Validity of Serum Cystatin C as an Early and Accurate Marker of Glomerular Filtration Rate in Type 1 Diabetes Mellitus Patients

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Received: 4/1/2016 Accepted: 12/2/2016

ABSTRACT

The present study aims at exploring the clinical validity of measuring cystatin C for the early and accurate assessment of GFR (as compared to measuring serum creatinine or β2 microglobulin) in patients suffering from type 1 diabetes mellitus who are at risk of developing diabetic nephropathy as well as those who have already developed the condition. This study included 80 subjects who were further subdivided into two groups: Control group (1) which comprised 20 healthy age and sex matched children. Patient group (2) comprised 60 patients of both sexes properly diagnosed with type 1 diabetes. The patients were further subdivided into 3 subgroups according albumin levels in their 24 hour urine: Group 2a: 20 patients who were considered normo-albuminuric. Group 2b: 20 patients who were considered micro-albuminuric. Group 2c: 20 patients who were considered macro-albuminuric. All subjects were subjected to the estimation of serum creatinine level as well as serum β2 microglobulin and serum cystatin C levels. They were also subjected to Isotope renogram using 99mTc-diethylenetriaminepentaacetic acid (DTPA) single injection technique for accurate measurement of glomerular filtration rate (GFR).

A positive correlation was observed between each of serum creatinine, β2 microglobulin, cystatin C with albumin in 24 hr urine in all the patient subgroups and this correlation was highly significant. However, the correlation between serum cystatin C levels in the diabetic patients and albumin in 24 hr urine was higher than that observed for either serum creatinine or serum β2 microglobulin. Cystatin C had the highest negative correlation with GFR (as measured by 99mTc-DTPA clearance) compared to either serum creatinine or serum β2 microglobulin in group II patients. It can be concluded that cystatin C could act as an early and accurate marker of GFR and renal function in patients with type 1 diabetes mellitus at risk of developing or who have already developed diabetic nephropathy.

Keywords: Diabetic Nephropathy, Creatinine, Cystatin C, β2 Microglobulin, 99mTc-DTPA, Glomerular Filtration Rate.

INTRODUCTION

Diabetes mellitus is a prevalent metabolic disorder characterized by deficiencies in insulin secretion, insulin resistance or both. Approximately 40% of patients with type I diabetes and 5-15% of patients with type II diabetes mellitus will ultimately develop End Stage Renal Disease (ESRD) (1). Therefore prevention of diabetic renal disease or the delay of the disease process has appeared to became a highly important issue (2). However, our current capacity to evaluate renal function is humble in early diabetic nephropathy, when active management is necessary (3).

Accurate glomerular filtration estimation is very important in the early diagnosis and treatment of kidney diseases. Serum creatinine is the most commonly used marker of renal function and is also used for the calculation of glomerular filtration rate (GFR), but its measurement carries a variety of analytical and significant standardization problems (4).

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Serum creatinine can be affected by age, gender, ethnicity, dietary protein intake, lean mass and may remain within the reference range despite marked renal impairment in infants with low muscle mass. Therefore, the sensitivity of serum creatinine for the early detection of kidney disease is poor and not a good predictor of renal function (5).

The estimation of creatinine clearance overcomes some of the difficulties presented by serum creatinine as a tool for the assessment of renal function and may improve the estimation of GFR. On the other hand, it has shown many disadvantages. These include the possibility of improper 24-hour urine collection especially by children and overestimation of GFR due to kidney tubular secretion of creatinine (6).

Although the estimation of GFR represents the best complete assessment of kidney function, the gold standard techniques for the measurement of GFR, such as inulin clearance, $^{125}$I iothalamate, $^{51}$Cr-EDTA, $^{99m}$Tc-diethyleneetriaminepentaacetic acid, and iohexol are too labor-intensive, may involve exposure of the patient to ionizing radiation and are costly for routine clinical use (7).

Several low molecular proteins such as β2-microglobulin and cystatin C have been proposed as alternative molecules whose measurement could better reflect GFR than serum creatinine especially for the early diagnosis and follow up of diabetic nephropathy (8).

Cystatin C is freely filtered, reabsorbed and completely metabolized by the proximal tubule and therefore is not subjected to tubular secretion. Compared to creatinine, cystatin C has a more stable rate of production with less intra variability (9).

**Aim of the Present Study**

The aim of the present study was to evaluate cystatin C as an early and accurate marker of renal dysfunction in type 1 diabetes mellitus patients.

**SUBJECTS AND METHODS**

**Subjects**

This study conducted on 80 children who attended the endocrine outpatient clinic at Abo-Elrish Children’s Hospital, Cairo University. These children were further subdivided into three groups:

1. **Control Group (1)**

This comprised 20 healthy age and sex matched children (including 10 healthy boys and 10 healthy girls). Their ages ranged between 2 and 16 years with a mean age ± SD of 7.5 ± 4.2. All control subjects had normal renal functions.

2. **Patient Group (2)**

It comprised 60 patients of both sexes properly diagnosed with type 1 diabetes mellitus whose ages ranged between 2.6 and 17.5 years of age with a mean age ± SD of 8.4 ± 5.5. Their glycosylated haemoglobin (HbA1c) levels ranged between 7.5 and 12 with a mean of 8.5 ± 2.6. They were admitted to the hospital between January 2014 and December 2014. Since abnormal thyroid function could affect the levels of cystatin C (10) the patients with thyroid disease, or taking the medication for thyroid disease in the past 6 months were excluded. Other exclusion criteria were the history of rheumatic disease, malignancy, liver, cardiac diseases and history of taking steroids or any chemotherapeutics. The patients were further divided into 3 subgroups according to the level of albumin in their 24 hour urine as described by Chiarelli (11):

**Group (2a):** comprised 20 patients who were considered normoalbuminuric (NA) Their urinary albumin levels were less than 30 mg/24 hr urine; equivalent to an albumin to creatinine ratio < 30mg/g.
Group (2b): comprised 20 patients who were considered microalbuminuric (MA). Their urinary albumin levels ranged between 30 and 299 mg/24 hr urine; equivalent to an albumin to creatinine ratio between 30 and 299 mg/g).

Group (2c): comprised 20 patients who were considered macroalbuminuric (300 mg or more/24 hr urine; equivalent to an albumin to creatinine ratio more than 300 mg/g). The patients belonging to this group were considered to be suffering from frank diabetic nephropathy (DN).

METHODS
The above mentioned groups were subjected to the following:

1. Full clinical history including name, age, gender, height, weight and past history of any chronic disease or drug intake was recorded.
3. Routine laboratory investigations to confirm the cause of nephropathy including blood picture, fasting and postprandial 2 hour blood glucose level, HbA1c as well as a complete urine analysis.
4. Estimation of serum and urea (12) creatinine (13) levels. Kits for these analyses were obtained from Sigma-Aldrich Inc., USA.
5. Isotope renogram using 99mTc-diethylenetriaminepentaacetic acid (DTPA) single injection technique for the measurement of GFR (14).
6. Estimation of serum β2 microglobulin. This was carried out by electro-immunosorbant assay technique (ELISA) (15). The kit for this assay was obtained from Genway Biotech Inc., USA.
7. Estimation of serum cystatin C level using ELISA technique as described by Tian (16). The kit for this assay was obtained from R& D systems Inc., USA.

Sampling
After taking care of all aseptic precautions, a sample of 2 ml of venous blood was drawn from each subject and was incubated in a clean, dry test tube at 37 °C until clot retraction. Then the sample was centrifuged at 4000 rpm for 15 minutes and each sample of serum was collected in an eppendorf tube and preserved at -20 °C till time of analysis.

Statistical Analysis
For statistical analysis, SPSS statistical analysis software program for Windows (version 21.0) was used. Data was presented as mean ± SD for normally distributed values. Differences between the groups were analyzed using analysis of variance (ANOVA) followed by the Bonferroni's test for normally distributed values and by the Kruskal-Wallis test for non-parametric values. Pearson's correlation coefficient was employed to test the correlations between different variables. The diagnostic rationale of employing cystatin C, β2- microglobulin or serum creatinine for the estimation of GFR in comparison with 99mTc-DTPA clearance was evaluated by the receiver operating characteristics (ROC) analysis, which was used to calculate the area under the curve (AUC) for these various parameters. Cross tabulation analysis was used to derive the sensitivity, specificity, positive predictive value, and negative predictive value of the reference GFR values. The reference cut off value for GFR was determined at ≥ 90 ml/min/1.73 m² (17). Statistical analysis was carried out in accordance to the methodologies described by Snedcor and Cochran (18). All results were considered significant if $p < 0.05$.

RESULTS
A gradual increase in all the renal function markers investigated in this study was observed as the level of albumin in 24-hour urine increased in the three participating diabetic subgroups (NA, MA and DN) and the differences between them was found to be highly significant as illustrated in table 1 and figure (1).
Table (1): A comparison between control subjects (group I) and diabetic patients (group II) as regards serum creatinine, β2 Microglobulin, cystatin C and GFR by $^{99m}$Tc-DTPA clearance

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control (n=20) Mean ±SD</th>
<th>Patients with NA Mean ±SD</th>
<th>Patients with MA Mean ±SD</th>
<th>Patients with DN Mean ±SD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine (mg/dl)</td>
<td>0.6±0.2</td>
<td>0.8±0.3</td>
<td>1.3±0.5</td>
<td>2.7±1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum β2 Microglobulin (mg/L)</td>
<td>1.2±0.2</td>
<td>1.4±0.3</td>
<td>2.5±0.2</td>
<td>3.2±0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum Cystatin C (mg/L)</td>
<td>0.7±0.1</td>
<td>0.9±0.2</td>
<td>1.7±0.4</td>
<td>3.5±0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GFR $^{99m}$Tc-DTPA clearance (ml/min/1.73 m$^2$)</td>
<td>87.3±15</td>
<td>85.1±17</td>
<td>77.2±12</td>
<td>44.6±10</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

NA= normoalbuminuric, MA=microalbuminuric, DN=Diabetic nephropathy, GFR $^{99m}$Tc-DTPA clearance= glomerular filtration rate calculation using GFR $^{99m}$Tc-diethelenetriamine pentaacetic acid

Fig (1): A comparison of the mean levels of Serum Cystatin C (±SD) in the three subgroups of patients participating in the current study.

A highly significant positive correlation was observed between serum creatinine, β2 Microglobulin, cystatin C and albumin measured in 24-hr urine in patients belonging to group II as demonstrated in table 2 below.

Table (2): Pearson’s correlation of albumin measured in 24 hr urine with serum creatinine, β2 Microglobulin, and cystatin C in group II

<table>
<thead>
<tr>
<th>Variables</th>
<th>Albumin in 24 hr urine</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td></td>
</tr>
<tr>
<td>Serum Creatinine</td>
<td>0.50</td>
<td>&lt;0.001 HS*</td>
</tr>
<tr>
<td>Serum β2 Microglobulin</td>
<td>0.55</td>
<td>&lt;0.001 HS*</td>
</tr>
<tr>
<td>Serum Cystatin C</td>
<td>0.6</td>
<td>&lt;0.001 HS*</td>
</tr>
</tbody>
</table>

*HS= highly significant. A highly significant positive correlation was also observed between serum creatinine, β2 microglobulin, cystatin C on one hand and HbA1c, age and body mass index (BMI) on the other in patients belonging to group II as shown in table 3 below.
Table (3): Pearson’s correlation between serum creatinine, β2 microglobulin, cystatin C and HbA1c, age as well as body mass index of type 1 diabetes mellitus patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>HbA1c r</th>
<th>P value</th>
<th>Age r</th>
<th>P value</th>
<th>Body Mass Index (BMI) r</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine</td>
<td>0.49</td>
<td>&lt;0.01 HS*</td>
<td>0.57</td>
<td>&lt;0.01 HS*</td>
<td>0.54</td>
<td>&lt;0.01 HS*</td>
</tr>
<tr>
<td>Serum β2 Microglobulin</td>
<td>0.51</td>
<td>&lt;0.01 HS*</td>
<td>0.60</td>
<td>&lt;0.01 HS*</td>
<td>0.63</td>
<td>&lt;0.01 HS*</td>
</tr>
<tr>
<td>Serum Cystatin C</td>
<td>0.62</td>
<td>&lt;0.01 HS*</td>
<td>0.64</td>
<td>&lt;0.01 HS*</td>
<td>0.65</td>
<td>&lt;0.01 HS*</td>
</tr>
</tbody>
</table>

* HS= highly significant, BMI= weight (kg)/height (m²). Serum cystatin C levels were highly positively correlated with serum creatinine, β2 microglobulin in group II patients as observable in table 4 below.

Table (4): Pearson’s correlation of serum cystatin C levels with serum creatinine, β2 Microglobulin in Group II patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Serum cystatin C (mg/L) r</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine</td>
<td>0.87</td>
<td>&lt;0.001 HS*</td>
</tr>
<tr>
<td>Serum β2 Microglobulin</td>
<td>0.74</td>
<td>&lt;0.001 HS*</td>
</tr>
</tbody>
</table>

* HS= highly significant. A highly significant negative correlation was observed between serum creatinine, serum β2 Microglobulin, and serum cystatin C on one hand and GFR (measured by ⁹⁹mTc-DTPA clearance) on the other in group II patients as demonstrated in table 5 below.

Table (5): Pearson’s correlation of GFR (measured by ⁹⁹mTc-DTPA clearance) with serum creatinine, serum β2 Microglobulin, and serum cystatin C in Group II patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>GFR by (⁹⁹mTc-DTPA clearance) r</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine</td>
<td>-0.72</td>
<td>&lt;0.001 HS*</td>
</tr>
<tr>
<td>Serum β2 Microglobulin</td>
<td>-0.79</td>
<td>&lt;0.001 HS*</td>
</tr>
<tr>
<td>Serum Cystatin C</td>
<td>-0.94</td>
<td>&lt;0.001 HS*</td>
</tr>
</tbody>
</table>

* HS= highly significant

Serum cystatin C demonstrated the highest dependability as a GFR marker in diabetes type I patients when compared to either serum creatinine or β2 Microglobulin with regard to positive and negative predictive values, sensitivity, specificity as well as validity (i.e. accuracy). GFR measured using ⁹⁹mTc-DTPA clearance technique was used as the golden standard reference for these 5 values in all renal function markers studied as illustrated in table 6 below.

Table (6): Dependability of serum creatinine, β2 microglobulin, cystatin C as markers of GFR as compared to ⁹⁹mTc-DTPA clearance

<table>
<thead>
<tr>
<th>Variables</th>
<th>Positive Predictive Value (%)</th>
<th>Negative Predictive Value (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Validity (Accuracy) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine</td>
<td>46.6</td>
<td>88.9</td>
<td>61.5</td>
<td>80.5</td>
<td>63.1</td>
</tr>
<tr>
<td>Serum β2 Microglobulin</td>
<td>80.4</td>
<td>85.5</td>
<td>88.6</td>
<td>82.0</td>
<td>86.2</td>
</tr>
<tr>
<td>Serum Cystatin C</td>
<td>82.1</td>
<td>95.1</td>
<td>91.3</td>
<td>94.1</td>
<td>95.4</td>
</tr>
</tbody>
</table>
DISCUSSION

Diabetes mellitus has increasingly started to become the most common single cause of end stage renal disease (ESRD). In the U.S alone, diabetic nephropathy encompasses about 40% of novel cases of ESRD each year. Early and proper assessment and follow up of renal impairment through accurate glomerular filtration rate (GFR) estimation is very important in improving the management and outcome of diabetic nephropathy including cases belonging to the type 1 diabetes mellitus group of patients.

Cystatin C is a 13 kD protein produced by a housekeeping type gene in all nucleated cells. This cysteine protease inhibitor is spontaneously filtered by the glomerulus without limits, and does not appear to be secreted by the renal tubules. Some of the limitations of serum creatinine as a renal function indicator, i.e. the effect of gender, body muscle mass and diet do not appear to be factors that impact serum cystatin C levels. Cystatin C is relatively stable, and can be rapidly and accurately analysed by automated analysers, thereby meeting the practical requirements of a suitable laboratory test.

Cystatin C concentration has thus been proposed as an endogenous indicator of GFR and a superior alternative to creatinine in the evaluation of diabetic nephropathy patients.

In the present study, the levels of serum creatinine, β2 microglobulin and cystatin C were measured in the control subjects as well as type 1 diabetes mellitus patients who were further categorized according to their levels of albumin in urine into normoalbuminuric (NA) microalbuminuric (MA) and macroalbuminuric or diabetic nephropathy (DN) subgroups. GFR values in all participants were measured using the gold standard 99mTc-DPTA clearance marker and were compared to the above mentioned parameters.

A stepwise increase in all the above mentioned markers was observed as the level of albumin in 24 hour urine increased in the three participating diabetic subgroups (NA, MA and DN) and the differences between them was found to be highly significant (P<0.001). In addition, a positive correlation was observed between each of serum creatinine, β2 microglobulin, cystatin C with albumin in 24 hr urine in all the patient subgroups and this correlation was highly significant (p<0.001). However, it is worth noting that the correlation between serum cystatin C levels in the diabetic patients and albumin in 24 hr urine was higher than that observed for either serum creatinine or serum β2 microglobulin (r=0.6 vs.0.55 and 0.5 respectively).

Similar results showing a positive correlation between serum cystatin C and albumin/creatinine ratio and its superiority over creatinine as an early detector of renal dysfunction were observed in a recent clinical study by Jeon carried out on patients with type 2 diabetes mellitus suffering from diabetic nephropathy with either microalbuminuria or macroalbuminuria. Yoo found that serum cystatin C level reflects a trend in albuminuria level more accurately than serum creatinine level does in type 2 diabetes mellitus patients.

Yang found that, serum cystatin C was also correlated with urine albumin excretion in type 2 diabetes mellitus patients, which was not true for serum creatinine.

Albuminuria is considered to be a marker for early diabetic nephropathy (DN), an independent predictor for morbidity and mortality and is associated with a higher risk of renal damage. Macroalbuminuria is the general finding in progressive renal disease, and is viewed as a measure of the severity and an indicator of diabetic renal disease development.

Several authors have also considered that a positive correlation between serum cystatin C and albuminuria could act as a good and early predictor for the progression to chronic renal disease. The results of the present study suggest the importance of serum cystatin C as an early indicator for the development of renal impairment in patients with type 1 diabetes mellitus through its positive correlation with albumin in 24-hour urine concentrations.
The present study showed a positive correlation between serum creatinine, serum β2 microglobulin, serum cystatin C and the levels of HbA1c in group II patients (r=0.49, 0.51 and 0.62 respectively). This correlation was found to be highly significant for all the markers mentioned (p<0.01). However it was noted that the correlation between serum cystatin C and HbA1c was the highest among these three markers. The study by Jeon (22) and another study by Assal (28) found a positive correlation between serum cystatin C and HbA1c in type II diabetes mellitus patients who were at risk of developing renal impairment in the future. These results point out to the suitability of using cystatin C as a marker of renal function in the follow up of patients with type I diabetes mellitus.

The present study also showed a positive correlation between serum creatinine, serum β2 microglobulin, serum cystatin C levels and the body mass index of patients in group II that was highest for cystatin C (r=0.54, 0.63 and 0.65 respectively) and the correlation was considered to be highly significant for all markers mentioned (p<0.01). Rentakaran et al. have demonstrated a positive correlation between cystatin C and BMI (29). A positive correlation between serum creatinine, serum β2 microglobulin, cystatin C and the age of patients was found in this study, the highest correlation being that for serum cystatin C (r=0.57, 0.60 and 0.64 respectively). This correlation was considered to be highly significant for all markers mentioned (p<0.01). The positive correlation between the age of patients participating in this work and serum cystatin C levels is confirmed in a study by Groesbeck (30) concluding that serum cystatin C is significantly related to age and race/ethnicity in adolescents.

Levels of cystatin C in group II patients were found to correlate positively with both serum creatinine and serum β 2 microglobulin (r=0.87 and 0.74 respectively). This correlation was found to be highly significant for both of the latter markers (p<0.01). These results are confirmed by several authors such as Askun (8), and Mojininiyi (32) who found similar correlations between serum cystatin C levels and both serum creatinine and serum β 2 microglobulin in diabetic patients at risk of developing diabetic nephropathy.

As regards the soundness of using cystatin C as an accurate marker of renal function in type I diabetes mellitus patients, the current study found that cystatin C had the highest negative correlation with GFR (as measured by 99mTc-DPTA clearance) compared to either serum creatinine or serum β 2 microglobulin in group II patients (r= -0.94 vs. -0.72 and -0.79 respectively).

However, the negative correlations between the three markers studied and GFR were all considered to be highly significant (p<0.001). A significant negative correlation with GFR determined by 99mTc DPTA clearance methodology confirms the dependability of these markers especially cystatin C in the assessment of renal function. Trimarchi (33) demonstrated similar inverse correlations between serum cystatin C levels, serum creatinine levels and 99mTc-DTPA clearance values in a sample of chronic kidney disease patients. Askun (31) showed a significant negative correlation between both cystatin C and β2-microglobulin and GFR values in type 2 diabetics.

It is worth noting that a good diagnostic test for any disease should have high positive and negative predictive values as well as high sensitivity, specificity and validity values. A positive predictive value is the percentage of patients with a positive test who actually have the disease while a negative predictive value is the percentage of patients with a negative test who do not have the disease. Sensitivity is the ability of a test to correctly classify an individual as being diseased. Specificity is the ability of a test to correctly classify an individual as disease-free. Validity is the extent to which a test measures what it is supposed to measure or it is the accuracy of the test (34). In the present study, serum cystatin C demonstrated the highest positive and negative predictive percentages in addition to high percentages of sensitivity, specificity and accuracy in reference to GFR values (82.1%, 95.1%, 91.3%, 94.1 % and 95.4% respectively) as evaluated by the receiver operating characteristics (ROC) analysis which was used to calculate the area under the curve (AUC) for each marker as mentioned above. The second highest values for the parameters mentioned above was demonstrated by β 2 microglobulin (80.4%, 85.5%, 88.6%, 82.0%, and 86.2% respectively). These were followed by those for creatinine (46.6%, 88.9%, 61.5%, 80.5%, and 63.1% respectively). These results suggest that using
serum cystatin C levels as a marker of renal function is superior to using either serum β 2 microglobulin or serum creatinine in diabetes mellitus type 1 patients. Hojs and his colleagues (35) previously showed that serum cystatin C is a reliable marker of GFR in patients with mildly to moderately impaired kidney function and has a higher diagnostic accuracy than serum creatinine. Mussap (36) demonstrated that cystatin C may be considered as an alternative and more accurate serum marker than serum creatinine in discriminating type 2 diabetic patients with reduced GFR from those with normal GFR. On the other hand these results are contradicted by authors such as Louvar and colleagues (37) who could not establish the superiority of serum cystatin C over serum creatinine as a marker of renal function in a sample of former kidney donors.

It can be concluded from the present study that cystatin C could act as an early and accurate marker of GFR and renal function in patients with type 1 diabetes mellitus at risk of developing diabetic nephropathy. However, larger population samples are further needed to establish and confirm serum cystatin C as an early and valid marker of renal function in these patients.

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