Original Article

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An Association of Fasting C-Peptide Levels and Vascular Complications in Chronic Type 2 Diabetes Mellitus Patients

Internal Medicine Section

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ABSTRACT

Introduction: Numerous biochemical markers are being used in clinical practice for the prediction and prognostication of vascular complications among non diabetic individuals. Of late, fasting C-peptide levels is being investigated for its possible role in the prediction and protection of vascular complications of diabetes. It is also being explored for its protective role in prevention of vascular complications among patients with diabetes mellitus.

Aim: The present study was undertaken with an objective to assess the strength of association of fasting C-peptide levels in the development of microvascular and macrovascular complications.

Materials and Methods: An observational cross-sectional study involving 100 subjects with Type 2 Diabetes mellitus (T2DM) having an objective evidence of vascular complications were included into the study. The study period was 18 months from October 2017 to September 2019. After an overnight fasting of atleast 12 hours, C-peptide level estimation was done by Electro-Chemiluminescence Assay (ECLA) method.

Results: The overall mean fasting C-peptide level among subjects with microvascular complications (0.73±0.55 ng/mL) was significantly decreased compared with subjects having macrovascular complications (2.44±0.72 ng/mL, with p-value being <0.001). Among microvascular complications, the mean fasting C-peptide level was least in subjects with diabetic retinopathy (0.64±0.35 ng/mL). Among patients with macrovascular complications, preserved C-peptide levels were observed in subjects with ischemic heart disease (2.35±0.75 ng/mL).

Conclusion: Fasting serum C-peptide levels are significantly reduced among subjects with chronic T2DM having microvascular complications when compared to macrovascular complications. Also, with preserved serum levels, fasting C-peptide might have a protective role in the prevention of macrovascular complications among subjects with diabetes mellitus.

Keywords: Macrovascular complications, Metabolic syndrome, Osteoporosis

INTRODUCTION

Patients with diabetes mellitus develop a spectrum of vascular complications over a period of time [1]. The vascular complications can be microvascular complications such as diabetic nephropathy, diabetic neuropathy and diabetic retinopathy or macrovascular such as cerebrovascular accidents, cardiovascular and peripheral vascular diseases [2]. These complications occur at a variable time frame since the onset of diabetes as they are dependent on the individual's glycaemic control, fasting C-peptide levels, degree of insulin resistance and genetic susceptibility in addition to other factors [3].

The diagnosis of such vascular complications can be made during routine follow-up, clinical signs and supported by objective evidences such as fundoscopy, urine for microalbuminuria, ECG, Echocardiography, filament test reports, ENMG studies, Coronary angiogram respectively [4]. Various biochemical markers are also being used in patients with diabetes mellitus in predicting the at-risk population developing the above said complications [5]. Out of these markers, evidences are accumulating that C-peptide is now considered as a novel hormone with defined physiological action and the elevated levels of the C-peptide might have a protective role in preventing certain diabetic vascular complications [6]. The variation in the blood concentration of this hormone has been correlated with microvascular and macrovascular complications of diabetes. In addition to this, decreased C-peptide levels are also associated with the development of reduced bone mineral density and rapid ageing [7]. However, most of these data are from the studies done from outside of Indian subjects. Hence, the present study was undertaken with an objective to assess the strength of association of fasting C-peptide levels with vascular complications in diabetic patients among Indian population.

MATERIALS AND METHODS

The present cross-sectional observational study was conducted after obtaining the Ethical Clearance from Institutional Ethics Committee (JSSMC/PG/4700/2017-18). It included patients attending JSS Hospital Medicine Out-Patient Department and admitted as in-patients to the wards during the study period of 18 months from October 2017 to September 2019.

Patients were screened for vascular complications of diabetes and were randomly included in the study after the fulfillment of inclusion and exclusion criteria as mentioned below. Microvascular complications include patients with retinopathy, neuropathy and nephropathy. Macrovascular group include patients with cerebrovascular complications, ischemic heart disease and peripheral vascular disease.

Sample size: Sample size was calculated using the formula $S=z^2pq/d^2$, considering the prevalence of diabetes in India to be 7%, with 95% confidence levels and 5% error, the sample size was calculated to be 101. After verifying inclusion/exclusion criteria, 100 such patients were included into the study by simple random sampling method.

Inclusion criteria: Patients aged more than 40 years, diagnosed with diabetes mellitus and are on insulin/oral hypoglycaemic agents or both with atleast one of the vascular complications were included in the study.

Exclusion criteria: Pregnant women and patients with secondary diabetes mellitus, on steroids or who are undergoing dialysis were excluded from the study.

Method of collection of data: The data obtained was studied using general proforma during the period of study. Type 2 Diabetes mellitus patients admitted to JSS hospital in medicine wards who are on oral hypoglycaemic agents or insulin or both were screened for the presence of atleast one of the vascular complications. Patient with classical presenting or past symptoms about vascular events, clinical signs and other objective evidences (as proof of vasculopathy like fundoscopy, urine for microalbuminuria, ECG, ECHO, filament test reports, Electroneuromyography (ENMG) studies, Coronary Angiography (CAG) reports) either in the past or present were taken into consideration in diagnosing such vascular complications. After verifying inclusion/exclusion criteria, 100 such patients were included into the study by simple random sampling method. Blood samples (5 mL per patient) were estimated for C-peptide levels by electrochemiluminescence assay method with the normal range being 0.8-3.4 ng/mL after an overnight fasting of atleast 12 hours.

STATISTICAL ANALYSIS

Summary statistics was done by means of proportions for categorical/binary variables and mean, median, Standard deviation, Inter Quartile Range (IQR) for continuous variables. Inferential statistics was done by using Mann-Whitney test, Chi-square test/ Fisher's exact test, Independent t-test and Pearson's correlation test.

All the statistical methods were done using Statistical Package for Social Sciences (SPSS) 21.0 version for windows. $p<0.05$ was considered statistically significant.

RESULTS

Among 100 subjects, 48 subjects were female (48) and 52 subjects were male (52). Out of these 100 subjects, 24 subjects (24) were less than 50 years of age, 27 subjects were between 51 and 60 years of age (27), 33 subjects were between 61 and 70 years of age (33), 10 subjects (10) were between 71 and 80 years of age and 6 subjects (6) were greater than 80-year-old.

Among 100 subjects, 46 had macrovascular complications and 54 had microvascular complications. Out of these 100 subjects, 22 subjects had Cerebrovascular accident and 24 subjects had Ischemic Heart Disease, 10 subjects had diabetic nephropathy, 20 subjects had diabetic neuropathy and 24 subjects had diabetic retinopathy.

The above 100 subjects were subdivided into 4 groups based on the duration of diabetes mellitus [Table/Fig-1]. A total of 36 subjects were diabetic for less than 5 years and had a mean fasting C-peptide level of 2.49±0.76 ng/mL, 18 subjects had DM between 6-10 years and had a mean fasting C-peptide level of 1.93±0.87 ng/mL, 21 subjects had DM between 11-15 years and had a mean fasting C-peptide level of 0.56±0.24 ng/mL and finally 25 subjects were diabetic for more than 15 years and had a mean fasting C-peptide level of 0.63±0.22 ng/mL [Table/Fig-2].

Groups	Duration of diabetes	Number of subjects	Mean C-peptide levels
Group A	<5 years	36	2.49±0.76 ng/mL
Group B	6-10 years	18	1.93±0.87 ng/mL
Group C	11-15 years	21	0.56±0.24 ng/mL
Group D	>16 years	15	0.63±0.22 ng/mL

[Table/Fig-1]: Duration of diabetes and C-peptide levels.

	Fasting C-peptide ng/mL					
	n	Mean	SD	Median	Q1	Q3
Cerebrovascular accident	22	2.34	0.69	2.25	2.00	2.60
Ischemic heart disease	24	2.53	0.75	2.55	2.20	2.80
Macrovascular complications	46	2.44	0.72	2.50	2.10	2.80

[Table/Fig-2]: Fasting C-peptide levels and macrovascular complications.

The overall mean fasting C-peptide levels among subjects with macrovascular complications was found to be 2.44±0.72 ng/mL. Among the subjects with macrovascular complication group, the mean fasting C-peptide level among subjects having cerebrovascular accident was 2.34±0.69 ng/mL and ischemic heart disease was 2.53±0.75 ng/mL [Table/Fig-1].

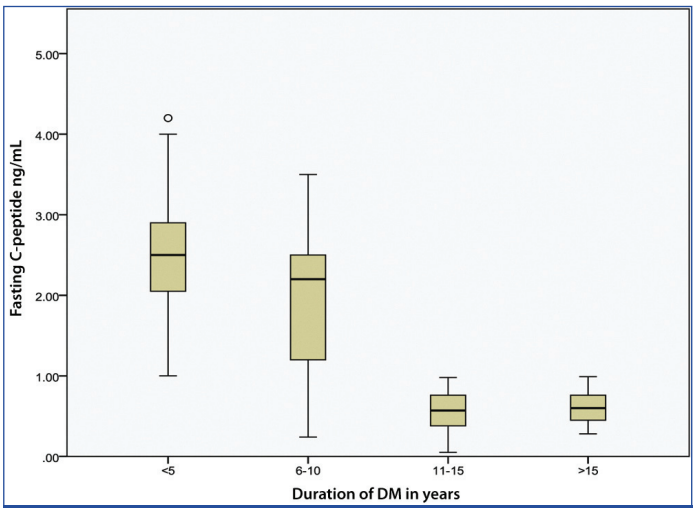
The overall mean fasting C-peptide level among subjects with microvascular complications was 0.73±0.55 ng/mL. In the microvascular complication group, the mean fasting C-peptide level among subjects with diabetic nephropathy was 0.74±0.54 ng/mL, diabetic neuropathy was 0.75±0.71 ng/mL and among subjects with diabetic retinopathy was 0.64±0.35 ng/mL [Table/Fig-3].

	Fasting C-peptide ng/mL					
	n	Mean	SD	Median	Q1	Q3
Diabetic nephropathy	15	0.74	0.54	0.72	0.44	0.80
Diabetic neuropathy	20	0.75	0.71	0.61	0.32	0.93
Diabetic retinopathy	24	0.64	0.35	0.55	0.45	0.73
Microvascular complication	54	0.73	0.55	0.63	0.44	0.80

[Table/Fig-3]: Fasting C-peptide levels and microvascular complications.

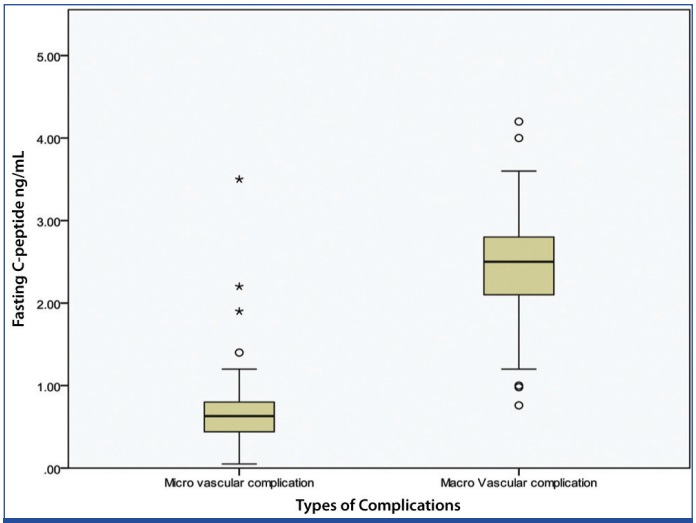
DISCUSSION

Duration of diabetes and C-peptide levels: Fasting C-peptide levels decreased with the duration of the diabetes although not linearly [3]. In the present study, it was observed that patients with diabetes duration of more than 15 years had slightly preserved C-peptide levels (0.63±0.22 ng/mL) when compared to patients with diabetic duration of 11-15 years (0.56±0.24 ng/mL), the significance of which needs to be explored [Table/Fig-4]. Otherwise, it is consistent with the previous studies earmarking decreasing trend of fasting C-peptide levels with the increase in duration of diabetes [6] Leighton E et al., in their study made a similar observation of decreasing levels of fasting C-peptides with duration of diabetes and concluded that progressive decline in C-peptide levels will contribute for increased fluctuations in blood glucose levels which in turn contribute for development of various vascular complications [6]. Further in their study, they highlighted that fasting C-peptide estimation by itself can predict the future overall outcome among diabetic patients independent of HbA1c levels [6,7].



[Table/Fig-4]: C-peptide levels and duration of diabetes.

C-peptide levels and macrovascular complications: The mean fasting C-peptide levels among subjects with macrovascular complications was found to be 2.44±0.72 ng/mL. Individually, the mean fasting C-peptide level among subjects having Cerebrovascular Accidents (CVA) were 2.34±0.69 ng/mL and patients with Ischaemic Heart Disease (IHD) had 2.53±0.75 ng/mL [Table/Fig-5].



[Table/Fig-5]: Fasting C-peptide levels and micro and macrovascular complications.

A study done by Patel N et al., compared individuals in the lowest quartile (≤0.418 nmol/L) and highest quartile of C-peptide levels (≥0.984 nmol/L) among non-diabetic adults found that latter had a 60% increased hazards of mortality for IHD, cerebrovascular disease and all-cause mortality compared with those in the lowest quartile [8]. They reaffirmed that the preserved β-cell function in the long run is known to reduce the insulin resistance state and thereby contributing for reasonably good control of sugars. This in turn could be reason for the protection against the development of macrovascular abnormalities in patients with diabetes but not microvascular complications as they are dependent on duration of diabetes than C-peptide levels. They also concluded that estimation of fasting C-peptide levels might be a good predictor of cardiovascular outcome even in normoglycaemic non diabetic adult individuals [8]. However, this hypothesis needs to be strengthened by further larger population based studies [9]. A study done by Sari R and Balci MK also found that chronic diabetic patients with macrovascular complications had near normal levels of fasting C-peptides when compared to low levels of fasting C-peptide among subjects with microvascular complications [10].

C-peptide levels and microvascular complications: The mean fasting C-peptide level among subjects with microvascular complications was 0.73±0.55 ng/mL. Among these group, mean fasting C-peptide level was least in subjects with diabetic retinopathy (0.64±0.35 ng/mL) when compared to diabetic nephropathy (0.74±0.54 ng/mL) and diabetic neuropathy (0.75±0.71 ng/mL) [Table/Fig-3]. This observation shows that there is a uniform decline in fasting C-peptide levels among patients with microvascular complications irrespective of the type of microvascular complications. The levels were lowest with subjects having diabetic retinopathy.

A study done by Kim B et al., in 1410 Korean patients showed that subjects with lower fasting serum C-peptide levels had higher prevalence of diabetic retinopathy and diabetic nephropathy (p=0.035, p<0.001) and similarly lower delta C-peptide levels had higher prevalence of diabetic retinopathy, nephropathy and neuropathy (p<0.001) [11]. In a study, done by JZ Kuo et al., among 585 Latinos from Los Angeles in 2014, statistical analysis of C-peptide levels among different stages of diabetic retinopathy revealed that the mean plasma C-peptide level decreased progressively from 1.23±0.04 nmol/L in subjects with no diabetic retinopathy, to 0.87±0.14 nmol/L in severe non proliferative diabetic retinopathy and paradoxically increased to 1.14±0.08 nmol/L in proliferative diabetic retinopathy [12].

In a community-based study done in China by Qiao X et al., fasting C-peptide level were significantly lower (0.35±0.17 nmol/L, p=0.030) among subjects with peripheral neuropathy [13]. Further, they also cautioned against the use of the drugs that over stimulate beta cells thereby resulting in the beta cell exhaustion that may lead to initiation and progression of various vascular complications [13]. Similar observation is also evident from the present study that all the patients having microvascular complications irrespective of the type were having significantly lower level of fasting C-peptide levels.

C-peptide levels in macrovascular complications and microvascular complications: From the present study, it is evident that lower C-peptide levels were observed in both macrovascular and microvascular complications group. However, the patients with microvascular complications had a significantly lower mean fasting C-peptide levels (0.73±0.55 ng/mL) than those with macrovascular complications (2.44±0.72 ng/mL) [Table/Fig-4]. A similar study done by Kim B et al., in Korea concluded that "low C-peptide level is associated with diabetic microvascular, but not macrovascular complications in patients with T2DM" [11].

Limitation(s)

Lesser number of study subjects and no comparison between C-peptide level variation among patients who were on oral hypoglycaemic drugs and insulin or both.

CONCLUSION(S)

From our study among patients with chronic T2DM, it is evident that fasting serum C-peptide levels were significantly lower in subjects having microvascular complications when compared to subjects with macrovascular complications. Further, the development of microvascular complications is dependent on duration of diabetes. It is also possible that with the preserved fasting C-peptide among subjects with macrovascular complications, it might have a protective role in the development of macrovascular complications. More such studies on fasting C-peptide estimation among subjects with diabetes or by administering C-peptide for diabetic patients and proving its protective role in the prevention of macrovascular complications can be undertaken. This will also extend the scope of estimating fasting C-peptide from its current use in classification of diabetes to prediction and prognostication of diabetes related complications.

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