18.5-24.9 kg/m^2	BMI >30 kg/m^2	
N	11	20	
BMI	24.46 ±0.32	33.67±3.39	<0.001
Postprandial c-peptide	2.76±0.41	3.08±0.44	0.059
Postprandial index	0.96±0.18	1.64±0.25	<0.001
Group II (5-10 duration of diabetes): subdivided into healthy weight and overweight			
	BMI 18.5-24.9 kg/m^2	BMI 25-29.9 kg/m^2	
N	12	20	
BMI	23.45±1.83	28.07±1.39	<0.001
Postprandial c-peptide	2.58±0.28	2.29±0.33	0.016
Postprandial index	1.03±0.17	0.67±0.13	<0.001

Table 5
Area under curve, sensitivity, specificity and cutoff value for c-peptide and index

Parameter	**AUC**	**P value**	**Sensitivity**	**Specificity**	**Cutoff value**
Pre c-peptide	0.755	0.001	58.1%	59.4%	0.5
Postprandial c-peptide	0.865	<0.001	74.2%	75%	2.6
Pre-index	0.779	<0.001	71%	75%	0.3
Postprandial index	0.896	<0.001	80.6%	87.5%	1.1

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