

C-Peptide as a Marker for Diabetic Nephropathy

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Abstract

Diabetes mellitus is a metabolic disorder of multiple aetiology. Destruction of pancreatic beta cells, hyperglycaemia, and insulin deficiency cause type 1 diabetes mellitus. Diabetic nephropathy is the damage to kidneys because of diabetes. It is predominantly seen in patients with type 1 diabetes (insulin-dependent type) and type 2 diabetes (non-insulin-dependent type). An active peptide hormone, C-peptide has the likelihood of causing major physiological effects. C-peptide is the best indication of endogenous insulin secretion occurring in patients with diabetes. In this regard, the current study undertakes a comprehensive study of C-peptide and kidney (renal) failure in patients with diabetes mellitus in order to assess their association. A prospective cross sectional study is conducted at King Abdul Aziz University Hospital. The subjects for this study were patients with type 2 DM. Laboratory tests such as HbA1c, serum creatinine, urine albumin and creatinine, fasting serum C-peptide, and blood urea nitrogen are conducted. Data was analysed using analysis of variance (ANOVA) test to compare the values between different category patients. The study also found that there exists a significant mean difference between Cystatin C and C-peptide levels. However, the study has certain limitations. Firstly, the number of patients with elevated levels of serum C-peptide was very small, and hence, valid conclusions with respect to the association of serum C-peptide with renal parameters could not be discerned. Therefore, there is a need for further studies with more number of patients.

Keywords: C-peptide; Diabetes mellitus; Insulin; Neuropathy

Introduction

Diabetes mellitus

Diabetes mellitus is a metabolic disorder of multiple aetiology. Destruction of pancreatic beta cells, hyperglycaemia, and insulin deficiency cause type 1 diabetes mellitus [1,2]. According to WHO reports in 1999, diabetes mellitus can cause long-term damage which includes dysfunction or failure of various organs. The prevalence of diabetes which was 7.4% among adults in 1995 is predicted to rise to 9% in 2025 [3]. Many research studies have confirmed that the complications resulting from diabetes mellitus can be prevented or at least delayed with good metabolic controls. The fundamental objective for diabetes treatment is to reduce the increased blood sugar level to the normal range to inhibit or postpone diabetic complications. To achieve this objective, health care system much plan for an extensive, patient-oriented approach [3]. Achieving this goal requires a comprehensive, coordinated, patient-centred approach on the part of the health care system [4].

Diabetes mellitus and renal failure

Diabetic nephropathy is the damage to kidneys because of diabetes. It is predominantly seen in patients with type 1 diabetes (insulin-dependent type) and type 2 diabetes (non-insulin-dependent type). It is also seen in patients showing secondary forms of diabetes mellitus (DM) following pancreatitis when the duration of DM is sufficiently long and when the glycemia is to up to level that can result in diabetic complications [5,6]. Nearly 20% to 30% of patients who have type 1 DM have been found to have microalbuminuria after an average period of diabetes of 15 years. Almost half the number of these patients

will gradually develop macroalbuminuria which is otherwise known as overt nephropathy [5,7]. Overt nephropathy, in a significant number of patients progresses and eventually results in end-stage renal disease (ESRD) with reported rates of 4% to 17% at 20 years and around 16% at 30 years from the first diagnosis of diabetes mellitus.

C-peptide

An active peptide hormone, C-peptide has the likelihood of causing overt nephropathy [5,7]. C-peptide and insulin are produced in equal amounts. It has the capacity to weaken glomerular hyperfiltration and bring down urinary albumin excretion in experimental as well as human type 1 diabetes. C-peptide is the best indication of endogenous insulin secretion occurring in patients with diabetes [8]. The amount of C-peptide in the blood indicates the amount of insulin produced by the pancreas. Blood sugar level in the body is not affected by C-peptide. The purpose of performing c-peptide test, done after the initial diagnosis of DM, is to ascertain whether it is type 1 or type 2 diabetes.

In the individual whose pancreas does not produce insulin (type 1 diabetes) has a reduced level of insulin and C-peptide [9]. Determination of C-peptide levels is preferred to determination of insulin levels as insulin concentration in the portal veins is two to ten times greater than in the peripheral circulation. About half the amount of insulin that reaches liver plasma, is observed by the liver. However, this varies with the nutritional state. In type 1 DM, there is a reduced level of insulin production by the pancreas, and, in this case, the patients will also have a reduced level of C-peptide. Whereas, in type 2 DM, the C-peptide levels in patients are more than the normal levels. In the study conducted by Jones and Hattersley et al. use of C-peptide in the clinical management of patients with diabetes was evaluated. The study included the interpretation and choice of C-peptide test. Use

of C-peptide use for assisting diabetes classification and choice of treatment were also examined.

The study concluded that C-peptide measurement is a cost-effective and commonly available test which will be highly helpful in clinical management of diabetes, especially for patients whose diabetes subtype is uncertain. Rebsomen et al. reviewed on most convincing theories related to C-peptide effect on renal function. The authors concluded that there though were mechanisms were not fully understandable, hormonal therapeutic role of C-peptide as a protective factor for diabetic kidney should not be ignored [10]. In the study conducted by Chowta et al. the authors studied the correlation of serum C-peptide level with the level of renal clearance, urinary albumin excretion and duration of diabetes [11]. The study found that there was a weak association between serum C-peptide and micro albuminuria and creatinine clearance, and there was increased risk of albuminuria in patients with low serum C-peptide level. In the background of the studies mentioned above, the current study will undertake a comprehensive study of C-peptide and kidney (renal) failure in patients with diabetes mellitus in order to assess their association.

Material and Methods

The current study is a prospective cross sectional study conducted at King Abdul Aziz University Hospital. The subjects for this study were

patients with type 2 DM. They included newly diagnosed patients and patient who have had DM for a long time. The patients comprised both males and females and every one was above the age of 18. Baselines clinical and laboratory profile of the patients were evaluated.

Data of the patients who were screened for the clinical trials on type 2 diabetes mellitus were collected. Consent of every patient who was screened was taken. All the trials were ratified by the Ethics Committee of King Abdul Aziz University Hospital. Details of the patient history including duration of the disease were collected. All the patients underwent extensive physical examination. Patients' details about anti-diabetic medication and concomitant diseases were collected. Body weight and body mass index (BMI) were estimated for all the patients. Laboratory tests included HbA1c, serum creatinine, urine albumin and creatinine, fasting serum C-peptide, and blood urea nitrogen. Using MDRD formula, creatinine clearance was estimated from serum creatinine value.

Statistical analysis

Statistical analysis was done using SPSS 20.0 software. Analysis of data was done using student "t" test. The test compared the values between different categories of patients. Pearson correlation was employed for correlation analysis. P value less than 0.05 was considered significant (Table 1).

Characteristics	C-Peptide			p-value
	0.5 to 2.0 (Normal)	>2.1 (Elevated)	<0.5 (low)	
	Mean ± SEM			
Age (years)	58.46 ± 1.05	63.89 ± 3.52	56.22 ± 2.10	>0.05
Males n(%)	24 (20.2)	4 (44.4)	10 (43.5)	0.024*
Females n(%)	95 (79.8)	5 (55.6)	13 (56.5)	
DM duration (years)	8.94 ± 0.59	6.11 ± 1.07	9.09 ± 1.22	>0.05
HbA1C (%)	8.38 ± 0.20	8.67 ± 0.78	9.06 ± 0.60	>0.05
Creatine (ml/min)	73.55 ± 4.02	77.44 ± 5.19	81.48 ± 5.82	>0.05
Urea (mmole/min)	6.49 ± 0.68	4.41 ± 0.37	5.61 ± 0.74	>0.05
Total protein	75.95 ± 0.74	76.88 ± 2.99	77.72 ± 1.09	>0.05
Albumin (mg/L)	34.08 ± 0.83	36.38 ± 1.36	36.89 ± 1.13	>0.05
Cystacin C	1246.56 ± 58.69	890.25 ± 37.41	864.61 ± 64.59	0.011**
Microalbumin	97.87 ± 17.28	57.44 ± 44.99	52.10 ± 22.56	>0.05
Creatine/microalbumin	123.64 ± 28.13	89.42 ± 80.53	40.81 ± 19.13	>0.05
All values are expressed as mean ± SEM, **p<0.01, *p<0.05				

Table 1: Comparison of baseline characteristics among different categories of patients

C-peptide was normal (category 1) in 119 patients (68.0%), among them 95 were females (79.8%) and 24 were males (20.2%). C-peptide was elevated (category 2) in 9 patients (5.1%), among them 5 were females (55.6%) and 4 were males (44.4%). C-peptide below normal (category 3) in 23 patients (13.1%), among them 13 were female

(56.5%) and 10 male (43.5%) (Table 1). Mean Cystacin C is found to statistically significant and high in category 1 patients was 1246.56 $\pm$ 58.69, compared to category 2 patients was 890.25 $\pm$ 37.41 and category 3 patients was 864.61 $\pm$ 64.59.

Results

Data was analysed using analysis of variance (ANOVA) test to compare the values between different category patients. Correlation analysis was done by using pearson correlation. A P value <0.05 were considered significant.

Discussion

Determination of serum C-peptide levels can be considered in diabetes clinical practice for patients under insulin treatment [8]. C-peptide measurement is particularly useful when there is uncertainty about the treatment. With the discovery of the method of insulin biosynthesis, many initial studies focused on the possible physiological effects of C-peptide. Efforts to find insulin-like effects on blood glucose levels, glucose disposal after glucose loading were in vain [12,13]. In the recent times, new data that have been presented confirms a specific binding of C-peptide cells to cell surfaces that indicate G-protein-coupled membrane receptors. Therefore, it can be stated that C-peptide can induce certain intracellular processes and thereby influence nerve and renal function in C-peptide deficient type diabetes patients [14]. With the increasingly common clinical context, C-peptide can be highly useful in disease classification and in providing appropriate treatment.

The aim of the current study is to present the correlation between C-peptide level with that of renal clearance, urinary excretion and duration of diabetes. The study undertaken at King Abdul Aziz University Hospital, Saudi Arabia enrolled patients with type 2 diabetes mellitus. They were both men and women were above 18 years of age. Newly diagnosed patients were also included in the study. The current study showed significant correlation between C-peptide and microalbumin (0.000**)/creatinine ratio microalbumin (002**). Total of 175 patients were enrolled for this study. There were 129 females and 46 males. The mean age of the patients was 58.30 years (Table 2).

Characteristics	Value
Age (years)	58.30 ± 0.88
Males (n (%))	46 (26.3)
Females (n (%))	129 (73.7)
DM duration	8.59 ± 0.5
HbA1C (%)	8.59 ± 0.2
Creatinine (ml/min)	75.36 ± 3.0
Urea (mmole/min)	6.09 ± 0.5
Total protein	76.26 ± 0.6
Albumin (mg/L)	34.91 ± 0.63
C-peptide (nmol/L)	1.07 ± 0.05
Cystacin C	1145.9 ± 45.31
Microalbumin	117.36 ± 29.0
Creatine/microalbumin	122.41 ± 26.0

Table 2: Demographic characteristics of the patients

A total of 175 patients were included in the study, 129 females (73.7%) and 46 males (26.3%). The mean age of the patients was 58.30 years. Demographic data of patients were shown in Table 2.

In the research study conducted among Zuni Indians by [15] it was found that the prevalence of diabetes was 57% higher among females than males. Differences in lifestyle, tradition and culture were presumed to be the possible reasons for higher prevalence of obesity and diabetes among female of Zuni Indians. In the study conducted by [16], the authors found that the prevalence of diabetes varied from 2.7% to 4.1% and, it was more prevalent in males (2.3%) than females (1.4%). Pearson Correlation test presented a negative correlation between C-peptide level and DM duration (Table 3). In the study conducted by Almeida et al. it was reported that the frequency of residual C-peptide gets reduced with the passage of time independent of age of the patient at diagnosis [17]. However, diagnosis at adulthood has an increased frequency and higher values of C-peptide. In the study by [18] it was found that C-peptide was common in patients with type 1 DM, especially soon after they have been diagnosed and it would have clinical implications. The current study showed a significant correlation between C-peptide level and microalbumin ($r=0.301$, $P<0.01$)/creatinine ratio microalbumin ($r=0.268$, $P<0.01$).

C-Peptide	Correlation coefficient (r values)	P value
DM duration	-0.051	>0.05
HbA1C	-0.044	>0.05
Creatinine	-0.03	>0.05
Urea	-0.082	>0.05
Total protein	0.084	>0.05
Albumin	0.087	>0.05
Cystacin C	-0.04	>0.05
Microalbmin	0.301	0.000**
Creatine/microalbumin	0.268	0.002**

Table 3: Correlation of serum C-peptide level with other parameters

In the study conducted by Chowta et al. it was found that there was a weak association between C-peptide level with microalbumin and creatinine clearance. The study, in addition, found that there was an increased risk of albuminuria in patients with low serum peptide level [11].

In the study conducted by Gomes et al. it was reported that there was no correlation between low C-peptide level and frequency of microalbuminuria [19]. The study found no variation in the basal C-peptide level of microalbuminuric and normoalbuminuric patients. In 68% of the patients in the normal C-peptide category, 79.8% were females and 20.2% were males. In the elevated category, 55.6% were females and 44.4% were males. In the C-peptide below normal category, 56.5% were females and 43.5% were males. Mean Cystacin C was found to be statistically significant and high in normal category patients.

Conclusion

The study that examined the correlation between C-peptide and renal involvement in diabetes mellitus found that there was a significant correlation between C-peptide and microalbumin/creatinine ratio and micro albumin. The study also found that there exists a significant mean difference between Cystatin C and C-peptide levels. However, the study has certain limitations. Firstly, the number of patients with elevated levels of serum C-peptide was very small, and hence, valid conclusions with respect to the association of serum C-peptide with renal parameters could not be discerned. Therefore, there is a need for further studies with more number of patients.

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