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Serum Cystatin C and Creatinine Levels in Type 2 Diabetes Mellitus Patients of Sub-Himalayan Region

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ABSTRACT

Background: The present study was aimed at evaluating serum cystatin C in diabetes mellitus (DM) and its comparison with serum creatinine to investigate whether cystatin C can be used as a marker for detection of early diabetic nephropathy (DN). **Methods:** The study design comprised of 200 subjects viz. 100 healthy controls and 100 type 2 diabetes mellitus (T2DM) cases. The cases were further classified into normoalbuminuria, microalbuminuria and macroalbuminuria groups according to the urinary albumin to creatinine ratio (ACR). Whole blood was used for glycated hemoglobin (HbA1c) estimation and serum was analyzed for quantitative estimation of fasting blood sugar (FBS), urea, creatinine, cystatin C along with estimated glomerular filtration rate (eGFR) creatinine and eGFR cystatin C. **Results:** HbA1c and FBS levels established T2DM in cases as compared to the control group. A significant rise was observed in the mean serum creatinine values in the macroalbuminuria group. However, a significant augmentation was also observed in the mean serum cystatin C values in the microalbuminuria along with the macroalbuminuria groups as compared to the control group. A significant reduction was observed in eGFR values by creatinine and cystatin C based equations in the microalbuminuria and macroalbuminuria groups as compared to the control group. **Conclusion:** The present study showed that cystatin C was effective in detecting early DN in comparison to creatinine levels with an added advantage of being able to analyse eGFR to stage DN over microalbuminuria. Thus, cystatin C can be used as a suitable marker in development of early DN.

Keywords: Creatinine, Cystatin C, Diabetic nephropathy, estimated glomerular filtration rate.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic syndrome characterized by hyperglycemia that occurs due to lack of insulin secretion or cellular resistance to insulin causing anomalies in the metabolism of carbohydrates, fats and proteins. The clinical manifestations include polyphagia, polydipsia, polyuria and glycosuria.[1] It has been estimated that 85-95 % of all cases of diabetes are type 2 diabetes mellitus (T2DM) and it is projected that by 2025, nearly 380 million adults will have diabetes worldwide.[2]

One of the most important microvascular complication associated with diabetes is diabetic nephropathy (DN), that has now a days turned out to be the most common cause for end stage kidney disease (ESRD).[3] DN involves thickening of glomerular basement membrane and mesangial expansion with progression into glomerulosclerosis, tubular necrosis, and interstitial fibrosis, that eventually leads to kidney failure.[4]The early manifestations of DN are glomerular hyper filtration and increased excretion of urinary albumin (microalbuminuria). Various functional abnormalities of the kidneys are also associated with DN such as increased serum creatinine, urea, decreased glomerular filtration rate (GFR), fluid retention and elevated arterial blood pressure.[5]

An ideal marker most commonly used to assess renal function is GFR and serum creatinine is an important biochemical parameter used to measure GFR. However, many a times serum creatinine levels may be normal in patients with significantly declined GFR.[6] Additionally, the presence of albuminuria is also less specific to the incidence of DN, as roughly around 20-40 % of T2DM patients with microalbuminuria develop overt nephropathy.[7] Moreover, short-term hyperglycemia, exercise, urinary tract infections, marked hypertension, heart failure and acute febrile illness may cause transient elevation in urine albumin levels.[8] The restriction posed by these markers has led to the search for a more sensitive laboratory biomarker for DN.

One such molecule is Cystatin C, a 13 kilo Dalton protein produced by housekeeping genes of all the nucleated cells. It is a cysteine protease inhibitor that is freely filtered at the glomerulus and is not secreted by the tubules.[9] Thereafter, it is reabsorbed and completely catabolized in the proximal tubule. Moreover, there are no known extra renal routes for removal of cystatin C. An increase in the serum cystatin C levels is observed if there is a decline in GFR and kidney functioning.[10] The serum cystatin C levels do not depend upon muscle mass, diet, or gender and its levels are not influenced by infections, liver diseases or inflammatory

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diseases.[10,11]Additionally, cystatin C is sensitive to changes in the so-called creatinine blind GFR range (40-70 ml/min/1.73 m2).[11]As long-term DM is associated with microvascular complications such as nephropathy, retinopathy and neuropathy[4] even when DM is under control, the disease can cause chronic kidney disease (CKD) and kidney failure.[12] Since the disease is clinically silent until later stages, the patient may suffer from irreversible damage or mortality in absence of proper screening and intervention. Early detection can help in proper clinical management of patients along with new research into therapies for kidney disease. Therefore, the clinical utility of cystatin C as a diagnostic marker of GFR can be explored.

Thus, keeping in mind the above-mentioned facts, the present study was aimed at evaluating serum cystatin C in DM and its comparison with serum creatinine to investigate whether cystatin C can be used as a marker for detection of early DN in a tertiary care centre in Sub Himalayan region of north India.

MATERIALS AND METHODS

A comprehensive study was carried out in the Department of Biochemistry in collaboration with the Department of Medicine, Dr. Rajendra Prasad Government Medical College, Kangra (Tanda), District Kangra, Himachal Pradesh, India. The permission and approval for the study was obtained from the Institutional Ethics Committee vide letter number HFW-H-DRPGMC/Ethics/2017-72 Dated 26/12/2017.

Patients

Sampling population comprised of all adult subjects coming to the Centralized Collection Centre of the Hospital and out-patient clinic of the Department of Medicine of the Hospital already diagnosed with DM for a period of one year. Subjects voluntarily willing to serve as control group were also recruited for the study. After obtaining the written consent demographic features, personal history, general physical examination were recorded on a predesigned proforma. There were 100 controls and 100 patients with T2DM. The cases were further classified into three groups according to the urinary albumin to creatinine ratio (ACR) viz. normoalbuminuria group (urine ACR value < 30 mg/gm), microalbuminuria group (urine ACR value 30-300 mg/gm) and macroalbuminuria group (urine ACR value > 300 mg/gm).Subjects were excluded from the study with chronic illness like tuberculosis, cancer or immuno-compromised states, thyroid disorders. Smokers and those taking drugs like steroids, immunosuppressant were also excluded from the study.Patients on dialysis, pregnant or lactating mothers and those with active urinary tract infection, liver dysfunction, history of acute myocardial infarction, stroke or occlusive peripheral vascular disease were not included in the study.

Methods

Whole blood sample of 5 ml was collected from the median cubital vein after venipuncture; 2 ml in ethylene diamine tetraacetic acid (EDTA) tube for glycated hemoglobin (HbA1c) estimation and 3 ml in plain vial. The clear supernatant serum was collected in serum tubes, analyzed for quantitative estimation of fasting blood sugar (FBS), urea, creatinine and cystatin C. The urinary ACR was estimated in spot urine samples.

The estimation of HbA1c was carried out using NycoCard reader (Alere Technologies, AS, Oslo, Norway). The quantitative analysis of serum FBS, serum urea, serum creatinine, and urinary creatinine was carried out on XL-300 (Erba, Mannheim, Germany), a fully automated chemistry analyzer. Estimation of serum cystatin C and urinary microalbumin were carried out on Mispa-i2 (Agappe Diagnostics Ltd., Ernakulum, Kerala, India) based on nephelometric and turbidimetric measurement using ready to use kits supplied by Agappe Diagnostics Ltd. (Ernakulum, Kerala, India).

The estimated glomerular filtration rate (eGFR) was calculated using the 2009 Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation.[13,14]

eGFR (CKD-EPI) = 141 x Min (Serum Creatinine / k, 1) Alpha x Max (Serum Creatinine / k, 1)-1.209 x 0.993 Age x 1.018 (If patient is female) x 1.159 (If patient is black).

Where Age is in years, k is 0.7 for Females and 0.9 for Males, Alpha is -0.329 for Females and -0.411 for Males, Min indicates the minimum of Serum Creatinine / k or 1, Max indicates the maximum of Serum Creatinine / k or 1.

The eGFR cystatin C was calculated using CKD-EPI cystatin C equation, expressed as a single equation.[15]

eGFR = 133 x Min (Serum Cystatin C / 0.8, 1)-0.499 x Max (Serum Cystatin C / 0.8, 1)-1.328 x 0.996Age x 0.932 [if female],

Where Min indicates the minimum of Serum Cystatin C / 0.8 or 1, and Max indicates the maximum of Serum Cystatin C / 0.8 or 1.

Statistical Analysis

The data was analyzed using by Statistical Package for Social Sciences (SPSS) software version 20. Data was expressed as mean ± standard deviation (SD) for continuous variables. Values with $p < 0.05$ calculated at 95 % confidence limit, were considered statistically significant. Due to slightly different sample sizes among groups, the Gabriel procedure was used as the post hoc test, whereas the Games-Howell procedure was used when variances were not equal between groups for analysis of variance (ANOVA).

RESULTS

In the present study according to ACR the normoalbuminuria group (urine ACR value < 30 mg/gm) comprised of 39 patients, microalbuminuria group (urine ACR value 30-300 mg/gm) consisted of 44 patients and macroalbuminuria group (urine ACR value > 300 mg/gm) comprised of 17 patients.

The mean FBS value of control group was 90.06 ± 7.87 (mean ± SD) mg/dl. A significant increase was observed in the mean FBS levels in normoalbuminuria group (171.84 ± 24.18 mg/dl), microalbuminuria group (177.79 ± 41.69 mg/dl) and macroalbuminuria group (205.76 ± 43.39 mg/dl) as compared to the control group ($p < 0.05$).Similarly, a significant augmentation was observed in the mean HbA1c value in normoalbuminuria group (7.76 ± 1.54 %), microalbuminuria group (7.6 ± 1.24 %)and in macroalbuminuria group (8.51 ± 1.52 %) as compared to control group (5.44 ± 0.25 %) [Table1].

As far as serum urea levels were concerned, no significant difference was observed between control group (24.35 ± 6.14 mg/dl) and the normoalbuminuria group (28.75 ± 9.2 mg/dl). However, a significant increase was observed in the serum urea levels in the microalbuminuria (30.65 ± 9.04 mg/dl) and macroalbuminuria (50.17 ± 25.21 mg/dl) groups as compared to the control group ($p < 0.05$) [Figure 1]. A significant rise was observed in the mean serum creatinine values in the macroalbuminuria group (1.81 ± 0.56 mg/dl) as compared to the control group (0.94 ± 0.18 mg/dl). However, no significant difference was observed in the serum creatinine levels between control, normoalbuminuria (0.89 ± 0.18 mg/dl) and microalbuminuria group (0.98 ± 0.23 mg/dl) [Figure 2]. However, contrary to serum creatinine levels, a significant augmentation was also observed in the mean serum cystatin C values in the microalbuminuria (1.21 ± 0.24 mg/L) along with the macroalbuminuria groups (1.6 ± 0.39 mg/L) as compared to the control group (0.85 ± 0.29 mg/L). However, no significant difference was observed in the serum cystatin C levels between control and the normoalbuminuria group (0.81 ± 0.23 mg/L) [Figure 3].

The calculated mean eGFR value by creatinine based equation for control group was 85.04 ± 19.44 ml/min. A significant decrease in the eGFR value was observed in the microalbuminuria (76.04 ± 17.83 ml/min) and macroalbuminuria groups (41.29 ± 17.85 ml/min) as compared to the control group. However, no difference was observed in eGFR in the normoalbuminuria group (86.58 ± 15.64 ml/min) as compared to the control group [Table 2]. Similarly, the calculated mean eGFR value by cystatin C based equation for control group was 99.46 ± 27.25 ml/min. A significant reduction was observed in the calculated eGFR values in the microalbuminuria (61.29 ± 15.14 ml/min) and macroalbuminuria groups (44.23 ± 15.06 ml/min) as compared to the control group ($p < 0.05$). However, no significant difference was observed in the eGFR levels between control and the normoalbuminuria group (100.2 ± 24.44 ml/min) [Table 2].

Table 1: Mean values of FBS and HbA1c in Controls and Cases.

Test Parameter	Controls (N=100)	Normoalbuminuria (N=39)	Microalbuminuria (N=44)	Macroalbuminuria (N=17)
FBS (mg/dl)	90.06 ± 7.87	171.84 ± 24.18*	177.79 ± 41.69*	205.76 ± 43.39*
HbA1c (%)	5.44 ± 0.25	7.76 ± 1.54*	7.6 ± 1.24*	8.51 ± 1.52*

Significantly different from Control group. (P<0.05)

Table 2: Mean values of eGFR Creatinine and eGFR Cystatin C in Controls and Cases.

Test Parameter	Controls (N=100)	Normoalbuminuria (N=39)	Microalbuminuria (N=44)	Macroalbuminuria (N=17)
eGFR Creatinine	85.04 ± 19.44	86.58 ± 15.64	76.04 ± 17.83*	41.29 ± 17.85*
eGFR Cystatin C	99.46 ± 27.25	100.2 ± 24.44	61.29 ± 15.14*	44.23 ± 15.06*

Significantly different from Control group. (P<0.05)

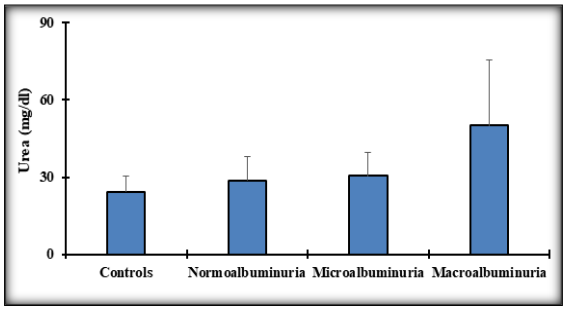

Figure 1: Histogram showing mean Urea values in Controls and Cases viz. Normoalbuminuria, Microalbuminuria and Macroalbuminuria group. Values are expressed as Mean ± SD. *Significantly different from Control group.* (P<0.05)

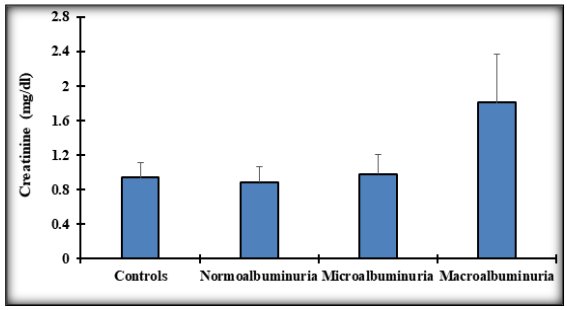

Figure 2: Histogram showing mean Creatinine values in Controls and Cases viz. Normoalbuminuria, Microalbuminuria and Macroalbuminuria group. Values are expressed as Mean ± SD. *Significantly different from Control group.* (P<0.05)

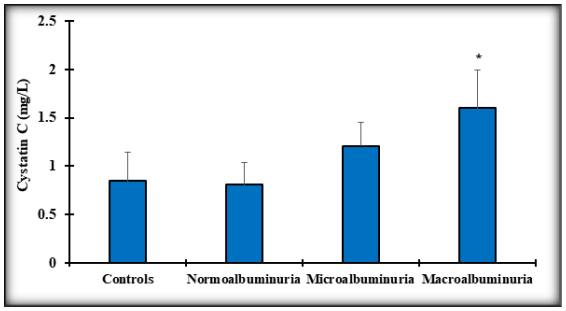

Figure 3: Histogram showing mean Cystatin C values in Controls and Cases viz. Normoalbuminuria, Microalbuminuria and Macroalbuminuria group. Values are expressed as Mean ± SD. *Significantly different from Control group.* (P<0.05)

DISCUSSION

The present study exhibited a significant increase in the FBS levels in normoalbuminuria, microalbuminuria and macroalbuminuria groups as compared to the control group. The results suggest that FBS may have a predictive value in the progression of DN and corroborated well with findings of Diabetes Control and Complications Trial research group.[16] A significant augmentation was observed in the mean HbA1c levels in the normoalbuminuria, microalbuminuria and macroalbuminuria groups as compared to the control group in the present study. These observations suggest that HbA1c levels were higher in DN patients and hence exhibited poor glycemic control thereby increasing the chances of development of micro vascular complications. Additionally, the results also suggest a progressive loss of glycemic control with an increase in the duration of disease. The observations are in line with findings of Stratton et al., (2000).[16] Moreover, in a study carried out by Shetty et al., (2017) HbA1c levels were 5.56 ± 0.44 in non-diabetic subjects with normoalbuminuria, 7.32 ± 0.48 in diabetic patients with normoalbuminuria and normal plasma creatinine (< 1.2 mg/dl) and 7.62 ± 0.54 in diabetic patients with microalbuminuria and moderately raised plasma creatinine (1.2-1.8 mg/dl).[17]

The present study displayed a significant increase in the serum urea levels in microalbuminuria and macroalbuminuria groups as compared to the control group. However, no difference was observed in the serum urea levels between control and the normoalbuminuria group. These observations point towards the fact that serum urea is a non-specific marker to assess the renal status in patients of DN. However, in the later stages of the disease when renal function was compromised to a higher degree, there was significant increase in serum urea levels. The results are in line with that of Nsonwu et al., (2006) where an increase in the serum urea levels was observed in long standing diabetic cases only.[18]

A significant increase was observed in the mean serum creatinine values in the macroalbuminuria group as compared to the control group. However, no difference was observed in the serum creatinine levels between control, normoalbuminuria and microalbuminuria groups in the present study. The findings suggest that serum creatinine values were not raised in early stages of DN but an increase was observed after there was a substantial renal damage as depicted by high values of urinary albumin in the macroalbuminuria group. In a study carried out by Middleton et al., (2006), 48.8 % and 54.7 % of patients with diabetes and CKD were found to have normoalbuminuria and normal serum creatinine levels respectively.[19] 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.[20] 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.[21]

The present study exhibited a significant increase in the mean serum cystatin C values in the microalbuminuria along with the macroalbuminuria groups as compared to the control group. However, no significant difference was observed in the serum cystatin C levels between control and the normoalbuminuria group. Moreover, the serum creatinine levels in microalbuminuria group were not significantly increased in the present study. So it may be noted that serum cystatin C might be an earlier marker of DN in comparison to serum creatinine. However, in the macroalbuminuria group a significant augmentation was observed in serum creatinine and serum cystatin C values suggesting that both serum creatinine and serum cystatin C are good markers of DN when disease has advanced.

In a study carried out by Rao et al., (2014) on Indian T2DM patients, the levels of serum cystatin C were found to be significantly elevated in patients with normoalbuminuria as compared to healthy controls. The study demonstrated that measurement of serum cystatin C was a useful, practical, non-invasive technique for the evaluation of renal involvement in the course of diabetes, especially in patients with normoalbuminuria.[22] In an another study on T2DM patients done by Dayanidhi et al., (2015) the levels of serum cystatin C were significantly higher in the microalbuminuric group (1.74 ± 0.66) than normoalbuminuric group (1.19 ± 0.62), and was found to be higher in patients with GFR ≤ 60 ml/min/1.732 m^2, suggesting that cystatin C is a predictor of early renal damage in patients even before the appearance of microalbuminuria. The study concluded that the determination of serum cystatin C is a valuable tool to describe GFR loss independently and together with ACR in patients with diabetes, and can optimize the early detection of renal damage.[23]

Mojiminiyi et al., (2000) evaluated the role of cystatin C as a marker of nephropathy in T2DM patients who were normoalbuminuric, microalbuminuric and macroalbuminuric, 40 % of the patients with DN were identified by cystatin C as compared to 12 % by serum creatinine.[24] Additionally, Shimizu et al., (2003), demonstrated that serum cystatin C was better than serum creatinine in terms of sensitivity and specificity and was thus helpful in predicting early prognostic stages of patients with T2DM.[25] Another study assessed serum cystatin C and renal tubular enzymes as screening markers for early renal dysfunction in patients with T2DM. Receiver operating characteristic (ROC) curve analysis of the study showed that serum cystatin C was the most sensitive and specific marker of macroalbuminuria and damage progress for follow-up and monitoring nephropathy.[26] In a study carried out by Suzuki et al., (2012) on T2DM patients, abnormal values of serum cystatin C were found in 28.7 %, 54.8 % and 80.0 % of normoalbuminuric, microalbuminuric, and macroalbuminuric DN patients, respectively compared to abnormal serum creatinine values viz. 5.7 %, 19.0 % and 40.0 %, respectively.[27] Being elevated even before the appearance of serum creatinine, serum cystatin C may serve as an efficient marker for evaluating all stages of renal insufficiency in diabetic patients with normoalbuminuria, microalbuminuria and macroalbuminuria.

A significant decrease was observed in the eGFR creatinine in the microalbuminuria and macroalbuminuria groups as compared to the control group in the present study. However, no difference was observed in eGFR creatinine in the normoalbuminuria group as compared to the control group. Clinical assessment of kidney function is part of routine medical care for adults with more than 80 % of clinical laboratories now reporting an eGFR when serum creatinine is measured.[28,29] In spite of standardization of serum creatinine, GFR estimations remain somewhat imprecise.[30] This is due to variation in non-GFR determinants of serum creatinine, that may be affected in both acute and chronic illness. Such imprecision can potentially result in the misclassification of patients whose eGFR is less than 60 ml/min/1.73 m^2 of body-surface area as having chronic kidney disease, leading to unnecessary diagnostic and therapeutic interventions. The Cockcroft-Gault and Modification of Diet in Renal Disease (MDRD) study equations are serum creatinine-based equations that are used to estimate GFR.[28] Thus, GFR determinations by creatinine based equations are not precise, so other substances, such as cystatin C, are being explored to estimate GFR.

The present study exhibited a significant decrease in the eGFR values based on cystatin C equation in the microalbuminuria and macroalbuminuria groups as compared to the control group. However, no significant difference was observed in the eGFR levels between control and the normoalbuminuria group. Cystatin C has the potential to improve estimates of GFR, because it is thought to be less influenced by muscle mass or diet. Cystatin C has desirable traits as a marker of GFR. It is thought to be filtered solely at the glomerulus, not secreted by renal tubules, completely reabsorbed by the tubules and then catabolized, and generated at a constant rate by all cells in the body. More information is needed, however, because the filtration properties of cystatin C are difficult to determine since it is not excreted in the urine. It is also important to note that serum creatinine is being standardized nationwide. This has not yet happened for cystatin C, although it is in progress. GFR is needed to determine the stage of CKD and is used to determine the appropriate clinical action plan. Two meta-analyses have concluded that serum cystatin C is superior to serum creatinine as a marker of kidney function.[20,31] One of them evaluated 29 studies (21 in adults) reported before 2009, that compared serum creatinine with cystatin C in CKD patients. Of those, 17 studies showed that cystatin C was a better predictor of GFR, while 12 studies showed no difference in the prediction of GFR.[20] When compared to MDRD formula, the cystatin C formula was more likely to be predictive if GFR was below or above 60 mL/min/1.73 m2 ($P < 0.0005$).[32] The addition of parameters like age, sex and race to cystatin C equation has helped to make it more accurate predictor of GFR. Pucci et al., (2007) compared the accuracy of cystatin C with creatinine and the Cockcroft-Gault formula and MDRD study equation for the assessment of early decline in renal function in diabetic patients with renal impairment. It included the largest cohort of DM patients ($n = 125$) and demonstrated that cystatin C better correlated with GFR than creatinine based formulae.[33]

CONCLUSION

The present study suggests that cystatin C was effective in detecting early DN in comparison to creatinine levels with an added advantage of being able to estimate GFR to stage DN over microalbuminuria. Thus, cystatin C can be used as a suitable marker in development of early DN.However, the findings of present study are only suggestive. A longitudinal study with larger patient group can be done to arrive at definite conclusions.

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