

Original Research Article

Cystatin C based eGFR - for early detection of diabetic kidney disease

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ABSTRACT

Background: Diabetic kidney disease is the leading cause of premature death in young diabetic patients. Detection of diabetic kidney disease as early as possible in the disease process currently offers the best chance of delaying or possibly preventing progression to end-stage renal disease. The present study was aimed to evaluate utility of serum cystatin C based eGFR for early diagnosis of diabetic kidney disease.

Methods: Diagnosed patients of type 2 diabetes mellitus having frank proteinuria were excluded. Patients without proteinuria were tested for microalbuminuria. 50 patients having microalbuminuria were tested for 24 hour urine creatinine, serum creatinine and serum cystatin C. Both cystatin C based eGFR and eGFR by Cockcroft and Gault equation were compared with standard GFR by 24 hour urine Creatinine clearance respectively.

Results: There was statistically significant positive correlation between cystatin C based eGFR and standard GFR by 24 hr Creatinine clearance ($r=0.87$). For eGFR by Cockcroft-Gault equation, it was 0.36 ($r=0.36$).

Conclusions: The results of this study suggest that serum cystatin C based eGFR measurement is a useful, practical tool for the evaluation of renal involvement in the course of diabetes. As serum creatinine values are affected by many factors like age, sex, muscle mass and diet, serum cystatin C based eGFR estimation offers a hope that diabetic kidney disease can be well prevented with appropriate interventions.

Keywords: Cockcroft-Gault equation, Diabetic kidney disease, eGFR, Microalbuminuria, Serum cystatin C

INTRODUCTION

Diabetes is one of the most challenging health problems of the 21st century. The prevalence of diabetes is increasing globally. Type 2 Diabetes Mellitus (Type 2 DM) constitutes about 85% to 95% of total diabetic cases in developed countries and accounts for higher percentage in developing countries.¹ Moreover, type 2 DM is a significant cause of premature mortality and morbidity related to cardiovascular disease, macrovascular complications and microvascular complications in older adults.²⁻⁴

Diabetes leads to various chronic complications which can be divided into vascular and nonvascular complications. Diabetes has become the most common single cause of end stage renal disease (ESRD) worldwide.⁵ About 20-30% of patients with type 1 or type 2 DM develop evidence of nephropathy, but in type 2 DM, a considerably smaller fraction of these progresses to ESRD. However, because of much higher prevalence of type 2 DM, these patients constitute over half of patients with nephropathy needing dialysis.⁶ The diabetic kidney disease progresses from appearance of low but abnormal levels of (≥ 30 mg to 299 mg/day) albumin in urine (stage of microalbuminuria) to stage of

macroalbuminuria ($\geq 300\text{mg/day}$) to ESRD. Microalbuminuria may remain under-diagnosed or progress to macroalbuminuria in 10-15 years. Type 2 DM may be present for decades before diagnosis and patient may present with complications at the time of diagnosis.⁷ So, early recognition of diabetic kidney disease by health care professionals is vital for proper management.

Although serum creatinine has been widely used as a marker, it is not able to pick up early decreased renal function. Therefore, various plasma low molecular weight proteins have been suggested as valuable early markers of decreased renal function in place of serum creatinine.

Although many investigations are available, many of these are not done in public hospitals, so diagnosis of diabetic kidney disease at early stage is missed. This study was aimed to evaluate serum cystatin C based eGFR vs. Serum Creatinine based eGFR (Cockcroft-Gault equation) as a potential better marker for early diagnosis of diabetic kidney disease.

METHODS

The diagnosed patients of type 2 DM were enrolled for the study.

Patients having frank proteinuria ($\geq 300\text{mg/day}$), any known renal disease, taking any medications affecting renal functions (captopril, ciprofloxacin, aspirin, omeprazole, phenytoin etc.), patients with urinary tract infections or hematuria or febrile illness, patients having paraplegia, muscle wasting disease, or any neuromuscular disorders were excluded.

On fulfilling the criteria, the study design was explained to the patients with the help of information sheet. Then the written consent was taken. 24 hr urine sample was tested for frank proteinuria by using Trichloroacetic acid (TCA) method. 50 diagnosed diabetic patients without frank proteinuria, but with microalbuminuria, were included in the study group, which included 30(60%) males and 20(40%) females between 41-66 yrs age group. Urine albumin by immunoturbidimetric method, serum and urine creatinine by modified Jaffe’s method and serum cystatin C by immunoturbidimetry were estimated.⁸⁻¹¹

GFR was calculated by using following equations:

*Cockcroft-Gault Equation*¹²

$$\text{GFR (ml/min)} = [(140 - \text{age in years}) / \text{S. Creatinine}] \times \text{body weight (kg)} / 72$$

(X 0.85, if female)

*Rule’s equation (Cystatin C based eGFR)*¹³

$$\text{GFR (ml/min)} = 76.6 \times \text{S. Cystatin C (mg/L)}^{-1.16}$$

24 hr creatinine clearance (Standard GFR)

$$\text{GFR (ml/min)} = (\text{Urine Creatinine} \times \text{volume of urine}) / \text{S. creatinine}$$

Serum cystatin C based eGFR and GFR calculated by using Cockcroft-Gault equation were correlated with standard GFR (24 hr urine creatinine clearance).

RESULTS

Authors measured serum Creatinine and serum cystatin C levels in 50 type 2 diabetic patients having microalbuminuria. It was found that the mean value of serum cystatin C was increased, whereas mean value of serum Creatinine was within reference range. (Table 1)

Table 1: Comparison of serum Creatinine and serum cystatin C levels.

Parameter	Serum Creatinine (mg/dl)	Serum Cystatin C (mg/L)
Mean±SD	0.77±0.13	1.61±0.27
Reference Range	0.6 to 1.2 mg/dl	0.55 to 1.15 mg/L

Table 1 shows the statistically significant increased levels of serum cystatin C (1.61±0.27 mg/dl) as compared with serum creatinine (0.77±0.13 mg/dl). This indicates early diabetic kidney disease can be detected with the help of serum cystatin C level. Serum Creatinine level does not prove as a helpful marker in such situations.

Authors calculated eGFR by using Cockcroft-Gault equation (based on serum Creatinine) and Rule’s equation (based on serum cystatin C). Both values were compared with standard GFR by 24 hour Creatinine clearance. It was observed that the value of eGFR (78.56 ml/min) calculated by using Rule’s equation (based on serum cystatin C) was much closer to standard GFR (73.39 ml/min) than value of eGFR (89.78 ml/min) calculated by Cockcroft-Gault equation (based on serum Creatinine) (Table 2).

Table 2: Comparison of GFR values.

Parameter	Mean (ml/min)	Range (ml/min)
GFR by Cockcroft-gault equation (based on serum creatinine)	89.78	62-229
GFR by rule’s equation (based on serum cystatin c)	78.56	42.27-154
GFR by 24 hr urine creatinine clearance	73.39	35-141

Authors compared correlation coefficients of eGFR calculated by Rule's equation and eGFR calculated by Cockcroft-Gault equation with standard GFR by 24 hr Creatinine clearance. It was observed that correlation coefficient of eGFR based on serum cystatin C was 0.87, which showed significant positive correlation with standard GFR. The correlation coefficient of eGFR by serum Creatinine with standard GFR was 0.36. (Table 3)

Table 3: Comparison of correlation coefficients of cystatin C based eGFR and GFR by Cockcroft-Gault equation with standard GFR.

Variable	R value
Cystatin C GFR and 24 hr creatinine clearance	0.87
Cockcroft gault GFR and 24 hr creatinine clearance	0.36

Table 3 shows statistically significant positive correlation between cystatin C based eGFR and standard GFR by 24 hr Creatinine clearance.

DISCUSSION

Overt diabetic nephropathy classically begins with proteinuria (>300 mg/day) accompanied by the development of hypertension and falling glomerular filtration rate (GFR).^{14,15} At this stage, the progression towards end stage renal disease may be slowed but not reversed.¹⁶

Overt nephropathy is preceded by a variable period, which is called as 'incipient nephropathy'.¹⁵ This phase of diabetic nephropathy has been defined as an elevation of urinary albumin excretion, which is 30-300 mg/day which is predictive of nephropathy risk. The lower limit of urinary albumin excretion, which is said to be predictive of the later development of overt nephropathy, has been variably reported as around 30 mg/day.¹⁷⁻²⁰

Some patients with microalbuminuria with hypertension and falling GFR have advanced glomerular lesions.²¹ Before these stages, there are many silent years during which no clinical or laboratory parameter is indicative of underlying renal structural lesions or of eventual nephropathy risk.

It is likely that microalbuminuria predicts the later development of overt diabetic nephropathy by serving as a functional indicator of underlying renal structural changes.²² The concept of a prognostic role for microalbuminuria has been extended to suggest that normoalbuminuria ensures no reduction of renal function.²³ Based on this, we included 50 patients of type 2 DM having microalbuminuria in the study group. Our data is in accordance with the studies carried out.²⁴ Out of 50 patients of study group, the increase in serum cystatin C was observed in 47 patients and maximum

value was 2.05 mg/L. Our results are in accordance with the studies carried out.²⁵⁻²⁹

The routine classical evaluation of diabetic kidney disease includes appearance of microalbuminuria, decreased creatinine clearance and increased serum creatinine. Many clinicians use serum creatinine in evaluating such patients. However, serum creatinine depends on creatinine production, extrarenal elimination and tubular handling.³⁰

Moreover, tubular involvement may precede glomerular involvement. Therefore, other biomarkers like cystatin C for measurement of GFR was included in the study.³¹ Cystatin C is one of the additional tubular factors which represents kidney state of diabetic patients.

It was thought that increment in serum Cystatin C was probably due to the tubular phase before glomerular manifestation. This suggests that the serum cystatin C levels are related to subclinical tubular impairment and can be an earlier measurable marker of renal involvement.³¹ Our results indicate that serum cystatin C is a novel and reliable marker of GFR. Zahran et al reviewed a number of studies to compare the diagnostic accuracy of serum cystatin C levels and serum creatinine levels in many clinical situations, including transplant patients, patients with native kidney disease. They found that serum Cystatin C was superior to serum creatinine.³²

Authors evaluated the diagnostic efficacy of using serum cystatin C levels and compared with serum creatinine. Our study found that the diagnostic accuracy of GFR based on serum cystatin C levels was superior to that of serum creatinine.

Although serum creatinine has become the most popularly used serum marker of renal function, it may be unreliable because it is frequently affected by muscle mass, age, gender, aberrant renal tubular regulation and methodology of determining serum creatinine level. Using serum cystatin C has some advantages over serum creatinine, in that serum Cystatin C level is independent of age, gender, muscle mass, diet, inflammatory status and renal tubular secretion.³³ So serum cystatin C can be considered an ideal indicator of renal function.

CONCLUSION

The results of this study suggest that serum cystatin C measurement is a useful, practical tool for the evaluation of renal involvement in the course of diabetes. Though serum creatinine levels are used to assess kidney function, creatinine values are affected by many factors like age, sex, muscle mass, diet etc. Further investigations with a larger sample size and a prospective design are required to confirm the potential application of serum cystatin C based eGFR as useful biomarker for the early detection of diabetic kidney disease.

Diabetic kidney disease is the leading cause of chronic kidney disease and ESRD. Early recognition is vital for further management. Serum cystatin C based eGFR can be used as an early independent marker of diabetic kidney disease, as routine biochemical parameters like serum creatinine fail to recognize early diabetic kidney disease.

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