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COMPARISON BETWEEN SERUM CREATININE AND SERUM CYSTATIN C LEVEL IN DIAGNOSING EARLY DIABETIC NEPHROPATHY IN NEWLY DIAGNOSED TYPE 2 DIABETES MELLITUS

Dr. Janmeshwar Prasad[1], Dr. Manish Kumar Singh[2], Dr. Md. Rashid Anwer[3], Dr. Shyama[4]

[1]*Senior Resident, Department of Medicine, AIIMS, Patna*
[2]*Senior Resident, Department of Medicine, AIIMS, Patna*
[3]*Senior Resident, Department of Medicine, AIIMS, Patna*
[4]*Assistant Prof, Department of Medicine, AIIMS, Patna*

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Corresponding author: Dr. Md. Rashid Anwer
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Abstract

Background: This study was done to evaluate clinical usefulness of cystatin C levels of serum and urine in predicting renal impairment in normoalbuminuric patients with type 2 diabetes and to evaluate the association between albuminuria and serum/urine cystatin C. Cockroft-Gault equation was previously used for GFR calculation. The most recently advocated formula for calculating the GFR are The modification of diet in renal disease study group ,CKD-EPI equation(2009),CKD-EPI cystatin C(2012), CKD-EPI creatinine –cystatin C(2012). The cystatin C levels of serum and urine could be useful markers for renal dysfunction in type 2 diabetic patients with normoalbuminuria.

Conclusion; This finding has major implications for clinical research and early intervention to prevent development of chronic kidney disease in patients with type 2 Diabetes mellitus.

Keywords: Cystatin C, Diabetic Nephropathies, Albuminuria

Introduction:

Diabetic nephropathy is the leading cause of CKD, End stage renal disease and CKD requiring renal replacement therapy. It is defined as presence of persistent Albuminuria (>300mg/24 hour or 200mcg/min) in diabetic patients usually with retinopathy, elevated blood pressure and declining glomerular function in the absence of clinical or laboratory evidence of other kidney or renal tract disease. Screening for DM nephropathy is currently done by monitoring patient for development of microalbuminuria and as an adjunct, the estimation of GFR, serum creatinine and creatinine clearance. Therefore, it is of worth to develop a more sensitive or specific indicator for detecting early renal impairment in diabetic patients.

Though timed urinary collection is the gold standard for screening of diabetic nephropathy, the cumbersome procedure of collection of urine makes other methods like early morning spot urine microalbuminuria more popular. Albumin creatinine ratio is convenient and reliable, but several factors such as strenuous exercise, urinary tract infection and menstruation can give false positive results. Serum creatinine is the commonly used assay for kidney function, but serum creatinine does not change until around 50% kidney function is impaired and varies with muscle mass, age, sex, medication and hydration status. Lag time between injury and loss of function risks missing the therapeutic opportunity and may explain high mortality. Cockroft-Gault equation was previously used for GFR calculation. The most recently advocated formula for calculating the GFR are The modification of diet in renal disease study group, CKD-EPI equation(2009), CKD-EPI cystatin C(2012), CKD-EPI creatinine –cystatin C(2012).

Novel markers of AKI and failure include neutrophil gelatinase associated lipocaline, N acetyl beta D glucosaminidase, kidney injury molecule I, IL 18 and cystatin C.

Properties of an ideal biomarker have been defined as :

- It must be generated by the damaged cells and exhibit the organ specificity.
- Its concentration in body must be proportional to extent of damage.
- It should be expressed early after organ damage, when such damage is still potentially reversible.
- Its concentration should decrease quickly after the acute injury episode to enable its use as therapeutic monitoring tool.
- It should be rapidly and reliably measurable.

Cystatin C is a nonglycosylated 13-kDa basic protein of the cystatin super-family of cysteine proteinase inhibitors. Produced by all nucleated cells, its production rate is unaltered in inflammatory conditions. Determination of the structure of the cystatin C gene and its promoter has shown that the gene is of the house-keeping type, which is compatible with a stable production rate of cystatin C by most cell types. The low molecular mass of cystatin C, in combination with its stable production rate, strongly suggests that the major determinant of cystatin C

concentrations in blood plasma is the glomerular filtration rate (GFR).

Glomerular filtration rate is the best overall index of renal function in health and disease. Inulin and Cr EDTA plasma clearance are considered gold standard methods for estimation of GFR. Unfortunately these methods requires specialized technical personal over a period of several hours and high cost. In clinical practice, serum creatinine is the most widely used index for non-invasive assesment of GFR. It has been suggested that cystatin C could be especially useful in detection of early nephropathy, as demonstrated by the increased cystatin C level in patient with microalbuminuria, but with normal GFR. This study attempts to determine the utility of serum Cystatin C in predicting early decline in renal function so that appropriate and timely interventions can be instituted to delay or arrest the progression of diabetic nephropathy.

Aims and Objectives

1. To compare between serum creatinine and serum cystatin C as better marker for early renal injury

2. To study the prevalence of diabetic nephropathy in newly diagnosed type 2 diabetes mellitus patients

Material and Methods

Study site: All india institute of Medical Science patna Bihar.

Study population: Newly diagnosed type 2 diabetes mellitus Patients in OPD

Study design: cross sectional study to find out early Diabetic Nephropathy

Sample size: 65 based on previous study mention in review of literature and using formula as follows

Methodology:

1. Newly diagnosed Type 2 DM patients were investigated for renal involvement. Parameters Checked included: Serum creatinine, serum Cystatine C, urine routine and urine Microalbumin.

2. Comparing efficacy of Serum creatinine and Serum Cystatine C in view of diagnosing early renal injury .Serum creatinine was measured by the "Jaffes method" and cystatine C by the "Immunoturbidimetric method".

Glomerular filtration rate was calculated using the MDRD and CKD - EPI 2012 formula and further statistical comparisons were made.

Inclusion criteria:

Newly diagnosed type 2 diabetes mellitus patients age group 30-65 yrs

Exclusion criteria

- Patient with hypertension or pathology in kidney.
- Age less than 30yrs and age more than 65 yrs
- Pregnant and lactating females
- Patient not willing for studies.

Observations and Results

Table 1: Age distribution in study group

Age	
Mean	45.86
Median	45.00
Std. Deviation	7.925
Minimum	35
Maximum	64

Table 9 shows age distribution in study group with minimum age of 35 years and maximum of 64 years with mean of 45.86 and standards deviation of 7.925

Table 2: Diabetic retinopathy in study group

		Count	Column N %
Fundus	Diabetic retinopathy	6	9.2%
	Normal	59	90.8%
	Total	65	100.0%

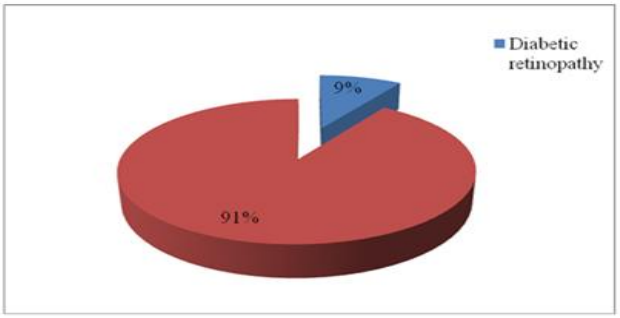

Figure 1: Graphical presentation of diabetic retinopathy in study group

Table 3: Percentage of proteinuria in study group

		Count	Column N %
Urine glucose	Present +	39	60.0%
	Present ++	13	20.0%
	Present +++	10	15.4%
	Trace	3	4.6%
	Total	65	100.0%

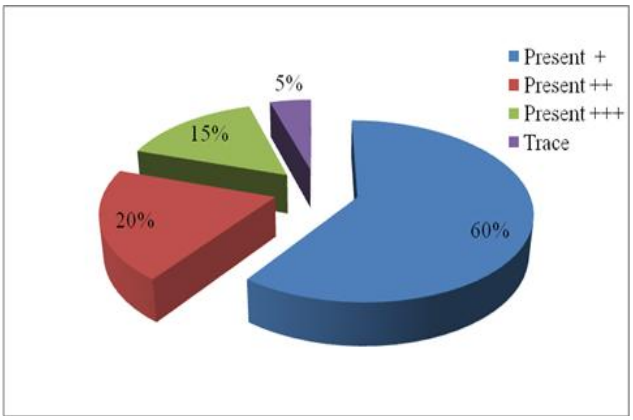

Figure 2: shows proteinuria and grading accordingly semi quantitative test

Table 4: Comparison of creatinine based GFR, cystatine C based GFR and combined GFR and grading acc. CKD classification

		Count	Column N %
Calculated GFR with creatinine	>90	18	27.7%
	60-89	29	44.6%
	30-59	18	27.7%
	15-29	0	.0%
	<15	0	.0%
	Total	65	100.0%
Calculated GFR with cystatin C	>90	26	40.0%
	60-89	28	43.1%
	30-59	11	16.9%
	15-29	0	.0%
	<15	0	.0%
	Total	65	100.0%
Combined GFR	>90	19	29.2%
	60-89	37	56.9%
	30-59	9	13.8%
	15-29	0	.0%
	<15	0	.0%
	Total	65	100.0%

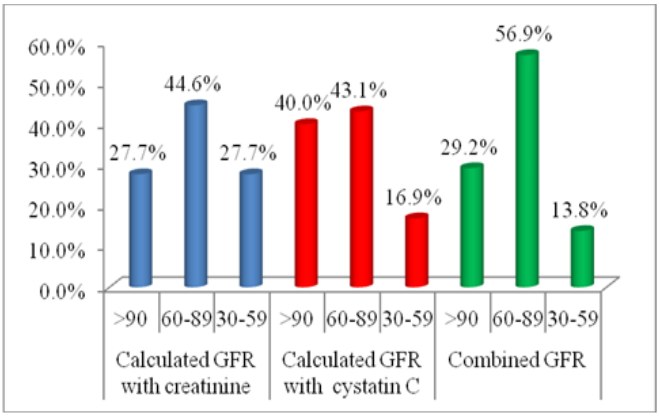

Figure 3: Grading of renal function on based GFR calculated with serum creatinine cystatin C and combined

Fig. No. 3 shows grading of renal function on based GFR calculated with serum creatinine, serum cystatin C and combined and classified as CKD classification.

Table 5: Comparison between serum creatinine and ACR

Sr. Creatinine		Normal	
		Count	Column N %
Microalb/ urine creat	Normal	29	44.6%
	Microalbiminuria	26	40.0%
	Macroalbuminuria	10	15.4%
	Total	65	100.0%

Table 20 shows comparison of ACR and serum creatinine out of 65 patient 29 with normal ACR and creatinine. 26 patients have normal creatinine but microalbiminuria and rest shows macroalbuminuria

Discussion

Cystatin C is a low- molecular weight proteins (13kd) produced by all nucleated human cells , with a stable production rate .It is freely filtered by the glomerulus and catabolized primarily by proximal tubular cells. Cystatin C seems to be a promising candidate as a novel marker of the GFR.

It has been suggested that cystatin C could be especially useful in the detection of early nephropathy, as demonstrated by the increased cystatin C level in patient with microalbuminuria, but with normal GFR.

In this study it was observed that serum cystatin C is a better marker for estimating GFR and detecting early renal damage than conventional serum creatinine. It has been observed that GFR calculation using serum creatinine and serum Cystatin C was more correlating with ACR than cystatin C alone. In this study, 56% of the included population already had a baseline derangement in ACR which is considered the gold standard in screening methods for detecting deranged renal function.

Out of 65 patients 36 patient were found to have deranged ACR suggestive of altered renal function namely early diabetic nephropathy.

Similar study was conducted earlier by Neil V. McNamara , Roger Chen , Margaret R. Janu , Phillip Bwititi , George Car , Markus Seibel (2016) , they studied Type 2 diabetes mellitus patients (n = 48) and tested for serum cystatin C, urine albumin, haemoglobin A1c, serum creatinine, serum urea, urinecreatinine, glucose, triglycerides and low density lipoproteins (LDL).His study also Concluded that Cystatin C is a more sensitive marker of renal disease in Type 2 diabetes mellitus where estimated GFR is unreported at >60 mL/min and where antihypertensive medications render microalbuminuria detection unreliable.

Another study conducted by M.S.N.Murthy et al (2013) comprised 200healthy subjects and 130 AKI patients. Study Serum creatinine and serum cystatin C were studied and analyzed in relevance to early AKI. They found that 56.2% of patients of AKI group had normal levels of serum creatinine in early phase, while all patients had elevated serum cystatin C at same time. Hence they concluded, serum cystatin C is a better marker of renal function in early stages of AKI. They also concluded that use of serum cystatin C-based GFR may be more accurate and useful for early therapeutic intervention and possibly a favorable outcome.

Our study results were similar with the other studies conducted earlier on this subject.

Further in our study, we co-related levels of glycosylated hemoglobin with renal function derangement. Glycosylated hemoglobin gives idea regarding control of sugar over

approximately 3 months. Patients with a mean HbA1c around 8.1% had higher chances of developing macroalbuminuria, where as mean HbA1c of 7.41% had microalbuminuria and patient with mean HbA1c around 7.1% had normal ACR. Hence it can be concluded that poor control of DM have higher risk of developing diabetic nephropathy than better control.

We also observed the relationship of fasting BSL and post prandial BSL with albumin creatinine ratio. Patients with a mean post prandial BSL around 294.8 had higher rate of macroalbuminuria, mean sugars around 260.8 developed microalbuminuria and mean sugar around 222.5 had normal ACR. Higher postprandial sugar was associated with more alteration of ACR. Fasting BSL had no relationship with ACR like post prandial BSL. Out of total 65 patient 36 patients had abnormal ACR and out of these 36 patients, 12 patient had abnormal cystatin C levels. In this study patients with thyroid disorder, hypertension or renal pathology due to other etiology were excluded. Therefore abnormal cystatin C level indicates derangement in renal function related to diabetes mellitus.

Although serum creatinine has become the most popularly used serum marker of renal function, serum creatinine may be unreliable because it is frequently affected by muscle mass, age, gender, and aberrant renal tubular regulation of serum creatinine resulting in an overestimation of GFR. Using serum cystatin C levels has some advantages over serum creatinine and creatinine-based calculated GFR formulas, because serum cystatin C levels are independent of age, gender, muscle mass, and renal tubular secretion. So, the diagnostic utility of cystatin C seen in our study is similar to that previously reported by other investigators. Many of our patients with renal dysfunction had high serum cystatin C levels at the time when serum creatinine was still in the normal range. Hence serum cystatin C is a better marker of GFR than serum creatinine especially in patients with type 2 diabetes mellitus.

Summary

It was a cross sectional study conducted at All india institute of Medical Science Patna Bihar. The aim of the study was to compare between serum cystatin c and serum creatinine as the better and earlier marker for diagnosing diabetic nephropathy in newly diagnosed Type 2 Diabetes Mellitus patients.

Based on eligibility criteria, 65 newly diagnosed type 2 diabetes mellitus patients in the age group of 30-65 were included in this study who visited OPD.These patients were investigated for routine clinical examination and pathological testing. Various parameters studied included Serum cystatin c, serum creatinine and albumin creatinine ratio.

The study showed that:

1. Out of total 65 patients, No patient was found to have abnormal creatinine value but 12 patient had abnormal serum Cystatin-c level.
2. Among total patients with abnormal serum cystatin-c, 58.3 % patients showed abnormal ACR , 41.7% patients had normal ACR. Hence showing ,there was no significant relationship in serum cystatin-c and abnormal ACR.
3. Patients with higher glycosylated Hb had higher risk of developing diabetic nephropathy.
4. Patients with normal ACR were having higher GFR calculation with serum cystatin-c than their counterpart having microalbuminuria . Thus showing serum cystatin-c is a better marker than serum creatinine for estimation of GFR.
5. Combined calculated GFR is a better marker for diabetic nephropathy than GFR calculated from either serum cystatin-c or serum creatinine.
6. Other associated findings were that poorer the control of DM, higher the risk of nephropathy. Patients with higher HbA1C were more prone for nephropathy.

Conclusion

Serum cystatin C may be used as an alternative and more accurate method than serum creatinine to screen for and monitor kidney function in diabetic patients. It may be especially useful in detecting early decreased renal function. This finding has major implications for clinical research and early intervention to prevent development of chronic kidney disease in patients with type 2 Diabetes mellitus, for whom hyperfiltration is a common feature of the early stages of kidney complications

References

1. Alvin c. power, Diabetes mellitus:- Complications, Harrisons principles of internal medicine, 20th edition :vol.2; 2877
2. Peter rossing.., Diabetic nephropathy, Brenner and Rectors THE KIDNEY,10th edition,1283
3. Coca SG, Yalvarthy R,Concato J,Parikh CR. Biomarkers for the diagnosis and risk stratification of acute kidney injury: a systematic review. Kidney int.2008; 73:1008-16
4. Katrina Chau, Laboratory assessment of kidney disease, Brenner and Rectors THE KIDNEY,10th edition, 784
5. BB Tripathy etl, diabetis and kidney, vol. 2, 895,
6. Grubb A, Lofberg H. Human y-trace, a basic microprotein: amino acid sequence and presence in the adenohypophysis. Proc Natl Acad Sal USA 1982;79:3024-7.
7. Barret AJ, Davies ME, Grubb A. The place of human y-trace (cystatin C) amongst the cysteine proteinase inhibitors.Biochem Biophys Res Commun 1984; 120:631-6.
8. Barret AJ, Fritz H, Grubb A, Isemura S, Jfirvinen M, Katunuma N, et al. Nomenclature and classification of the proteins homologous with chicken cystatin. Biochem J 1986; 236:312.

9. Indian J Nephrol. 2011 Apr-Jun; 21(2): 75–84.doi: 10.4103/0971-4065.82122
10. Grubb A. Diagnostic value of analysis of cystatin C and protein HC in biological fluids. Clin Nephrol 1992; 38(Suppl 1):20-7.
11. Simonsen 0, Grubb A, Thysell H. The blood serum concentration of cystatin C (y-trace) as a measure of the glomerular filtration rate. Scand J Clin Lab Invest 1985; 45:97-101
12. Grubb A, Simonsen 0, Sturfelt G, Truedsson L, Thysell H. Serum concentration of cystatin C, factor D and 2-microglobulin as a measure of glomerular filtration rate. Acta Med Scand 1985; 218:499-503.
13. Ahrahamson M, Olafsson I, Palsdottir A, UlvsbAck M, Lundwall A, Jensson 0, et al. Structure and expression of the human cystatin C gene. Biochem J 1990; 268:287-94.
14. Skeftruna AK, Jacobsson B. Immunoloca]ization of cystatin C. Distribution in normal human tissues. Laboratoriet 1993; 4:8-11 (in Swedish).
15. Bangs L. Uniform latex particles. Indianapolis, IN: Seradyn, Particle Technology Div., 1987:25-34
16. Gerth J,cohen CD,Hopfer U,et al.collagen type VIII expression in human diabetic nephropathy. Eur J Clin invest 2007; 37:767-73
17. D'Agati V, Yan SF, ramasamy R, Schmidt AM.RAGE, glomeruloclerosis and proteinuria : rolein podocytes and endothelial cells Trends Endocrinol Metab 2010;21:50-6
18. Herget-Rosenthal S, Bökenkamp A and Hofmann W (2007): How to estimate GFR-serum creatinine, serum cystatin C or equations? Clin Biochem; 40: 153-161
19. Early renal failure detection by cystatin C in Type 2 diabetes mellitus: varying patterns of renal analyte expression Neil V. McNamara, Roger Chen, Margaret R. Janu, Phillip Bwititi, George Car , Markus Seibel Royal College of Pathologists of Australasia Volume41, Issue3, April2016, Pages 269-275
20. M.S.N.Murthy et al,Indian Journal Of Nephrology2013-may June 23(3):180-183
21. Van Den, Noortgate NJ, Janssens WH, et al. (2004): Serum cystatin c Concentration compared with other markers of glomerular filtration rate. J Am Geriatr Soc; 52: 1278-1282.
22. MacIssac RJ, Tsalamandris C, Panagiotopoulos S, et al. (2004): Normoalbuminiric renal insufficiency in type 2 diabetes Diabetes Care; 27: 195-200