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Authors' Affiliation:

¹M.Sc. Medical Laboratory Technology student, Department of Paramedical and Health Sciences, Faculty of Medicine, Parul University, Vadodara, Gujarat, India

²Assistant Professor, Department of Paramedical and Health Sciences, Faculty of Medicine, Parul University, Vadodara, Gujarat, India

³MD Pathologist & Associate Professor of Department of Biochemistry Parul Institute of Medical Science and Research, Parul University, Vadodara, Gujarat, India

***Corresponding Author**

Assistant Professor, Department of Paramedical and Health Sciences, Faculty of Medicine, Parul University, Vadodara, Gujarat, India
Email: pateldhruvimayankbhai@gmail.com

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Early detection of acute renal failure by serum cystatin C in type 2 diabetes patients in Parul Sevashram hospital at Waghodia, Vadodara

Disha A Chandera¹, Dhruvi M Patel^{2*}, Ketan Mangukiya³

ABSTRACT

Aim: The early stages of acute renal failure are poorly diagnosed by current routine tests. We studied the correlation between cystatin C and creatinine in Type 2 diabetes patients. **Introduction:** The present study was carried out on 52 subjects with type 2 diabetes mellitus. All subjects were tested for various parameters like, serum cystatin C, serum creatinine, HbA1C, FBS, and, PP2BS. Analysis of Glomerular filtration rate was done using national kidney foundation formula. To analyze data Excel is used for SD value and Social Science Statistics for P value. **Method:** ScyC levels increased significantly in type 2 diabetes patients ($p < 0.001$) as compare to SCr level. A positive correlation was present between ScyC and SCr ($r = 0.309$, $p < 0.005$). Both SCysC ($r = -0.184$) and SCr ($r = -0.309$) had adverse correlation with eGFR ($p < 0.005$). **Result:** Serum cystatin C can be recognised as an immediate marker to detect nephropathy and renal dysfunction in diabetic patients than serum creatinine. Furthermore, this study needs to be conducted with a largest population to confirm this.

Keyword: Acute Renal Failure, Creatinine, Cystatin C, Glomerular Filtration Rate, Type 2 Diabetes

1. INTRODUCTION

Acute renal failure is defined as per risk of renal dysfunctional injury of kidney, failure of kidney function, and this condition in which the kidneys immediately stop purifying unproductive material from the blood. Eventually, no therapy for acute renal failure (ARF) existed (Marwaha et al., 2017). Sometimes symptoms may be or may not appear at all but people may experience an imbalance of water-electrolyte or fatigue, these symptoms are shown in patients' whole body urinary insufficient, urine production or urine retention. In Patients with ARF most common symptoms are shortness of breath, swelling or too much acid in blood and tissues (Randers et al., 1998). Therefore, the diagnosis of ARF at an early phase and prevention is becoming

critical. However, serum Creatinine known as diagnostically standard method to detect acute renal failure (ARF) but it contains major limitations, we may choose evaluation of serum cystatin C as detection of ARF before than serum Creatinine (Taglieri et al., 2000).

Current evaluation of renal function mostly involves estimation of serum or urinary markers and, in some cases, radiological and histopathological studies. SCr is generally used by physicians to monitor renal disease development and treatment reaction due to the ease of estimation. Several formulae are also obtainable to calculate eGFR based on a single SCr value (Randers et al., 1998). Nevertheless, SCr is not considered as potential diagnostic method to detect early phase kidney disease. It is known that suspected patients SCr level remains normal until their GFR rate becomes in a stage of 50% reduction that indicates the major drawback of serum creatinine (Elsayed et al., 2018).

Among the various novel biomarkers discovered, such as SCysC has been proposed to be a promising marker that can help detect the early stage of acute renal failure. Biochemical structure of serum Cystatin C is a group of proteins that contains tertiary structure with low molecular weight, and it has a capacity to bind tightly at the binding site of cysteine proteases to perform their activity. It is freely filtered by the glomerulus, gets reabsorbed in the proximal tubules, and degraded. These competitive inhibitors are useful for controlling protease activity in immune system modification, antiviral, and antibacterial activity and participate in the body's response to brain injury. Many pathological conditions are responsible for physiologic alteration of biomolecules such as Cystatins and Protease. Cystatins is a change in biochemical molecules with different specificities and distinguished by a common cystatin domain that spans about 100 amino group's presence of acid residues and stabilized disulfide bond. It has three families: stefins, competent cystatins, and kininogens. Cystatin C (cysC), also defined as cystatin 3, is continuously produced by nucleated cells. It is not just present in body fluids but also found in human tissue. It consists of one hundred twenty amino acids residues and has disulfide bonds (Onopiuk et al., 2015).

ScysC is superior in comparison to SCr in the estimation of renal function as it is never influenced by age, sex, and body mass. However, research has proven that the use of glucocorticoid drugs, altered thyroid status, pregnancy, malignant conditions, liver disorders, and cardiovascular abnormalities can also bring about alterations in SCysC level. As GFR declines, cystatin C levels begin to rise sharply. This study was undertaken to determine and differentiate the levels of SCr and SCysC in type 2 diabetes patients having different severity groups based on eGFR. In this study, we established a connection with ARF in early phase by analysing serum creatinine and serum cystatin C levels (Murty et al., 2017).

2. MATERIALS AND METHODS

The study was performed from Parul Sevashram Hospital, Vadodara; Gujarat, India by the Biochemistry laboratory, on 53 subjects diagnosed with type 2 diabetes mellitus who visited the OPD between December 2021 and March 2022. The study got approval from Institutional Ethical Committee of Parul University. Acute Renal Failure subjects aged between 21-89 years were added in the study. Subjects with other comorbidities related to heart, hormonal disease and other chronic illness were excluded from this study. For analysis venous blood was drawn to obtain serum sample and kept it at room temperature to clot for 30 minutes and later centrifuge it to obtain serum. The sample can be stored at -20°C until analysis. Biochemical parameters analysed were SCr and SCysC. The diagnostic principle used for SCr and ScysC is modified Jaffe's method and particle enhanced immunoturbidimetric method, respectively. The analyser used for this estimation is ERBA 360 clinical chemistry automated analyser. Estimated GFR was derived using NKF eGFR calculator.

According to NKF based CKD-EPI Creatinine-Cystatin formula (2021) as mentioned below:

$$eGFR_{Cr-cys} = 135 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa, 1)^{-0.544} \times \min(S_{cys}/0.8, 1)^{-0.323} \times \max(S_{cys}/0.8, 1)^{-0.778} \times 0.9961^{Age} \times 0.963 \text{ [if female]}$$

Where, eGFR (estimated glomerular filtration rate) = ml/min/1.73m²

S_{Cr} = serum creatinine in mg/dL

κ = 0.7 (females) or 0.9 (males)

α = -0.219 (female) or -0.144 (male)

Min (S_{Cr}/κ, 1) is the minimum of S_{Cr}/κ or 1.0

Max (S_{Cr}/κ, 1) is the maximum of S_{Cr}/κ or 1.0

S_{cys} = serum cystatin C in mg/L

Age = years

3. RESULT

The study was done from December 2021 to March 2022 at a Parul sevashram hospital. The study performed on 53 subjects of type 2 diabetes patients (35 male, 18 female, and age between 21 to 89 years). In this study I have excluded recently diagnosed diabetes patients (< 1 year), paediatric (< 21 year,) and pregnant women. All collected data which include age, gender, height, weight, co morbidities, Medicine history, physical complaints, and laboratory diagnosis. Plain Serum samples without anticoagulant from routine clinic collections were used, in serum sample cystatin C and creatinine test was performed and for HbA1C test EDTA plasma samples are used. Correlation studies revealed a comparatively better correlation between SCys C and e GFR than between SCr and e GFR is shown in (Table 1).

Table 1 Serum Cystatin C & Serum Creatinine, estimated eGFR, in type 2 Diabetic Participants

Parameter	GFR ≤60ml/Min Per 1.73m ²	GFR ≥60ml/Min Per 1.73m ²	All Patients GFR 6-130 ml/Min/173m ²
	N= 39	N= 19	N= 53
Serum Creatinine mg/dl	1.73(±1.52)	1.14(±0.74)	1.5(±1.3)
NKF Estimated GFRml/min Creatinine	33.78(±14.91)	84.57(±17.24)	52.15(±28.98)
Serum Cystatin C mg/L	2.36(±1.03)	1.90(±0.93)	2.22(±1.02)
NKF Estimated GFR ml/min Cystatin C	29.78 (+-13.01)	73.52 (+19.37)	46.20 (26.22)

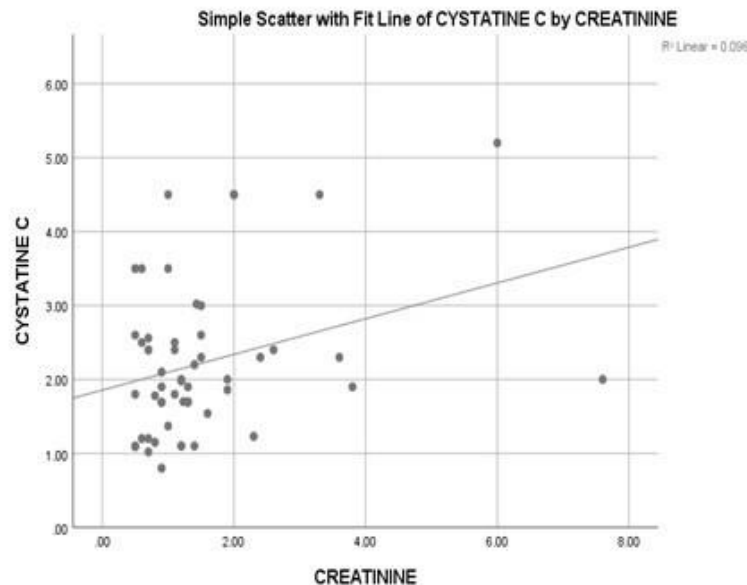


Figure 1 Relationship among serum creatinine and serum cystatin C

A strong positive correlation existed between SCr and SCys C levels which was statistically significant in this study (figure 1). So in this study I have introduced a positive relationship between SCr and ScyC ($r=0.309$, $p<0.05$). A strong correlation was reported between SCys C and e GFR ($r= -0.185$, $p>0.05$) (figure 2) in comparison with SCr and e GFR ($r= -0.309$, $p<0.05$) (figure 3). The cystatin C levels of serum and creatinine in patient of type 2 diabetes mellitus are found significantly correlated as biomarker ($p<0.05$). We found that 88.7% of patients of the acute renal failure, the group had normal level of creatinine in the early phase,

although same group of patient had enhanced serum cystatin C at the same time. The level of serum creatinine in patients with low GFR is 1.73 mg/dl and the level of serum cystatin C in patients with low GFR 2.36 mg/L hence its prove that patients with low GFR suggested ARF have higher level of cystatin C so we can consider serum cystatin C is early biomarker of acute renal failure. Cystatin C serum concentration continuously increased as GFR decreased.

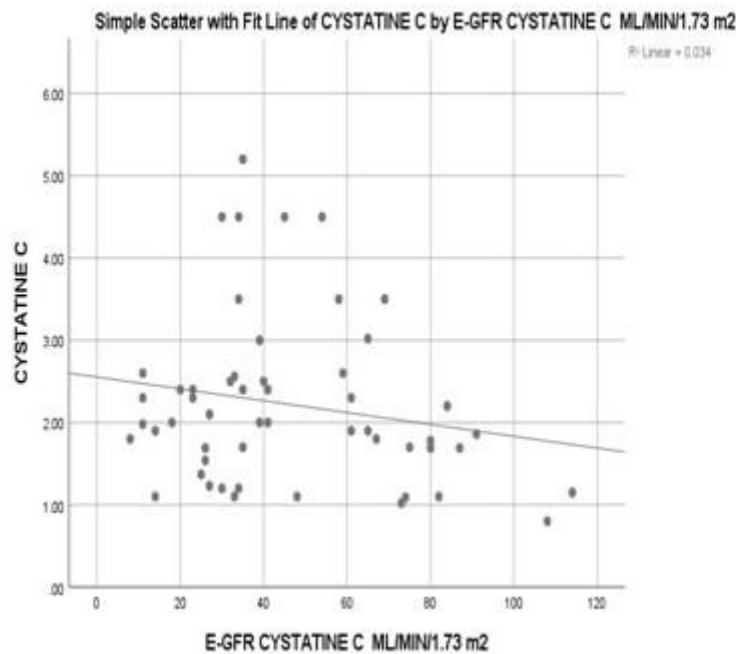


Figure 2 Association between serum cystatin C and estimated glomerular filtration rate

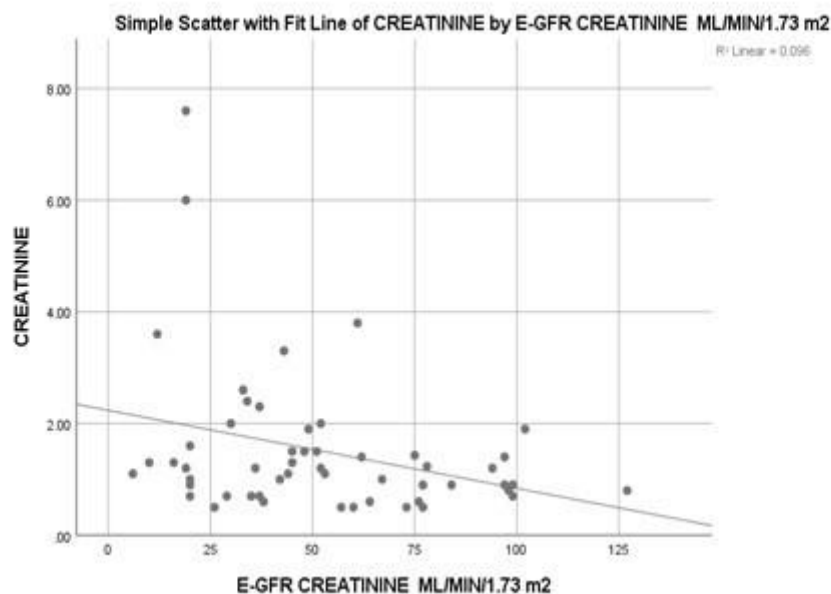


Figure 3 Connection between serum creatinine and measured glomerular filtration rate

4. DISCUSSION

The GFR is generally considered a better measure of kidney function in comparison with SCr, but direct measurement of GFR is costly, time consuming, and impractical in routine clinical care. For example, NKF based CKD-EPI Creatinine-Cystatin Equation (version 2021) is reported to be better than the GFR_{aMDRD} . Detection of ARF in type 2 diabetes patients in early stages is essential. At

present, SCr and GFR are the two parameters being used to diagnose, estimate the prediction, and monitor the response to treatment. Low cost, ease of estimation and specificity makes SCr a better parameter to depend on. However, SCr has certain diagnostic limitations. In this study, we analysed a use of alternate marker of SCr, such as ScyC in correlation with SCr with type 2 Diabetes patient to detect Acute Renal Failure. A study suggested an inverse relationship of both the parameters with eGFR (Kumaresan et al., 2011). In our study, A similar, result like, an increasing trend in each ScyC and SCr levels in type 2 diabetes patients ($p = <0.001$), was observed.

Level of eGFR in present population suggested comparatively better Correlation and highly significant between ScyC and measured eGFR ($r = -0.184$, $p = >0.05$), while in comparison to SCr and eGFR ($r = -0.309$, $p = <0.05$). If the p value is >0.05 it means two variables are highly significant and highly correlate. So this correlation is use to predict immediate diagnosis of acute renal failure in type 2 diabetes patients. If the r value is negative, it means two variables are inversely correlates and the mean difference is very high.

These findings are according to one previous study, mentioned a better correlation between ScyC and measured GFR ($r = -0.792$, $p < 0.05$) while in comparison to SCr and GFR ($r = -0.666$, $p < 0.05$) (Hojs et al., 2004). More recently, once study was finding the stronger correlation between ScyC and eGFR ($r = -0.877$, $p < 0.05$) a comparison with SCr and eGFR ($r = -0.777$, $p < 0.05$) (Dhupper et al., 2015). Our study, A strong positive correlation obtained between the SCr and ScyC levels which was statistically significant ($r = 0.309$, $p = < 0.05$). Similar correlation observed in study who has reported a positive correlation between SCr and ScyC ($r = 0.665$ and $r = 0.870$ respectively) (Tsai et al., 2010).

SCysC proves to be a definitive marker of kidney impairment. In this study, SCysC was significantly elevated in type 2 diabetes patients as compared to SCr. However, in type 2 diabetes subjects with mild to severe reduction in eGFR ($\text{eGFR} \geq 60 \text{ ml/min/1.73 m}^2$), SCysC level was found increased as compared to upper reference range. A normal serum creatinine level, during the early stage of kidney disease, does not necessarily indicate normal renal function.

Limitation

Our study has faced certain limitations like small sampling size. Thus, detailed analysis on large population needs to be done to consider SCys C as a biomarker of acute renal failure.

5. CONCLUSION

In conclusion, study suggested that estimation of SCys C level as a diagnostic tool to detect renal function in the early stage of acute kidney injury in contrast to serum creatinine level. The study declares positive correlation of increasing serum cystatin C level in individual with acute renal failure in type 2 diabetes mellitus patients. Moreover, the cystatin C level will not be affected by age, gender, food Intec and muscle mass. Additionally, when cystatin c level enhances in patients with ARF there GFR level decreases in contrast to serum creatinine and there GFR. Hence, it is suggested that cystatin C level required to measure first while patients having symptoms of ARF. But some limitations related to small sample and low acknowledgement to use cystatin C as assays of early detection of renal failure. Further studies need to be done at larger population to confirm this result.

Author Contribution

Disha Chandra: Topic selection, Data collection and analysis, Wrote the manuscript

Dhruvi Patel & Dr Ketan Mangukiya: Guidance, plan of study, Corrections, Proofreading, helps to form manuscript preparation as per journals requirement, drafting manuscript

Conflict of Interests

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report. We certify that the submission is original work.

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Conflicts of interest

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

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