Original Article:

Association between Serum C-peptide Level and Diabetic Nephropathy in Type 2 Diabetes Mellitus Patients on Oral Anti-diabetic Drug.

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Abstract:

Background: Diabetic Nephropathy (DN) treatment focuses mostly on preventing or delaying disease development. The most recent research indicates that C-peptide may have a favourable biological effect on DN. In type 2 Diabetes Mellitus, the link between C-peptide level and DN is poorly understood (DM). The purpose of this study is to evaluate the relation between serum C-peptide and diabetic nephropathy in type 2 DM patients taking an oral anti diabetic medication. ***Methods:*** From July 2019 to June 2020, a cross-sectional observational study was done at the Department of Pharmacology and Therapeutics at Dhaka Medical College, Dhaka. A total of 63 randomly selected type 2 diabetes patients met the inclusion criteria. SPSS was used to collect, record, and evaluate biochemical values including FBG, 2hrs ABF, HbA1c, urine for microalbumin, serum creatinine, and serum C-peptide. ***Result:*** Among 63 study participants, 40 (63.5%) were female and 23 (36.5%) were male. Mean age of patients was 50.30±10.55 years. Mean duration of DM of total study subjects was 6.29±3.15 years. Out of total study subjects, 17.5% (11) had low serum C-peptide, 74.6% (47) had normal serum C-peptide and 7.9% (5) had high serum C-peptide level. Correlations of clinical and biochemical variables showed negative correlation between serum C-peptide level and microalbumin, DM duration, FBS, 2hrs ABF, HbA1c, creatinine. Mean urine albumin was higher in patients with low serum C-peptide level. The microalbumin level and the duration of DM of study subjects are significantly associated with serum C-peptide. ***Conclusion:*** In this study we have found that type 2 diabetic individuals with low serum C-peptide levels have a high frequency of diabetic nephropathy and that serum C-peptide levels are significantly associated with diabetic nephropathy.

Keywords: C-peptide; Diabetic Nephropathy (DN); Oral Anti-diabetic drugs.

Introduction:

Patients who have type 1 diabetes usually show signs of glomerular hyperfiltration at an earlier stage in the progression of their condition[1]. Even with adequate insulin medication, this condition does not correct itself [2]. Patients who have type 2 diabetes, on the other hand, do not show any signs of glomerular hyperfiltration or hypertrophy. This is because their insulin and C-peptide levels are either within or above the normal range [3, 4].

C peptide is a polypeptide comprising 31 amino acids with a molecular weight of 3600. C-peptide is cleaved from pro-insulin, retained in secretory granules, and subsequently released into the

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bloodstream in levels equal to those of insulin during insulin biosynthesis [5]. The development of inter-chain disulfide bonds and accurate folding are both dependent on the presence of C-peptide, which fulfils an important role in the process of insulin manufacturing by acting as a connection between the A and B chains [6]. It has been hypothesized that the kidney is the primary organ responsible for the breakdown of C-peptide. C-peptide has a half-life in circulation that is two to five times longer than that of insulin. Insulin itself is not the most reliable predictor of whether or not insulin is being secreted; rather, C peptide is. In addition, the interference from insulin antibodies, which are frequently present in individuals who are undergoing insulin therapy, does not have an effect on the concentration of C peptide[7]. Recently, the indication for measuring C-peptide has been broadened to allow for the assessment of insulin dependent in patients with type-2 diabetes mellitus. It is generally agreed upon that C-peptide has very little, if any, biological activity and plays no other role outside its participation in the production of insulin. This function is underlined by the name of the peptide itself, which translates to "connection peptide" [8]. The information that is presently at our access demonstrates that C-peptide is not as physiologically inert as was previously supposed to be the case. Instead, it has been discovered that it functions as an active peptide hormone that may have crucial physiological consequences. Even though C-peptide is produced from pro-insulin and co-secreted along with insulin, we should not rule out the possibility that C-peptide is a distinct entity with biochemical and physiological properties that are distinct from those of insulin [9]. This is because C-peptide has been shown to play a role in the regulation of glucose homeostasis. In both experimental and type I diabetes, C-peptide has the ability to minimize the amount of glomerular hyperfiltration that occurs as well as the urine albumin excretion that takes place [10, 11]. The purpose of this study is to determine whether or not there is a correlation between the serum C peptide level and the duration of diabetes as measured by urinary albumin excretion.

Materials and Methods:

This study is prospective and cross-sectional of 63 randomly selected individuals with type-2 DM. We assessed the demographic, and laboratory profiles of patients with type 2 diabetes mellitus, including newly diagnosed cases. The Pharmacology & Therapeutics Department of Dhaka Medical College was where the data was gathered and the study was completed. From July 2019 to June 2020, there was a one-year study term in total. All clinical trials were authorised by the Institutional Ethics Committee, and informed consent was obtained from each patient evaluated. Every patient had a comprehensive physical check-up. In addition, information regarding anti diabetic medication and associated disorders was gathered. All patients had their weight and body mass index (BMI) measured. In the laboratory, tests such as FBG, 2hrsABF, HbA1c, urine for micro albumin, serum creatinine, and serum C-peptide were performed and entered in the appropriate fields of the data collecting form.

Statistical Analysis

Frequency distribution and percentages were used to express qualitative data. Quantitative information was presented as mean ± SD (standard deviation). At the 95 percent confidence interval, the p value of 0.05 was deemed statistically significant (confidence interval). SPSS, a statistical programme, was used to examine the data (version 26.0).

Results:

According to the predetermined criteria, a total of 63 participants were invited to take part in the study. In this setting, female patients accounted for 63.5 percent (40 total), while male patients made up 36.5 percent (23 patients). The mean age (Mean±SD) of total study subjects was 50.30±10.55 years. Here, mean age of male patients was 52.39±11.34 and mean age of female patients was 49.10±10.01 years. Out of total study population, 78.6% had positive family history of diabetes and 21.4% has no positive family history of diabetes. Demographic data of the patients were shown in (Table 1).

Table-1: Demographic characteristics of the patients.

Variables	Value
Age (Years)	50.30±10.55
Males (%))	50.30±10.55
Females (%))	49.10±10.01
Body mass index (mg/m²)	29±0.70
Duration of diseases (Years)	6.29±3.15
HbA$_{1C}$ (%)	7.93±1.25
Creatinine (mg/dl)	0.83±0.12
Microalbumin (mg/L)	26.93±13.97
Serum C-peptide	2.39±0.99

In this study, here, 74.6% (47 patients) had normal serum C-peptide level (**Group-1**) where male 28.6%

(18 patients) and female 46.0% (29 patients). Serum C-peptide was above normal (**Group-2**) in 5 patients, which accounts for 7.9%, among them male: 1.6% and female: 6.3%. Serum C-peptide below normal (**Group-3**) in 11 patients which constitute about 17.5%, where male accounts for 6.3% and female 11.1%. The duration of disease (DM) is longer in patients with blood C peptide levels below normal compared to the other two patient groups. In the current study, 74.6% (47 patients) had normal serum C-peptide level where duration of DM less than 5 years 31.7% (20 patients), 5 to 10 years 41.3% (26 patients) and more than 10 years 1.6% (1 patient). 17.5% (11 patients) had low S. C-peptide (less than 5 years: 1.6%, 5 to 10 years: 7.9% and more than 10 years: 7.9%) and 7.9% (5 patients) had high S. C-peptide where all the patients are in less than 5 years group. Here, the mean microalbumin in high serum C-peptide category was 15.72±2.81, normal C-peptide group was 25.57±13.54 and low C-peptide group was 37.87±12.63. According to serum C-peptide, there was a significant mean difference between the Normal-Low and High-Low groups of patterns microalbumin levels. Mean creatinine value in group-1 patients 0.83±0.12, in group-2 patient was 0.81±0.16 and in group-3 patients was 0.83±0.08. Although, creatinine value was less with elevated C peptide, it did not show any statistical significance. Moreover, HbA_{1C} was also higher in patient with low serum C peptide level compared to other two groups. Mean HbA_{1C} was 7.93±1.25 (male: 7.87±0.56, female: 7.97±1.52, p value 0.778). Mean serum creatinine level was 0.83±0.12 (male: 0.81±0.16, female: 0.83±0.08, p value 0.527) (Table-2).

Table-2: Comparing the baseline features of the various patient subgroups.

Variables	Group 1	Group 2	Group 3
Age (Years)	50.30±10.55	53.30±9.55	51.30±8.50
Males (%))	50.30±10.55	51.30±10.55	52.30±10.55
Females (%))	49.10±10.01	50.10±10.01	49.10±10.01
Body mass index (mg/ m²)	29±0.70	27±0.60	30±0.70
Duration of diseases (Years)	6.29±3.15	6.5±3.15	7.29±3.15
HbA_{1C} (%)	7.93±1.25	7.98±1.30	8.18±1.20
Creatinine (mg/dl)	0.83±0.12	0.81±0.16	0.83±0.08
Microalbumin (mg/L)	26.93±13.97	25.57±13.54	37.87±12.63
Serum C-peptide	2.39±0.99	2.33±0.92	2.42±1.03

Pearson correlation test shown negative correlation of serum C peptide level with DM Duration (-0.483,

P< 0.001**), vs. Micro-albumin (-0.268, P<0.05*), vs. HbA_{1c} (-0.004, P> 0.05), vs. Creatinine (-0.024, P>0.854). Here all the variables are negatively associated with serum C-peptide. This table shows the duration of DM of study subjects and microalbumin levels were significantly associated with serum C-peptide (Table-3).

Table-3: Correlation's of clinical & biochemical variables among participants.

Characteristics	C-peptide	
	r	p value
DM Duration	-0.483	0.001**
FBG	-0.157	0.220
2hrs ABF	-0.235	0.064
HbA1c	-0.004	0.973
Creatinine	-0.024	0.854
Micro-albumin	-0.268	0.034**

The results of a regression analysis of the clinical and biochemical characteristics of the study patients are depicted in (Figure 1). According to this, the duration of the DM is independently significant. But the significance of microalbumin depends on the context. Oral hypoglycemic medicines were being administered to every patient, either as a monotherapy or in combination with another treatment.

Figure-1: **Correlation of C-peptide and Microalbumin.**
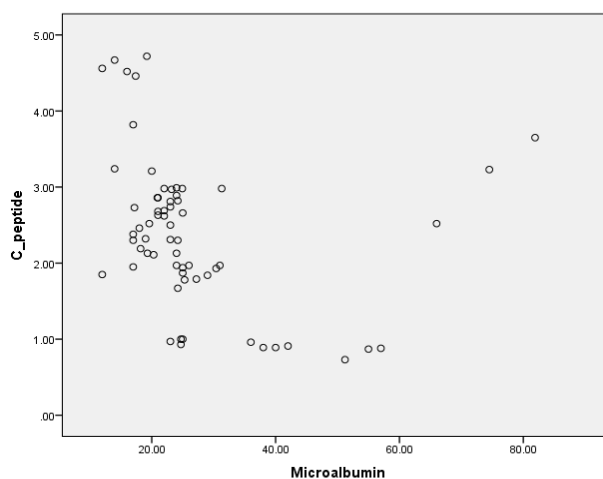
Discussion:

Several preliminary studies addressed the potential physiological effects of C peptide following the revelation of the mechanism of insulin production. The effects of insulin on blood glucose levels and glucose disposal were discovered but not detectable following glucose loading. Recent research

demonstrates that [12]. C-peptide can stimulate multiple intracellular processes; C-peptide depletion in type I diabetic individuals impairs renal and neural function. This study found a link between serum C peptide concentrations, renal indices, and duration of diabetes [13]. There was a negative correlation between serum C peptide levels and urine albumin excretion, diabetes duration, and creatinine concentration [14-16]. Unknown is the mechanism responsible for the beneficial effect of C-peptide on renal function in diabetic patients. C-peptide and albumin may have a direct effect on glomerular control, according to studies of the renal function of rats with experimental diabetes. Nonetheless, C-peptide albumin could have this effect [17]. The effects of C-peptide on glomerular hyperfiltration and renal protein leakage in streptozotocin diabetic rats were investigated. When diabetic mice were administered C peptide for 90 minutes, glomerulonephritis hyper-filtration and protein leakage were significantly reduced. C-peptides have the ability to stimulate both renal Na+-K+ ATPase and eNOS (endothelial nitric oxide synthase) [18]. Both of these enzyme systems have been shown to be affected in type 1 diabetes, most notably in renal and nerve C-peptide glomerular membrane permeability and transport, as well as regional blood flow to the kidneys. There is currently evidence that substituting C-peptide improves renal function in patients with type I diabetes. Correction of glomerular hyperfiltration and decreased urine albumin secretion are among the advantages, as is relief of nerve dysfunction [19].

According to the present study, there is a negative connection between serum C peptide levels and disease duration, which may indicate ongoing beta cell degeneration. In individuals with low blood C peptide levels, insufficient glycemic control and the requirement for insulin therapy were indicated by a negative correlation between HBA1c and serum C peptide levels. Additionally, our research indicated a negative association between C-peptide quality and urine albumin levels. C peptide reduces hyperfiltration and protein loss in the glomerulus.

Our investigation's limitations require discussion. The number of patients with low serum C peptide levels was insufficient to make conclusive findings on the relationship between serum C peptide levels and renal parameters. In addition, the timing of the link between exposure and result is uncertain due to the cross-sectional design of the study. Therefore, it would be beneficial to corroborate the association using potential longitudinal data.

Conclusion:

The study was carried out to find the association between serum C-peptide level and diabetic nephropathy in type 2 diabetes mellitus patients. This study has shown that majority of patients were female and most of the patients had positive family history of diabetes. Majority of patients in this study had uncontrolled DM. Most of the patients had microalbuminuria. The correlations of clinical and biochemical variables among participants showed significant correlation between serum C-peptide level and duration of DM as well as between serum C-peptide level and microalbumin. Microalbumin was negatively correlated with serum C-peptide level and was statistically significant. On the basis of the study findings, it can be concluded that serum C-peptide level associated with microalbumin that is C-peptide level associated with diabetic nephropathy.

Conflict of interest: In this review article there is no potential conflict of interest.

Ethical clearance: Not applicable.

Authors contribution: All the authors contributed equally to this review paper.

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