Serum cystatin C and serum creatinine levels in type 2 diabetes mellitus

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ABSTRACT

Background: Diabetes mellitus is a metabolic disorder resulting from deficient insulin secretion, inefficient insulin action or both leading to chronic hyperglycemia. Diabetic complications result from the toxic effects of chronic hyperglycemia combined with other metabolic derangements. Diabetic nephropathy eventually leads to loss of kidney function, which is the most common cause of End stage renal disease. Measurement of GFR is an important parameter in assessing kidney function for which Creatinine is currently being used despite its inherent fallacies. Cystatin C is an alternative marker with some advantages. Aims and objectives: To measure the serum cystatin C levels in type 2 diabetes mellitus patients. To compare serum cystatin C levels with serum creatinine levels in type 2 diabetes mellitus patients.

Methods: The study was carried out in 30 type-2 diabetic patients and 30 non-diabetic controls, in the age group of 35 to 75 years. Both the groups were age and gender matched. Serum cystatin C levels and serum creatinine levels were measured in both the groups. Serum creatinine was estimated by Jaffe's kinetic method, while the estimation of serum cystatin C was done by Immunoturbidimetric method.

Results: Serum creatinine as well as serum cystatin C levels were significantly elevated in the study group as compared to non-diabetic controls. There was a strong positive correlation of serum cystatin C with serum creatinine.

Conclusion: Serum cystatin C can be used as an alternative to serum creatinine in determining GFR in type 2 diabetes mellitus.

Keywords: Cystatin C, Creatinine, Type 2 diabetes mellitus, Diabetic nephropathy

INTRODUCTION

Diabetes mellitus is a metabolic disorder resulting from insufficient insulin secretion, inefficient insulin action or both and covers a wide range of heterogeneous diseases. The prevalence of diabetes is rapidly rising all over the globe at an alarming rate. Although there is an increase in the prevalence of type 1 diabetes, the major driver of the epidemic is the more common form of diabetes, namely type 2 diabetes accounting for more than 90% of all cases. Diabetic complications result from the toxic effects of chronic hyperglycemia combined with other metabolic derangements. Persons with diabetes are at substantial risk for tissue injury in organs supplied by an endarterial system due to microangiopathy. These microvascular complications include nephropathy, retinopathy and neuropathy. Diabetes is the most common cause of End Stage Renal Disease (ESRD). Approximately 40% of patients with type 1 and 15% of patients with type 2 Diabetes eventually develop ESRD.

In type 2 diabetes, hyperglycemia starts after forties, usually when the kidneys have already suffered the long term consequences of ageing and other recognized promoters of chronic renal injury like arterial hypertension, obesity, dyslipidemia and smoking. Diabetic nephropathy refers to a characteristic set of structural and functional kidney abnormalities in patients...
with diabetes. The structural abnormalities include hypertrophy of the kidney, increase in glomerular basement membrane thickness, nodular and diffuse glomerulosclerosis, tubular atrophy and interstitial fibrosis. The functional alterations include an early increase in glomerular filtration rate with intraglomerular hypertension, subsequent proteinuria, systemic hypertension and eventual loss of kidney function. 

Although microalbuminuria is the first detectable functional abnormality, Glomerular Filtration Rate (GFR) is the critical renal function.

The gold standard for estimation of GFR is clearance of endogenous substances such as inulin, ioxheol, 57Cr EDTA, 99mTc DTPA or [125I] iothalamate. These techniques are time consuming, labour intensive, expensive and require administration of substances that make them incompatible with routine monitoring.

The ideal marker of GFR should be an endogenous molecule which being produced at a constant rate is cleared solely by the kidneys via free glomerular filtration, being neither secreted by tubular cells, nor reabsorbed into peritubular circulation.

Measurement of serum creatinine is simple but the general view is that up to 50% of GFR can be lost before significant elevation of serum creatinine occurs. It also has significant limitations due to inter individual variation in muscle mass and tubular secretion of creatinine. As a result serum creatinine has a poor sensitivity for mild renal dysfunction and in elderly patients, with subsequent under recognition of renal impairment.

Cystatin C, a Cysteine protease inhibitor is freely filtered by the renal glomeruli, metabolized by proximal tubule and identified as a promising marker of renal failure. Cystatin C is produced at a constant rate by nucleated cells and released into the blood stream with a half-life of 2 hours. Its concentration is almost totally dependent on GFR, the independence from height, gender, age and muscle mass is advantageous.

Hence this study is being undertaken to measure the levels of serum cystatin C in type 2 diabetes mellitus as a marker of renal impairment.

**METHODS**

The study was carried out in 30 type-2 diabetic subjects and 30 non-diabetic controls who attended the outpatient and inpatient department of medicine of Kempegowda institute of medical sciences, Bangalore during the year 2012-13. The age of the diabetic subjects ranged from 35 to 70 years and age and gender matched healthy persons were chosen as controls.

Patients with hypertension, thyroid disorders, congestive cardiac failure, liver disease, rheumatoid disease, malignancy, fever, dehydration and patients on glucocorticoids, nephrotoxic drugs, smoking and alcohol users were excluded from the study.

The institutional ethical committee approved the study protocol. History and personal physical data was obtained from both cases and controls.

Informed consent was taken from patient and control subjects. A pre-structured and pre-tested proforma was used to collect the data. Baseline data including age and gender, detailed medical history including conventional risk factors, clinical examinations and relevant investigations were included as part of the methodology.

5 ml of venous blood sample was collected after overnight fasting of 12 hours from both cases and controls and the samples were centrifuged and separated for the estimations. Estimations of fasting blood glucose, blood urea and serum creatinine were performed using the serum. Estimation of serum cystatin C was done by immunoturbidimetric method.

**Statistical analysis**

The statistical software SPSS 17.0 was used for the analysis of the data. Descriptive statistical analysis was carried out in the present study. Results on continuous measurements were presented as Mean ± SD. P value <0.05 (95% confidence interval) was considered significant. Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups.

**RESULTS**

The basic characteristics of the control group and cases with type 2 diabetes mellitus are depicted in Table 1. There is no significant difference in age and BMI (Body Mass Index) between two groups.

**Table 1: Basic characteristics of study population.**

<table>
<thead>
<tr>
<th>Basic characteristics</th>
<th>Controls</th>
<th>Cases</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.1 ± 7.34</td>
<td>52.85 ± 8.69</td>
<td>0.032</td>
</tr>
<tr>
<td>Male:Female</td>
<td>13:17</td>
<td>16:14</td>
<td>0.795</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.22 ± 1.73</td>
<td>23.67 ± 1.18</td>
<td>0.17</td>
</tr>
</tbody>
</table>

The mean serum urea level was higher among cases when compared with controls and was statistically significant. The mean serum creatinine level was higher among cases when compared with controls and was statistically significant. The mean serum cystatin C level was higher among cases when compared with controls and was statistically significant (Table 2).
Table 2: Mean distribution of blood urea, serum creatinine and serum cystatin C levels in patients and controls.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Controls</th>
<th>Cases</th>
<th>t value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea (mg/dl)</td>
<td>22.13 ± 5.01</td>
<td>27.86 ± 8.94</td>
<td>2.86</td>
<td>0.008</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.82 ± 0.13</td>
<td>0.99 ± 0.26</td>
<td>3.26</td>
<td>0.003</td>
</tr>
<tr>
<td>Cystatin C (mg/dl)</td>
<td>1.11 ± 0.06</td>
<td>1.53 ± 0.34</td>
<td>6.43</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

There is a correlation of 80% between serum cystatin C and serum creatinine among cases and hence strongly positive correlation (r value is 0.80). This is graphically depicted using a scatter graph in Figure 3.

Figure 1: Scatter plot depicting correlation between cystatin C and creatinine among cases.

DISCUSSION

Diabetes mellitus is a chronic metabolic disorder of multiple etiologies. It is characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both.12

Diabetic nephropathy refers to a characteristic set of structural and functional kidney abnormalities in patients with diabetes. Diabetic nephropathy is generally associated with a progression from microalbuminuria to macroalbuminuria, which is then associated with progressive decline in renal function ultimately resulting in the need for renal replacement therapy.13

Gold standard methods of assessing GFR are replaced by an estimated GFR derived from endogenous substances.

Serum creatinine is the most widely used substance to estimate GFR. Creatinine concentration is influenced by sex, age, diet and muscle mass. It only increases once GFR reduction of about 50% is present. This leads to falsely high or low values, limiting its usefulness as an ideal marker of GFR.14

Cystatin C is a low molecular weight protein produced at a constant rate by all nucleated cells. It is freely filtered by glomerulus, completely reabsorbed and catabolized in the proximal tubule. Serum cystatin C is reported to be modulated by several non-renal factors like steroids, thyroid status, smoking, C-reactive protein and malignancy. Despite these limitations evidence continues to suggest superiority of serum cystatin C when compared with serum Creatinine in patients with early and moderately decreased renal function.15

The mean age of cases in this study was 52.85 ± 8.69 with a body mass index of 24.22 ± 1.73. This is comparable to studies by Punyakrit Deb et al.15 and Nazmu Saquib et al.16

The study shows significant increase in serum cystatin C levels in diabetic individuals compared to controls. These findings are similar to a study conducted by Borges et al.17

There was a strong positive correlation between serum cystatin C and serum creatinine (r = 0.80) among cases in this study. This is in conformity with a study done by Buysscheart M et al. who found a close linear relationship between serum cystatin C and serum creatinine (r = 0.92).18

Thus the study shows that serum cystatin C can be used as a marker for determining GFR in type 2 diabetes mellitus compared to serum creatinine.

CONCLUSION

Cystatin C in comparison with serum creatinine can be a useful maker in detecting renal impairment in type 2 diabetes mellitus individuals.

Further studies can be done with higher sample size using other parameters like urine microalbumin and gold standard methods for better evaluation of cystatin C as a marker of renal impairment.

Also studies can be done involving larger Indian population, for establishing Indian reference ranges for cystatin C as most of the published studies use western population. This can help in the early diagnosis and better management of diabetic nephropathy.

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REFERENCES


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