Correlation of Cystatin C with Glomerular Filtration Rate and Urine Albumin – An early prediction of kidney status in type 2 Diabetes Mellitus

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ABSTRACT

Objective: To correlate Cystatin C with GFR and urinary albumin in order to find it out as a marker of early detection of kidney disease (diabetic nephropathy).

Study Design: A cross sectional analytic study

Place and Duration: The Department of Biochemistry, Islamic International Medical College from 15th March, 2016 to 14th March, 2017.

Methodology: The diabetic patients having urinary albumin creatinine level between 30 mg/g to 300 mg/g were selected. The estimation of urinary albumin levels and cystatin C levels were carried out on IMAGIN Specific Protein Analyzer. GFR was calculated using standardized clinical and pathological parameters of creatinine levels, patients age, gender and body size and a cutoff value of GRF of < 60 ml was set for probable nephropathy.

Results: Mean age of patients was 56.1 ± 5.4 years with male predominance (58.5%). Non-parametric spearman's correlation coefficient found out that GFR was negatively correlated with Cystatin C (-.305). The correlation coefficient for and Cystatin C and urinary albumin was (0.517) showing a perfect positive linear relation.

Conclusion: Cystatin C was found significantly correlated with GFR and urinary albumin, thus, validating previous findings regarding Cystatin C's role as an early marker of kidney diseases.

Keywords: Diabetic nephropathy, Clinical predictor, Glomerular filtration rate, Urinary albumin, Cystatin C

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INTRODUCTION

Diabetic nephropathy (DN) is a sign of early kidney compromise in diabetes mellitus patients. The diabetic patients are on an increased risk of developing chronic kidney disease and thus, increased chances of complications like cardiovascular disease, kidney failure, severe morbidity and mortality[1]. Diabetic nephropathy is characterized by increased protein excretion, albumin in urine, decline in glomerular filtration (GFR) and elevation in blood pressure which may lead to end stage renal disease[2]. The overall reported rate of diabetic nephropathy has been 25–40% of people with type 1 or type 2 diabetes[3].

Microalbuminuria is used for screening of diabetic nephropathy. It is a proven marker of early detection of kidney disease[4]. At the time of diagnosis of type 2 diabetes mellitus, screening for diabetic nephropathy should also be done. Moreover, patients with poor glycemic and high normal blood pressure levels should undergo screening for diabetic nephropathy.Many screening methods are available for diabetic nephropathy[5].

Cystatin C a 13 kDa protein with low molecular weight is produced by all nucleated cells and renal glomeruli freely filters it and reabsorbs in the proximal tubule. Increased urinary Cystatin C is a marker of renal tubular dysfunction. Cystatin C is highly correlated with GFR and not influenced by inflammatory conditions or other factors[6].

Early diagnosis of diabetic nephropathy is important, and early therapy decreases the progression of renal disease[4]. This can also provide a chance of adequate management and avoidance

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of end stage renal conditions[7]. In Pakistan even the ill conditioned patients don't have clue about their kidney function status, the healthy population is beyond the health wise conscious status. This study added evidence on the early state of kidney disease in type 2 diabetic population. The primary aim of the current study was to correlate Cystatin C with GFR whereas as secondary aim was to assess any association with diabetic patients BP status and urinary albumin. We conducted with an objective to correlate Cystatin C with GFR and urinary albumin in order to find out it as a marker of early detection of kidney disease (diabetic nephropathy).

METHODOLOGY

A total of 53 patients with type 2 diabetes were selected in this cross sectional analytic study.The study was conducted in the Department of Biochemistry, Islamic International Medical College in collaboration with Department of Medicine, Railway Hospital, Rawalpindi. Over a period of one year from 15thMarch, 2016 to 14th March, 2017, the patients having urinary albumin creatinine level between 30 mg/g to 300 mg/g were screened to be enrolled in the study. This was a selective sub-analysis of an existing study data, the main study was published elsewhere[8].

The diagnosed cases of type2 diabetes with HbA1C >7, having increased albumin/creatinine ratio of ACR >30mg/g of both genders and aged between 45-70 years were included in the study. The patients with any systemic illness other than diabetic syndrome and any other renal pathology were excluded.

The estimation of urinary albumin levels were carried out on IMAGIN Specific Protein Analyzer for quantitative determination of human Microalbumin [MALB] in urine by immune-turbidimetry.Blood was drawn from peripheral veins, transferred to EDTA tube, gently mixed and made to stand upright. The blood samples were centrifuged at 2200 RPM for 10 minutes. The separated serum was stored at -70^{o}C till completion of sample collection.

Urine samples, preferably early morning midstream samples were collected in the jars provided to the patients. The sample was centrifuged at 1000 RPM for 10 mins and stored at -70^{o}C till analysis.

Sample size was calculated for a baseline level cross sectional survey with study power of 80%, margin of error of 10% and anticipated population with early diabetic nephropathy of 16.5%[9]. The study sample size was 53 cases.

Data Analysis: Data analysis was managed in SPSS version 16.0. The continuous variables age, cystatin C, albumin/creatinine ratio and eGFR were analyzed as means and standard deviations. The categorical variables like gender and GFR categories were analyzed as frequency and percentages. The primary outcome was correlation of cystatin C with GFR and urinary albumin. As a secondary outcome clinical parameter of systolic and diastolic BP was also correlated with cystatin C levels. Due to no evenly scattered results of Cystatin C marker, non-parametric spearmen's correlation coefficient was applied in this study.

RESULTS

A total of 53 cases were studied. The mean age of patients was 56.1 ± 5.4 years with majority 54.7% (n=29) between 51 and 60 years. Male gender was predominant with 58.5% (n=31) cases in this study. The mean systolic BP was 147.1 ± 11.1 mmHg whilst the diastolic BP was noted to be 89.9 ± 6.5 mmHg. In this study, mean Cystatin C level was 2.5 ± 2.6 mg/l and mean urine albumin was 103.9 ± 72.5 mg/l whereas GFR was found to be 76.9 ± 15.1 Ml/min/m^2.

As per study objective, Cystatin C was correlated with GFR and urinary albumin. It was found out that GFR was perfectly negatively correlated with Cystatin C giving a correlation coefficient of (-.305), revealing that increase in cystatin C was significantly associated with decrease in GFR levels. Moreover, the correlation coefficient for and Cystatin C and urinary albumin was (0.517) showing a perfect positive linear relationship. The systolic and diastolic blood pressure parameters did not had any significant correlation with cystatin C giving a correlation coefficient of (-.173) and (-.038) respectively. Further details on overall correlation among different parameters can be seen in Table-I.

Table-I: Correlation of Cystatin C with pathological and clinical parameters (N=53)

	Spearman's correlation (*r*)	p-value
Glomerular filtration rate	-.305	0.028
Urinary albumin	0.517	<0.001
Blood pressure		
Systolic	-.173	0.21
Diastolic	-.038	0.78

We conducted gender stratified analysis to see any difference in correlation coefficients. It observed that urinary albumin was significantly positively correlated with cystatin C in males (spearman's correlation = 0.705, p-value <0.001). GRF was found more negatively correlated with cystatin C in females when compared with males (-.174 vs -.085), however these were not statistically significant.

Table-II: Difference in correlation coefficient of Cystatin C with pathological and clinical parameters according to gender (N=53)

	Male (n=31)		Female (n=22)	
	Spearman's correlation (*r*)	p-value	Spearman's correlation (*r*)	p-value
Glomerular filtration rate	-.085	0.65	-.174	0.43
Urinary albumin	0.705	<0.001	0.043	0.85
Blood pressure				
Systolic	-.167	0.38	-.118	0.60
Diastolic	-.071	0.70	0.027	0.90

The clinical parameters of systolic and diastolic BP was also found not correlated with Cystatin C in both male and female categories. (Table-II)

DISCUSSION

Our study confirms a linear relation between cystatin C and early kidney disease in the form of diabetic nephropathy in patients with type 2 diabetes mellitus. The level of cystatin C was significantly high in patients with increased urinary albumin (30 to 300 mg/dl). This study found a significant negative correlation between GFR and Cystatin C levels (r = -.305, p = 0.028). Similarly a positive correlation between urinary albumin and Cystatin C level was also confirmed (r=.517, p = <0.001). Many previous studies have proven the relation between serum cystatin C and albuminuria and glomerulofilteration rate. Hu et al found out that GFR was significantly correlated with Cystatin C levels[10]. Another study by Tsuda et al also witnessed significant correlation between eGFR and Cystatin C[11]. Tan et al found out that serum cystatin C level of microalbuminuric patients was negatively correlated with eGFR (r=-0.892, p=0.001). This highlights the importance of cystatin C in the early prediction of nephropathy[12]. Many investigators have concluded that Cystatin C is a more reliable measure of GFR than creatinine clearance[12,13]. Gupta et al also found out that cystatin C is a significant marker of diabetic nephropathy in diabetic patients[14]. Similarly, Dominguiti et al revealed that Cystatin C was greatly related with albumin levels in patients with type 1 diabetes mellitus[15]. Bruce et al concluded that serum cystatin C accurately detects status of renal function in patients with normal or elevated GFR and provides means for studying early renal function decline in diabetes[16]. We selected patients in microalbuminuria and found a similar trend of significant positive association between cystatin C levels and albumin levels as reported by many investigators before. The linear association of Cystatin C was even stronger in males when results were stratified according to gender.

As observed in many previous observational studies, the diabetic patients due to effects on the central and peripheral nervous systems have raised cystatin C levels which is partly due to peripheral and central nervous disturbance and hyperglycemic condition of diabetic patients[17,18].

There are several advantages of the current study, firstly, this is one of the very few attempts seeking linear relation of Cystatin C with GFR and urinary albumin at local and national level. A reasonable sample of 53 patients with urinary albumin between 30 and 300 mg/l was selected.

There were few limitations of the study as well, as there could have been a comparative group of non diabetic cases in the study. The cross sectional design of study was weak and not all confounding effects were studied. Moreover, due to sub-analytical nature of the study, long term outcome of patients was not confirmed as to see how many of the cases finally developed chronic kidney condition and does anyone recovers to normalcy.

CONCLUSION

Cystatin C was found significantly correlated with GFR and urinary albumin, thus, validating previous findings regarding Cystatin C's role as an early marker of kidney diseases.

AUTHOR'S CONTRIBUTION

Zaman A: Conceived idea, Planned and conducted the study, Manuscript writing.
Malik A: Data collection, Data entry, Data interpretations.
Rahim A: Reviewed the manuscript, Final drafting.

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