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RESEARCH ARTICLE

CYSTATIN C- A BETTER PARAMETER FOR ASSESSMENT OF RENAL FUNCTION IN TYPE LL DIABETES MELLITUS

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ABSTRACT

Background: Diabetic nephropathy is the leading cause of End Stage Renal Disease (ESRD) worldwide and a leading cause of Diabetes Mellitus related morbidity and mortality, which can be assessed by estimating Glomerular Filtration Rate. The early detection of renal dysfunction in subjects with diabetes is of vital importance as appropriate interventions have been shown to retard the progression of ESRD. We compared advantages of serum Cystatin C over Serum Creatinine for determination of early Decline in Glomerular Filtration Rate in Type ll Diabetes Mellitus Patients.
Materials and methods: In the present study on 30 Type ll diabetic patients and 30 non-diabetic controls, we compared the estimated Glomerular Filtration Rate (eGFR) from serum Cystatin C and the estimated Glomerular Filtration Rate from serum Creatinine.
Result: Estimated Glomerular Filtration Rate (eGFR) from serum Cystatin C was significantly decreased in patients as compared with eGFR from Serum Creatinine.
Conclusion: Serum Cystatin C is a better parameter for assessing GFR In type ll Diabetes Mellitus for diagnosing early diabetic nephropathy than serum Creatinine.

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INTRODUCTION

Diabetes Mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction and failure of different organs, especially the eyes, kidneys, nerves, heart and blood vessels (American Diabetes, 2010). Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD) worldwide and a leading cause of DM related morbidity and mortality (Powers, 2005). The prevalence of chronic kidney disease (CKD) and end stage renal disease (ESRD) is increasing worldwide with ageing of the world population and a global epidemic of type II diabetes mellitus which is clinically characterized by increasing rates of urinary albumin excretion (Chew *et al.,* 2008). The early pathologic changes and albumin excretion abnormalities are reversible with normalization of plasma glucose. However, once overt nephropathy develops, the pathologic changes are likely irreversible (Powers, 2005). The early detection of kidney dysfunction in subjects with diabetes is of vital importance as appropriate interventions have been shown to retard the progression to ESRD and reduce risk of cardiovascular disease (CVD) (Unnikrishnan *et al.,* 2007).

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Glomerular Filtration Rate (GFR) is the most important measure of the renal efficiency for clearing various substances from the blood. A decrease in GFR precedes end-stage renal failure in all forms of progressive kidney disease and knowledge of GFR is therefore critical in the prevention and management CKD. In practice, serum Creatinine are the most widely used endogenous markers of GFR but it is influenced by Muscle mass, Sex, Age, Diet, Race, Nutritional status and Analytical interference. The sensitivity of serum Creatinine in the detection of CKD is consequently poor and it will fail to identify half of the patients with CKD (Chew *et al.,* 2008). In an attempt to overcome the limitations of serum Creatinine, the National Kidney Foundation (NKF) and Kidney Disease Outcomes Quality Initiative (KDOQI) published recommendations to use estimated GFR (eGFR) based on serum Creatinine and also including age, racial origin and gender i.e. abbreviated "175" modification of diet in renal disease (MDRD) formula and The Cockcroft and Gault (CG) formula (Chew *et al.,* 2008).

Although eGFR formulae from serum Creatinine are increasingly being used, their accuracy is debatable because the MDRD equation was originally validated in CKD patients and CG equation overestimates GFR, as Creatinine is filtered by the glomeruli and secreted by the tubules (Botev *et al.,* 2009). Therefore serum Creatinine formulas for estimating GFR are not reliable in individuals who Follow vegetarian diet,

who consume Creatinine supplements, who have unusual muscle mass, unusual body weight and in pregnancy (Israni, 9th edition). Due to the these problems encountered with measurements of Creatinine and its use as a GFR estimate, serum Cystatin C has been proposed as an alternative marker of renal function. The potential utility of serum Cystatin C in the laboratory lies in its capability to detect early renal failure (Chew *et al.,* 2008). Cystatin C is a 13-kDa protein, of the cysteine proteinase inhibitor super family, produced by all nucleated cells. Its production rate is constant throughout the ages of 1 to 60 years. Cystatin C is not affected by gender, muscle mass, malignancy and its plasma concentration is dependent only on GFR. It is freely filtered at the glomeruli and then reabsorbed and fully catabolised by proximal renal tubules. Although its clearance cannot be measured directly because of this catabolism, its plasma or serum concentration is a good measure of GFR, with possible advantages over more established markers such as serum creatinine (Chew *et al.,* 2008).

The ability to assess renal function in diabetic patients rapidly and early is of major importance for the possibility of preventing the development of nephropathy. Therefore, it is worth to discover a more sensitive or specific indicator for detecting early renal impairment in diabetic patients. So, corrective measures could be adopted to prevent the progression of kidney function impairment towards frank nephropathy. This study was undertaken to evaluate the value of this newer molecule in assessment of GFR for renal dysfunction at a phase when timely interventions can be instituted and the progression of nephropathy can be delayed.

MATERIALS AND METHODS

The present study was carried out in the Department of Biochemistry and Central Investigation Laboratory in collaboration with the Department of Medicine in our Institute on 30 patients of Type II Diabetes Mellitus of any sex of varied socioeconomic status between ages 30-60 years without any complications selected from Outpatient Department and Inpatient Department from December 2012 to June 2014. The study was approved by Institutional Ethical and Research Committee. Age and gender matched 30 non diabetic subjects were taken as control group. Patients with hypertension, thyroid disorders, congestive cardiac failure, liver disease, rheumatoid disease, malignancy, fever, dehydration and patients on glucocorticoid, nephrotoxic drugs, smoking and alcohol users were excluded from the study.

Measurements including height, weight were made by standard procedures and body mass index (BMI) was calculated. 5 ml of venous blood sample was collected from both cases and controls and the samples were centrifuged and separated for the estimations. Estimations of serum Creatinine was performed by Modified Jaffe's Reaction and estimated GFR was calculated from Cockcroft-Gault formula. Serum Cystatin C was estimated by turbudometric immunoassay and estimated Glomerular filtration rate was calculated using Hoek's formula. Comparison between two diagnostic procedures, eGFR- Creatinine and eGFR-Cystatin C in cases and controls was done.

Statistical analysis

The statistical software SPSS 17.0 was used for the analysis of the data. Results 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 between two groups.

RESULTS

The variables studied in cases and controls are shown in Table 1. There is significant difference in weight and BMI (Body Mass Index) between two groups

Table 1. Variables in study population

Basic characteristics	Controls	Cases	P value
Weight	59.65 ± 9.89	66.93 ± 7.48	0.002
Age (years)	49.15 ± 8.54	51.05 ± 6.91	0.34
BMI	24.53 ± 1.98	23.12 ± 1.68	0.004

There was not significant increase in levels of serum Creatinine in cases compared to controls (p=0.09) but there was significant increase in levels of serum Cystatin C in cases when compared with the controls (p<0.0001). There was highly significant decrease eGFR from Serum Cystatin C in the Cases when compared with the Control (p<0.0001). There was not significant decrease eGFR from Serum Creatinine in the Cases when compared with the Control (p=0.05).

Table 2. Mean distribution of serum Creatinine, serum Cystatin C their estimated GFR levels in cases and controls

Parameters	Controls	Cases	P value
Creatinine (mg/dl)	0.84± 0.11	0.90 ± 0.16.	0.09
Cystatin C (mg/l)	0.76 ± 0.14	1.08 ± 0.23	0.0001
eGFR Creatinine	103.64 ± 23.61,	92.71 ± 19.07.	0.053
eGFR Cystatin C	106.43 ± 17.08	72.96 ± 15.99	0.0001

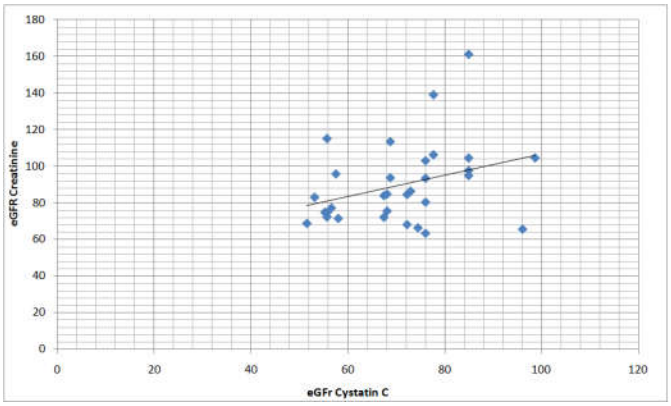

Figure 1. Scatter Plot showing correlation between eGFR Cystatin C and eGFR Creatinine in DM patients

There was not significant correlation between eGFR by serum Cystatin C and eGFR by serum Creatinine (r=0.28, p = 0.6) in cases group. There was significant correlation between eGFR by serum Cystatin C and eGFR by serum Creatinine (r=0.314, p<0.01) in control group. The cases have raised serum Cystatin C value and normal serum Creatinine values while controls have both serum Cystatin C value and serum Creatinine values in normal range. Also Cases have decreased eGFR from

Cystatin C than eGFR from serum Creatinine while controls have both eGFR in normal range. All the above findings conclusively prove that the eGFR calculated by Cystatin C was also more effective in detecting renal status than eGFR calculated by Creatinine for detecting Diabetic nephropathy.

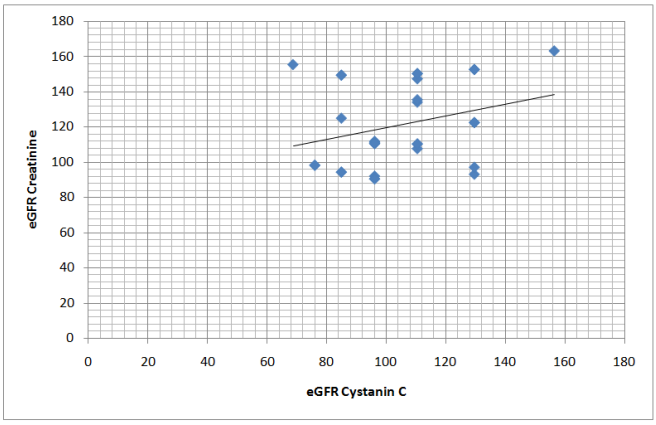

Figure 2. Scatter Plot showing correlation between eGFR Cystatin C and eGFR Creatinine in control

DISCUSSION

Glomerular filtration rate (GFR) is generally considered the best measure of renal function in health and in diseases. Inulin clearance or 125I – iothalamate Clearance are proved as the ideal for Glomerular filtration rate (GFR) determination. However, this method is not performed in clinical practice, because they are expensive, time consuming, technically complex and limited availability. Currently serum Creatinine is the most widely used method of assessing renal function in clinical practice; but results are affected by age, sex, muscle mass, diet, race and tubular Creatinine secretion, particularly when GFR is reduced. Also serum Creatinine levels remain within the normal range even when renal function is significantly impaired (Kannapiran *et al.,* 2010). Serum Cystatin C is a 13 kDa protein, of the cysteine proteinase inhibitor superfamily, constantly produced by all human nucleated cells. It passes freely through the Glomerular membrane, is completely reabsorbed and catabolised in the tubules. Cystatin C is not affected by gender, muscle mass, malignancy, and Serum Cystatin C levels in blood primarily depend on the GFR of the individual and thus it provides a tool to assess renal function by a simple blood test. It has been demonstrated that Cystatin C level increases even with Creatinine clearance decrease below 1.57ml/second (94.2 ml/min) when the Creatinine level has not yet changed (Mares *et al.,* 2013).

Serum Cystatin C levels have been shown to detect subtle changes in GFR in healthy individuals. Thus Cystatin C determination is given preference for its above mentioned independence of a variety of genetic and behavioral factors and its constant production and elimination via Glomerular filtration (Mares *et al.,* 2013). Soares *et al*., 2009 in their cross-sectional study have shown that Cystatin C presents a higher sensitivity than Creatinine to detect mild kidney disease. Cystatin C concentration has been reported to increase when GFR ranges between 70 and 90 ml/min in the so-called Creatinine blind range zone (Soares *et al*., 2009). Cystatin C provides greater sensitivity and specificity for identifying reduced GFR. Ayub Salma *et al*., 2014 had shown that accurate estimate of GFR can be achieved by Serum Cystatin C as it significantly correlates with established markers of GFR (Ayub *et al.,* 2014).

Bevc S *et al*. in their study on population with Type II DM showed a higher accuracy of the Cystatin C formulas compared to the CG and MDRD formulas. They also suggest that the Cystatin C-based prediction formula, which requires just one variable (serum Cystatin C concentration), achieved a diagnostic performance that was at least as good as the Creatinine based formulas using more variables (Bevc *et al.,* 2012). Inkar *et al*. suggested that estimated GFR based on serum Cystatin C could be used as confirmatory test for chronic kidney disease (Inkar *et al.,* 2012). In our study we compared eGFR from Cystatin C and eGFR from Creatinine in cases and controls we found that estimated GFR from serum Cystatin C using Hoek's formula is less than that of estimated GFR from Serum Creatinine using CG formula in cases whereas there is no such difference in control group. We could diagnose this decline in renal function using estimated GFR from serum Cystatin C which is not evident in estimated GFR using serum Creatinine. It suggests GFR using serum Cystatin C is better marker of renal function than serum Creatinine. Our result is in accordance with previous studies.

Conclusion

The results of the present study suggest that simple Cystatin C based equations for all ages offer advantages for determination of early decline in GFR compared with Creatinine based equations for diagnosing Diabetic Nephropathy in ll DM . But it should be emphasized that Cystatin C based equations cannot replace the use of gold standard procedures for GFR estimations, particularly in some clinical situations e.g. patients treated with large doses of corticosteroids or patients with thyroid dysfunction. However the use of Cystatin C based equation may reduce the need to perform invasive determinations of GFR. The cost of Cystatin C is the only factor, which will limit its use as a marker of renal function in a developing country like India.

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