CYSTATIN C IN DIABETIC PATIENTS

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ABSTRACT
Early identification of renal function impairment is crucial in diabetic patients. Clinically, serum cystatin C may be the most sensitive indicator of the glomerular filtration rate. The aim of this study was to propose the use of cystatin C test to evaluate kidney function in type 2 diabetic patients. The study was done on 60 patients with type 2 diabetic and 20 healthy subjects, serum level of glucose, total protein, urea, creatinine and cystatin C were measured and studied. The estimating glomerular filtration rate (eGFR) was estimated by using Hoek formula. The statistical results of biochemical tests showed high significant differences (P < 0.005) in mean serum levels of glucose, urea, creatinine, cystatin C and insignificant changes (P > 0.05) in mean serum levels of total protein for diabetic patients as compared with control mean. However, high significant negative correlation was appeared between eGFR values and serum levels of creatinine for both groups. Cystatin C-based GFR estimates showed high correlation to serum creatinine levels. Thus, we recommend cystatin C for GFR estimation in diabetic patients.

Keywords: Cystatin C, Creatinine, Type 2 Diabetes Mellitus, Glomerular filtration rate.

1. INTRODUCTION
The glomerular filtration rate (GFR) is essential for the clinical assessment of renal function. An optimal GFR biomarker should be constantly produced at the same level, independent of age, body or muscle mass, and exclusively eliminated by glomerular filtration without tubular secretion or reabsorption. The urinary clearance of exogenous substances, such as $^{51}$Cr-EDTA and inulin, are accepted as gold standards for GFR assessment. However, because of costs and inconvenience, plasma creatinine, creatinine clearance and creatinine-based estimation formulas are most commonly used to measure renal function. Creatinine is of limited value in early renal insufficiency since plasma levels only rise if the GFR decreases below 60mL/min/1.73 m². As it is generated by muscle metabolism, plasma levels are dependent on muscle mass, age, and gender. In addition, creatinine undergoes tubular secretion which varies with renal function.

Cystatin C, an endogenous 13 kDa protein of the cystatinsuperfamily of cysteine proteinase inhibitors, is expressed at a constant rate in all nucleated cells. It is freely filtered in the glomeruli without significant tubular secretion. Thus, plasma levels should be unaffected by muscle mass, age, race, or gender.
1.1 Patients and Methods
Sixty patients, (32 females, 28 males) their ages ranging from (40-65) year, with type 2 diabetic and 20 control subject (9 females, 11 males) aged (40-60) year recruited from Al-Yarmouk hospital. Diagnoses are made based on clinical symptoms and biochemical tests. Patients with liver disease, renal failure, heart failure and patients on high dose steroid treatment (effect on cystatin c level) were excluded from the study.

Blood samples are aspirated to measure serum levels of glucose, creatinine, urea, total proteins by Photometric Colorimetric Test and serum levels of cystatin C (Cys C) that assayed by the quantitative sandwich enzyme immunoassay technique (ELISA).

The estimating glomerular filtration rate (eGFR) was estimated by using Hoek formula: 
$$\text{eGFR (ml/min/1.73 m^2)} = \frac{[80.35/S.\text{Cystatin C (mg/L)}]}{4.32}$$

All blood samples were obtained after receiving patients' informed consent and followed a standardized protocol that approved by the institutional ethics committee of each study site.

Results are shown as mean ± SD with 95% confidence interval (CI), and P values of $0 < 0.05$ were regarded to be statistical significant. All statistical analyses were performed using SPSS version 16.

1.1.1 RESULT
The Results of biochemical tests tended to show high significant differences ($P < 0.005$) in mean serum levels of glucose, urea, creatinine, cystatin C for diabetic patients compared with control mean. Whereas insignificant changes ($P > 0.05$) were appeared in mean serum levels of total protein for diabetic patients as compared with control mean (Table 1; Figure 1 and 2).

Moreover, there were high significant negative correlation between eGFR values and serum levels of creatinine for control group ($r=-0.7464$, $P<0.001$), and for diabetic group ($r=-0.826$, $P<0.001$), (Figure 3 and 4 respectively).

1.1.2 DISCUSSION
The GFR is accepted as the best overall index of renal function. The current guidelines emphasize the need to assess kidney function using predictive serum creatinine-based equations rather than just serum creatinine. For clinicians, a GFR below 60ml/min/1.73 m² is very important because such values indicate the presence of renal insufficiency and represent an increased risk of cardiovascular events and mortality in these patients. However, the use of serum creatinine and serum creatinine-based equations has some limitations, and the development of new markers for more accurate evaluation of renal function was essential.

In recent years, serum cystatin C was proposed as a new endogenous marker of GFR, and various serum cystatin C-based equations were developed. In the study of Larsson et al., two different serum cystatin C formulas were developed and compared with iohexol clearance as the reference GFR method. In a study of 100 adult patients with different renal diseases was concluded by the authors that cystatin C formulas presented reliable GFR data based on a single measurement of serum cystatin C concentrations.

Bland and Altman analysis showed that the simple formula \(GFR = -4.32 + 80.35 \times \text{serum cystatin C(mg/L)}\), gave more accurate and more precise GFR estimates than obtained with the Cockcroft and Gault formula. The day-to-day variation (biological and analytical) for cystatin C was small in diabetic patients.

The serum concentrations of creatinine and cystatin C are namely inversely related to their clearances. Therefore, the reciprocals of creatinine and cystatin C can be used for the calculation of the GFR.

In our study, we compared serum cystatin C
-based equation to serum creatinine levels in patients with type 2 diabetic. The results of our study indicate that cystatinc formula is a reliable marker of GFR in these patients.

1.1.3 CONCLUSION

The serum cystatin c-based equation which requires just one variable (serum cystatinc concentration) could be used for evaluation of renal function in patients with type 2 diabetic.

Table 1: Clinical and biochemical characteristics of the studied groups

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Diabetic Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Number</td>
<td>20</td>
<td>60</td>
</tr>
<tr>
<td>-Female</td>
<td>9</td>
<td>32</td>
</tr>
<tr>
<td>-Male</td>
<td>11</td>
<td>28</td>
</tr>
<tr>
<td>-Age range (year)</td>
<td>(40-60)</td>
<td>(40 - 65)</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Age (year)</td>
<td>50± 7</td>
<td>55 ±10</td>
</tr>
<tr>
<td>-Glucose (mg/dl)</td>
<td>96.4 ±5</td>
<td>143.6 ±10 **</td>
</tr>
<tr>
<td>-Urea (mg/dl)</td>
<td>31.2 ±7.8</td>
<td>38.5 ±8.45**</td>
</tr>
<tr>
<td>-Total protein (g/dl)</td>
<td>7.06 ±0.55</td>
<td>7.2 ±1.06</td>
</tr>
<tr>
<td>-Creatinine (mg/dl)</td>
<td>0.98 ±0.15</td>
<td>1.24 ±0.23 **</td>
</tr>
<tr>
<td>-Cystatin C (mg/L)</td>
<td>0.75 ±0.2</td>
<td>0.97 ±0.22 **</td>
</tr>
<tr>
<td>-eGFR (ml/min/1.73m²)</td>
<td>98.7 ±19.5</td>
<td>85.3 ±20.07 **</td>
</tr>
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( **) high significant differences (P < 0.005)

Fig. 1: The mean serum levels of glucose (mg/dl), urea (mg/dl), total protein (g/dl) and eGFR (ml/min/1.73 m²) for control and diabetic patients.
Fig. 2: The mean serum levels of creatinine (mg/dl) and cystatin c (mg/L) for control and diabetic patients.

Fig. 3: The correlation coefficient (r) between estimated glomerular filtration rate values (ml/min/1.73 m²) and serum creatinine levels (mg/dl) for control group.
Fig. 4: The correlation coefficient (r) between estimated glomerular filtration rate values (ml/min/1.73 m²) and serum creatinine levels (mg/dl) for Diabetic patients.

REFERENCES


