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Research Article

Evaluation of cystatin C as marker of estimated glomerular filtration rate (eGFR) in different stages of chronic kidney disease (CKD)

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Abstract: Chronic Kidney Disease (CKD) is a worldwide public health problem, both for the number of patients and cost of treatment involved. Creatinine is the most widely used biomarker of kidney function. It is inaccurate at detecting mild renal impairment. cystatin C, a non-glycosylated 13 kDa protein, has the potential to improve estimates of glomerular filtration rate (GFR) because it isless influenced by muscle mass or age unlike creatinine. 40 known patients of CKD attending nephrology unit of medicine at PGIMS, Rohtak were enrolled as cases for this hospital based cross-sectional study, 40 age and sex matched healthy subjects were taken as controls. Both the cases and controls were analyzed for serum creatinine, cystatin C and urine creatinine. Estimated glomerular filtration rate (eGFR) was calculated from MDRD equation along with creatinine clearance using standard formula. Serum Cystatin C increased with stage wise progression of CKD with mean level of 2.31 ± 0.97mg/L (stage III), 2.80 ± 0.55 mg/L (stage IV), 3.01 ± 0.81 mg/L (stage V) in comparison to controls (0.68±0.17 mg/L). Serum creatinine was also increased with stage wise progression in CKD with mean level of 1.7 ± 0.19 mg/dL (stage III), 2.72± 0.58 mg/dL (stage IV), 7.66 ± 2.33 mg/dL (stage V) in comparison to controls (0.84± 0.15 mg/dL).Serum Cystatin C (r= - 0.877; CI: 1.44 to 1.96; p=0.000) has shown more significant Pearson correlation with eGFR than serum creatinine (r= - 0.777; CI: 1.88 to 3.06; p=0.000). Cystatin C has small variability and is unaffected by preanalytic factors such as routine clinical storage conditions, freezing and thawing cycles, or interfering substances, such as bilirubin or triglycerides. Thus, it may be better to use cystatin C for staging of CKD than indirect measurement of eGFR with serum creatinine based equations.
Keywords: Chronic kidney disease, Cystatin C, eGFR, Serum Creatinine, Creatinine Clearance.

INTRODUCTION

Chronic Kidney Disease (CKD) is a worldwide public health problem, both for the number of patients and cost of treatment involved. Globally, CKD is the 12th cause of death and the 17th cause of disability. Most common cause of CKD is diabetes mellitus especially type-II because of its higher prevalence. Non Diabetic group comprises of diseases including hypertensive nephropathy, glomerulonephritis, cystic kidney diseases, vascular diseases and tubulointerstitial nephropathy[1].

The term chronic renal failure applies to the process of continuing significant irreversible reduction in nephron number. Chronic renal failure is defined by a reduced GFR (< 60 mL/min/1.73m^2) and/or the presence of markers of renal injury for > or = 3 months. Chronic renal failure indicates increased risk of both end stage renal disease and cardiovascular mortality[2]. It is important to identify factors that increase the risk for CKD like hypertension, diabetes mellitus, autoimmune disease, older age, african ancestry, a family history of renal disease, a previous episode of acute kidney injury, and the presence of proteinuria, abnormal urinary sediment, or structural abnormalities of the urinary tract [3].

GFR is defined as the volume of plasma that can be completely cleared of a particular substance by the kidneys in a unit of time.There is no simple and practical way to measure GFR directly, so it is estimated. To estimate the GFR, an endogenous substance in the blood that is cleared by the kidney is used. This substance is currently serum creatinine, which is used to estimate GFR in equations that include age, race and gender, so it can be adjusted to account for average differences in muscle mass among subgroups. The Cockcroft-Gault (CG) and Modification of Diet in Renal Disease (MDRD) Study equations are serum creatinine-based equations that are used to estimate GFR[4]. Creatinine is derived from creatine metabolism in skeletal muscle and released into

circulation at a relatively constant rate. It is freely filtered, neither metabolized nor reabsorbed and inexpensive to measure. The serum creatinine production (i.e. GFR x serum creatine), serum creatinine and urinary output, do not vary throughout the day. Thus, creatinine clearance is the most widely used measurement for glomerular filteration rate (GFR). Its normal range is being90-140ml/min in men and 80-125ml/min in women[5].

Cystatin Cis a 13 KD a basic protein having 122 amino acids and belongs to cystiene protease inhibitor family. It is expressed by nucleated cells. It is produced at a constant rate and is freely filtered by the glomerulus. It is not secreted but reabsorbed by the tubular cells. Hence, it can be used as an ideal endogenous marker for estimation of GFR. The low molecular weight of cystatin C in combination with its stable production rate strongly indicates that the blood serum concentration of this protein is mainly determined by the GFR of the individual [6].

MATERIAL AND METHODS

The present study was conducted in the Department of Biochemistry in collaboration with Department of Medicine (Nephrology unit), Pt. B.D. Sharma Post Graduate Institute of Medical Sciences, Rohtak. A total of 40 known patients of chronic renal failure (CRF) attending nephrology unit of medicine were enrolled for this hospital based cross-sectional study. 40 age and sex matched healthy subjects were taken as controls. An informed written consent was taken from the patients for study.

40 patients known to be suffering with renal disease of more than 3 months duration were enrolled as cases of chronic renal failure (CRF) from nephrology unit of medicine for this hospital based cross-sectional study. The patient must be having eGFR <60 ml/minute/1.73m^2 (i.e. Stage III, IV and V). The eGFR was calculated by standard MDRD method. Patients on haemodialysis were excluded.

5 ml venous blood sample was collected in a plain evacuated blood collection tube under all aseptic precautions. Samples were processed within one hour of collection. Serum was separated by centrifugation at 3000 rpm for 10 minutes after clotting. Separated serum was analysed for serum creatinine on same day and rest serum was stored at -20^{0}C (maximum 3 months) for cystatin C analysis. 24 hr urine sample was taken for estimation of creatinine clearance.

Serum and urine creatinine estimated by modified jaffe's method using commercial kit from Randox on Randox Rx Suzuka autoanalyzer [7] while cystatin C analysis was done by immunoturbidimetric assay using kit from Accurax on Erba-XL 300 autoanalyzer[8].

Creatinine Clearance (ml/min):

$$= \frac{24 \text{ hour urine volume} \times \text{urine creatinine}}{1440 \times \text{serum creatinine}}$$

The eGFR was calculated by MDRD equation[9].

Estimated GFR (mL/min per 1.73 m^2) = 1.86 x $(P_{Cr})^{-1.154}$ x $(age)^{-0.203}$

Multiply by 0.742 for womenThe data was analysed by SPSS 20 (Statistical package for social sciences) using appropriate statistical methods.

RESULTS AND DISCUSSION

All the routine renal function parameters i.e serum urea, creatinine, uric acid, phosphate, alkaline phosphatase (ALP) in patients of CKD with mean level of 151.23 ± 71.85mg/dL, 4.11 ± 3.00 mg/dL, 9.06 ± 1.86 mg/dL, 6.70 ± 1.32 mg/dL, 141.00 ± 54.53U/L respectively were significantly raised ($p < 0.001$) in cases as compared to controls with mean of 37.30 ± 4.82mg/dL, 0.84±0.15mg/dL, 4.35±0.85mg/dL, 3.47±0.71mg/dL, 55.7±12.63U/L respectively. The serum calcium was significantly decreased in cases($p<0.001$) with mean level of 7.11 ± 0.47mg/dL in comparison to controls with mean level of 9.33 ± 0.66mg/dL. (Table 1)

The eGFR decreased with stagewise progression of CKD with mean level of 41.45±7.22 ml/min in stage III, 23.92±4.30 ml/min in stage IV, 7.96±3.14 ml/min in stage V in comparison to controls with mean level of 93.32±5.5 ml/min. Serum Cystatin C increased with stagewise progression of CKD with mean level of 2.31±0.97mg/L in stage III, 2.80±0.55 mg/L in stage IV, 3.01±0.81 mg/L in stage V in comparison to controls (0.68±0.17 mg/L). Serum creatinine was also increased with stagewise progression in CKD with mean level of 1.7±0.19 mg/dL in stage III, 2.72±0.58 mg/dL in stage IV, 7.66 ±2.33 mg/dL in stage V in comparison to controls (0.84±0.15 mg/dL). Creatinine clearance decreased with mean level of 41.96±8.30 ml/min in stage III, 36.73± 6.25ml/min in stage IV, 13.14±9.60 ml/min in stage V of CKD in comparison to controls (121.79 ±13.6ml/min)(Table 2, Figure 1 and 2).

Table 1: Comparison of demographic and renal parameters between cases and controls

	Control (n=40) Mean± SD/(%)	Case (n=40) Mean± SD	p value
Age (years)	47.68 ±8.65	50.63 ± 14.45	0.272
Sex (Male:Female ratio)	19: 21	21: 19	0.823
S.Urea (mg/dL)	37.30 ± 4.82	151.23 ± 71.85	<0.001
S.Creatinine (mg/dL)	0.84 ± 0.15	4.11 ± 3.00	<0.001
S.Uric Acid (mg/dL)	4.35 ± 0.85	9.06 ± 1.86	<0.001
S.Calcium (mg/dL)	9.33 ± 0.66	7.11 ± 0.47	<0.001
S.Phosphate(mg/dL)	3.47 ± 0.71	6.70 ± 1.32	<0.001
S.ALP (U/L)	55.7 ± 12.63	141.00 ± 54.53	<0.001
eGFR (ml/min)	93.3±5.5	24.03±14.79	<0.001
Cystatin C (mg/L)	0.69±0.17	2.72±0.83	<0.001
Creatinine clearance (ml/min)	21.79±13.6	30.17±15.12	<0.001

Table 2: Distribution of eGFR, serum cystatin c, serum creatinine, creatinine clearance in various stages of CKD (staging according to eGFR)

	Control (n=40)	Stage III (n=13)	Stage IV (n=13)	Stage V (n=14)
eGFR (ml/min)	93.32 ± 5.50	41.45 ± 7.22**	23.92 ± 4.30**	7.96± 3.14**
Cystatin C (mg/L)	0.68 ± 0.17	2.31 ± 0.97**	2.80 ± 0.55*	3.01 ± 0.81**
S. Creatinine (mg/dL)	0.84± 0.15	1.70 ± 0.19**	2.72 ± 0.58*	7.66 ± 2.33**
Creatinine Clearance (ml/min)	121.79 ± 13.6	41.96 ± 8.30**	36.73 ± 6.25*	13.14 ± 9.60**

** p Value <0.05 (in comparison to previous stage)*
*** p Value <0.001(in comparison to previous stage)*

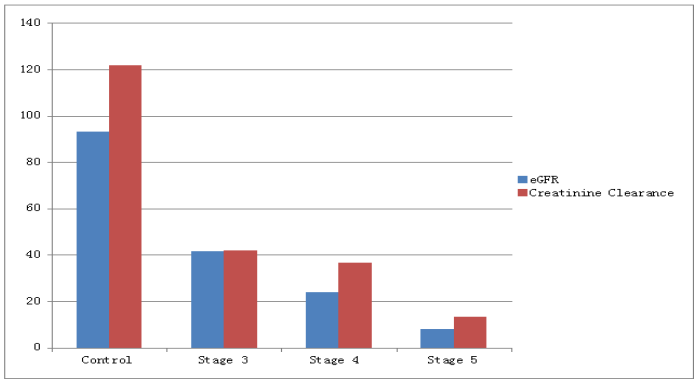

Fig-1: Graph showing stagewise decrease in eGFR and Creatinine Clearance in CKD patients.

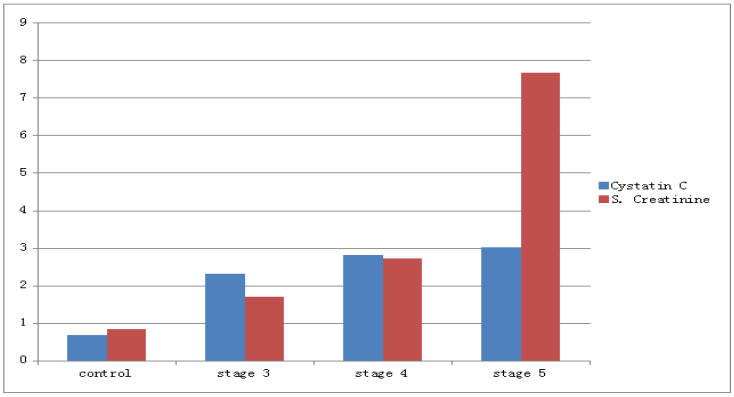

Fig-2: Graph showing stagewise increase in cystatin C and serum creatinine in CKD patients

Pearson correlation coefficient calculation revealed that Serum Cystatin C (r= - 0.877; CI: 1.44 to 1.96; p=0.000) was found to be more significantly inverse correlated with eGFR than Serum Creatinine (r= - 0.777; CI: 1.88 to 3.06; p=0.000).

Serum cystatin C was significantly correlated with eGFR (r= -0.877; p<0.001), creatinine clearance (r= -0.864; p<0.001) and serum creatinine (r= 0.665; p<0.001).

Table 3: Correlation of serum cystatin c with eGFR, serum creatinine, creatinine clearance

	Cystatin C (n = 80)	
	r value	**p Value**
eGFR	- 0.877	<0.001
S. Creatinine	0.665	<0.001
Creatinine Clearance	- 0.864	<0.001

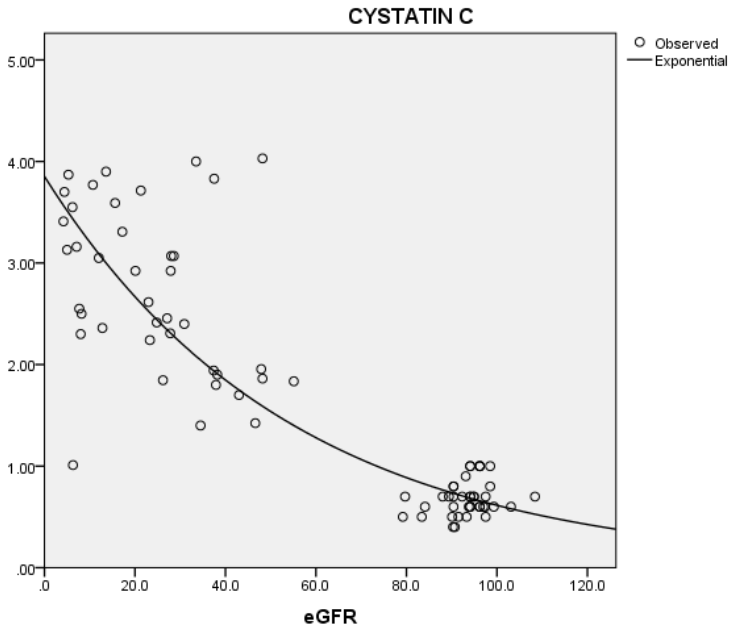

Fig-3: Graph showing exponential correlation between cystatin C and eGFR in different stages of CKD (r = 0.877; p<0.001)

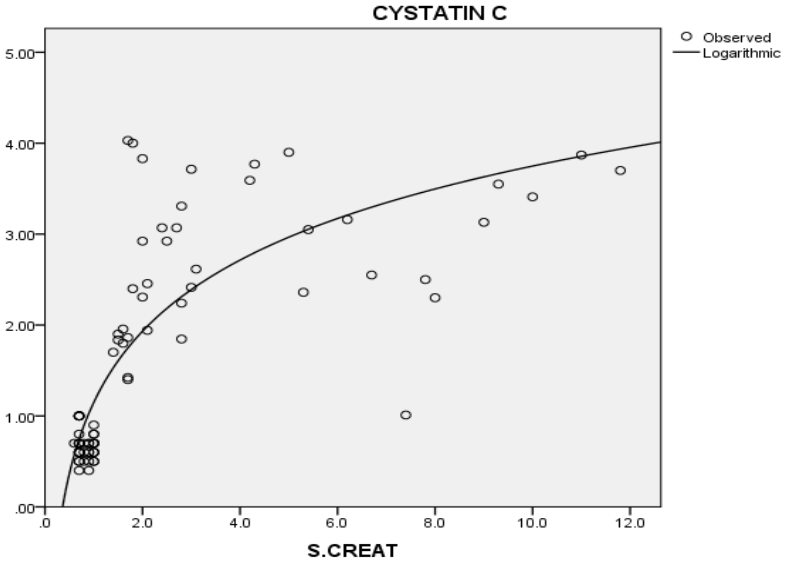

Fig-4: Graph showing logarithmiccorrelation between serum Cystatin C and serum creatinine in different stages of CKD (r=0.665; p<0.001)

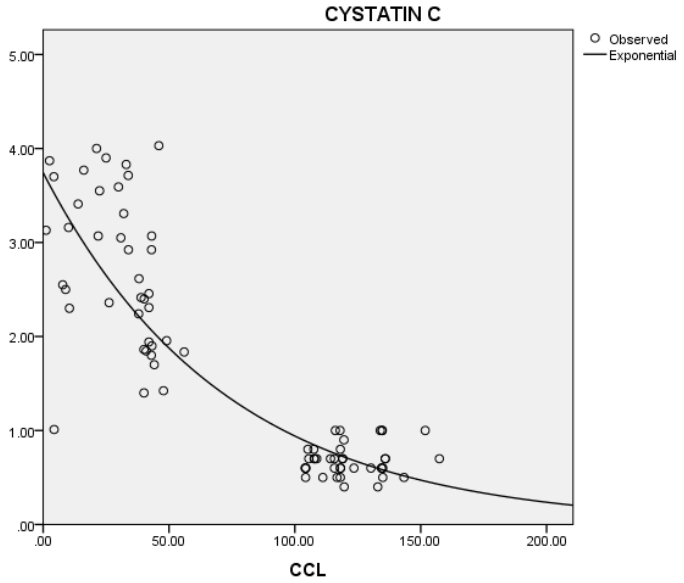

Fig-5: Graph showing exponential correlation between serum cystatin C and Creatinine Clearance in different stages of CKD (r=-0.864;p<0.001)

Creatinine is the most widely used biomarker of kidney function. It is inaccurate at detecting mild renal impairment, and levels can vary with muscle mass and age.The formulas such as the Cockcroft and Gault formula and the MDRD (Modification of Diet in Renal Disease study) formula try to adjust for these variables.[5]

Cystatin C, a non-glycosylated 13 kDa protein, has the potential to improve estimates of GFR, because it is thought to be less influenced by muscle mass or diet.Cystatin C is unique among cystatins as it seems to be produced by all human nucleated cells. The structure of the cystatin C gene is compatible with a stable production rate of Cystatin C by most nucleated cells. The low molecular weight of cystatin C in combination with its stable production rate strongly indicates that the blood serum concentration of this protein is mainly determined by the glomerular filtration rate of the individual. Several other low molecular weight proteins like β-2 microglobulin, Retinol Binding Protein (RBP), complement factor D, have been investigated for their utility in monitoring GFR but none have proven useful to the influence of non renal factors on their circulating concentrations.[6]In patients with impaired renal function receiving corticosteroids, β-2 microglobulin concentration is decreased in a dose dependent manner reflecting the antilymphoproliferative effect of corticosteroids on mononuclear cells which are the principle source of β-2 microglobulin and this limits the use of β-2 microglobulin as a GFR marker[10].

Among the controls in our study, the mean cystatin C was 12.5% higher in males (0.72 ± 0.20 mg/L) as compared to females (0.64 ± 0.12 mg/L). Studies with Northern-blot experiments have revealed that the cystatin C gene is expressed in every human tissue examined, including kidney, liver, pancreas, intestine, stomach, antrum, lung and placenta. The highest cystatin C expression was seen in seminal vesicles[11].Hojs R et al. had shown earlier that cystatin C were 9% lower for women than men[12].The normal range Serum cystatin C reference values differ in many populations with sex and age across different studies. The average reference interval is 0.52-0.90 mg/L (mean 0.71 mg/L) in adult females while 0.56-0.98 mg/L (mean 0.77 mg/L) in adult male[13].

Our study evaluates the use of cystatin C as a marker for chronic kidney disease and its progression. Cystatin C and serum creatinine were found to be significantly high in CKD patients as compared to controls ($p < 0.001$ for all markers) while eGFR and creatinine clearance were significantly decreased in patients of CKD as compared to controls ($p<0.001$).

In the earlier research, concentrations of serum creatinine and cystatin C increased progressively with decreasing GFR and their diagnostic performance for the detection of even minor deterioration of renal function (GFR <90 mL min^{-1} $(1.73\ m^2)^{-1}$) was similar. Patients experienced progression of CKD, defined as doubling of baseline creatinine and/or terminal renal failure during prospective follow-up. It was concluded that serum creatinine and cystatin C for detecting even minor degrees of deterioration of renal function is good and these markers provide reliable risk prediction for progression of kidney disease in patient with CKD[14].

In present study, serum cystatin C increased with stage-wise progression of CKD with mean level of 2.31 ± 0.97mg/L in stage III, 2.80 ± 0.55 mg/L in stage IV, 3.01 ± 0.81 mg/L in stage V in comparison to controls (0.68±0.17 mg/L). Serum creatinine was also

increased with stage-wise progression in CKD with mean level of 1.7 ± 0.19 mg/dL in stage III, 2.72± 0.58 mg/dL in stage IV, 7.66 ± 2.33 mg/dL in stage V in comparison to controls (0.84± 0.15 mg/dL). Thus, the levels of both serum cystatin C and serum creatinine were significantly increased in each successive stage of CKD (stage III, p <0.001 and <0.001; stage IV, p = 0.013 and 0.05; and stage V, p = 0.04 and <0.001 for serum cystatin C and serum creatinine respectively in comparison to their previous stage).

This was similar to earlier research by Zati Iwani et al in 2013, which illustrated that serum cystatin C increased with the progression of CKD, and it was significantly higher in the subjects with mild to moderate eGFR (stages II and III)[15].

In addition to this we also found that eGFR was decreased significantly with progression of CKD for each successive stage i.e. stage III, IV and V. Similarly, creatinine clearance was also significantly reduced with progression of CKD stage. Lastly, in each successive stage both cystatin C and serum creatinine were significantly increased. These findings were in congruence with NKF-KDOQI guidelines (National kidney foundation Kidney Dialysis Outcomes Quality Initiative) classification and staging of CKD[4].

In our study, serum cystatin C did show highly significant negative correlation with eGFR (r = -0.877), creatinine clearance (r = -0.864). Cystatin C inversely related with eGFR and creatinine clearance. Serum cystatin C (r = -0.877) had more significant inverse correlated with eGFR than serum creatinine (r = -0.777).Dharnnidharka VR et al calculated overall correlation coefficient for the reciprocal of serum cystatin C (r = 0.816) was superior to that of the reciprocal of serum creatinine (r = 0.742) and thus concluded that serum cystatin C is clearly superior to serum creatinine as a marker of GFR[16]. Newman et al in 1995 proved diagnostic sensitivity of cystatin C for abnormal GFR to be significantly (p < 0.05) more sensitive than creatinine (71.4 vs. 52.4%)[17]. Roos et al in 2007 reported a systematic review by comparing the diagnostic accuracy of cystatin C with serum creatinine which included studies that assessed accuracy of cystatin C for all grades of renal function[18].

Certain longitudinal studies on cystatin C predominantly support our finding that serum cystatin C reflects GFR changes more rapidly compared to serum creatinine[19-21]. One explanation may be that cystatin C, unlike creatinine, resembles more closely an ideal endogenous marker of glomerular filtrationexcept for a few, negligible exceptions[22-24].This is in contrast to the numerous nonrenal factors that influence the generation of creatinine, its tubular secretion, and backleak, which may result in inaccurate reflection of GFR by creatinine[25].Another potential explanation emerges from recent observations that cystatin C and creatinine differ in regard to their glomerular filtration characteristics during pregnancy and diabetic nephropathy[26,27]. It remains speculative whether this phenomenon occurs also in CKD but this still demands to be well described.

Cystatin C has been identified as a superior marker to creatinine in chronic renal insufficiency with small variability. Serum cystatin C measurement is highly accurate and precise. The commercially available immunoturbidimetric assay provides rapid, automated measurement of cystatin C and requires few minutes until results are available. Additionally, it has been well established earlier that preanalytic factors such as routine clinical storage conditions, freezing and thawing cycles, or interfering substances, such as bilirubin or triglycerides, do not affect cystatin C measurement[17].

Thus, use of cystatin C for staging of CKD may be more accurate in comparision to using eGFR, which is a calculated parameter and require adjustment of variables which can significantly alter serum creatinine. Larger studies are required to evaluate use of cystatin C or both serum cystatin C and serum creatinine more specifically as suggested by recent studies as by Stevens et al, an equation that used both serum creatinine and cystatin C with age, sex, and race was better than the equations that use only one of these markers[28].

Besides use in CKD, Cystatin C has also been linked with other diseases. It has been used to evaluate ARF where no other factor was identified to modify serum cystatin C levels, which enhances its usefulness as detection marker. Neither the etiology of ARF nor urine volume demonstrated any effect on the predictive value of serum cystatin C in ARF[29].

REFERENCES

1. Grassmann A, Gioberge S, Moeller S, Brown G; ESRD patients in 2004: global overview of patient numbers, treatment modalities and associated trends. Nephrology Dialysis Transplantation, 2005; 20(12):2587-2593.
2. Joly D; Chronic kidney disease what is it? Rev Prat, 2012; 62:34-7.
3. Palmer BF; Disturbances in renal autoregulation and the susceptibility to hypertension induced chronic kidney disease. Am J Med Sci, 2004; 328:330-43.
4. National Kidney Foundation; KDOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis, 2002;39:1-266.
5. King AJ, Levey AS; Dietary protein and renal function. J Am Soc Nephrol 1993;3:1723–37.
6. Stevens LA, Coresh J, Greene T, Levey AS; Assessing kidney function--measured and

estimated glomerular filtration rate. N Engl J Med. 2006 ; 8(354):2473-83.
7. Lamb EJ, Price CP; Kidney function tests. In: TIETZ Textbook of clinical chemistry and molecular diagnostics.Fifth Edition.St.Louis, Missouri: Elsevier Publication; 2012; 680
8. Sonntag O, Scholer A; Drug interference in clinical chemistry: recommendation of drugs and their concentrations to be used in drug interference studies. Ann. Clin. Biochem, 2001;38:376-85
9. Bargman JM, Skorecki K; Chronic kidney disease. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. Harrison's Principles of Internal Medicine. 18th ed. McGraw Hill Medical Publishers; 2011; 2309
10. Bökenkamp A, Van Wijk JA, Lentze MJ, Stoffel-Wagner B; Effect of corticosteroid therapy on serum cystatin C and β2-microglobulin concentrations. Clinical chemistry, 2002; 48(7):1123-1126.
11. Shlipak MG, Sarnak MJ, Katz R; Cystatin C and the risk of death and cardiovascular events among elderly persons. N Engl J Med, 2005; 352: 2049-60.
12. Hojs R, Bevc S, Ekart R, Gorenjak M, Puklavec L; Serum cystatin C-based equation compared to serum creatinine-based equations for estimation of glomerular filtration rate in patients with chronic kidney disease. Clinical nephrology, 2008; 70(1):10-17.
13. Croda TMT, Soto MXJ, Hernández CPA, Juárez AE; Adult cystatin C reference intervals determined by nephelometric immunoassay. Clin Biochem, 2007; 40:1084–87.
14. Katharina-SS, Barbara K, Eberhard R, Martin H ,Florian K,Arnold von E; Serum Creatinine, Cystatin C, and {beta}-Trace Protein in Diagnostic Staging and Predicting Progression of Primary Nondiabetic Chronic Kidney Disease. Clin. Chem, 2010; 56:740-49.
15. Zati Iwani AK, Ruziana Mona WZ, Nor Idayu R, Wan Nazaimoon WM; The usefulness of cystatin C as a marker for chronic kidney disease.Universal J Cln Med, 2013;28:33.
16. Dharnidharka VR, Kwon C, Stevens G; Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta analysis. Am J Kidney Dis, 2002;40:221-26.
17. Newman DJ, Thakkar H, Edwards RG, Wilkie M, White T; Serum cystatin C measured by automated immunoassay: a more sensitive marker of changes in GFR than serum creatinine. Kidney Int, 1995;47:312–18.
18. Roos JF, Doust J, Tett SE, Kilpatrick CM; Diagnostic accuracy of cystatin C compared to serum creatinine for the estimation of renal dysfunction in adults and children - a meta-analysis. Clin Biochem, 2007;40:383–91.
19. Le Bricon T, Thervet E, Benlakehal M, Bousquet B, Legendre C, Erlich D; Changes in plasma cystatin C after renal transplantation and acute rejection in adults. Clinical chemistry, 1999; 45(12): 2243-2249.
20. Christensson A, Ekberg J, Grubb A, Ekberg H, Lindström V, Lilja H; Serum cystatin C is a more sensitive and more accurate marker of glomerular filtration rate than enzymatic measurements of creatinine in renal transplantation. Nephron. Physiology, 2002; 94(2):19-27.
21. Julier K, da Silva R, Garcia C, Bestmann L, Frascarolo P, Zollinger A, Zaugg M; Preconditioning by sevoflurane decreases biochemical markers for myocardial and renal dysfunction in coronary artery bypass graft surgery: a double-blinded, placebo-controlled, multicenter study. Anesthesiology-Philadelphia Then Hagerstown, 2003; 98(6):1315-1327.
22. Fricker M, Wiesli P, Brändle M, Schwegler B, Schmid C; Impact of thyroid dysfunction on serum cystatin C. Kidney international, 2003; 63(5), 1944-1947.
23. Jayagopal V, Keevil BG, Atkin SL, Jennings PE, Kilpatrick ES; Paradoxical changes in cystatin C and serum creatinine in patients with hypo-and hyperthyroidism. Clinical chemistry, 2003; 49(4): 680-681.
24. Shi GP, Sukhova GK, Grubb A, Ducharme A, Rhode LH, Lee RT, Chapman HA; Cystatin C deficiency in human atherosclerosis and aortic aneurysms. Journal of Clinical Investigation, 1999; 104(9):1191.
25. Bellomo R, Kellum JA, Ronco C; Defining acute renal: Physiological principles. Intensive Care Med, 2004; 30: 33–37.
26. Oberbauer R, Nenov V, Weidekamm C, Haas M, Szekeres T, Mayer G; Reduction in mean glomerular pore size coincides with the development of large shunt pores in patients with diabetic nephropathy. Experimental nephrology, 2000; 9(1):49-53.
27. Strevens H, Wide-Swennson D, Torffvit O, Grubb A; Serum cystatin C for assessment of glomerular filtration rate in pregnant and non-pregnant women. Indications of altered filtration process in pregnancy. Scand J Clin Lab Invest ,2002; 62: 141–48.
28. Stevens LA, Coresh J, Schmid CH; Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. Am J Kidney Dis, 2008;51:395–406.
29. Herget-Rosenthal S, Marggraf G, Hüsing J, Göring F, Pietruck F, Janssen O, Kribben A; Early detection of acute renal failure by serum cystatin C. Kidney international, 2004; 66(3):1115-1122.