Serum cystatin C as an endogenous marker of kidney function in elderly with chronic kidney failure

H. Resic [1] and A. Mataradzija [2]

[1]Center for Haemodialysis, [2]Nephrology Institute, Clinical Center, Sarajevo, Bosnia and Herzegovina

Abstract

Concentration of serum cystatine C primarly dependes on the glomerular filtration rate (GFR), and cystatin C concentration in serum can be used as an endogenous marker of kidney function. Use of cystatin C in the assesment of GFR in elderely, childern and pre - dialysis patients could be usful. The aim of the study was to evaluate the use of cystatin C as a renal marker of the glomerular filtration rate (GFR) in patients with various degrees of kidney failure.
The study icluded the total of 104 patients (various etiology of kidney disease) with different degrees of kidney failure. All of them were on conservative tretmant and 10 healtly patients will comprised the control group. Mean values of cystatin C and creatinine in serum hes been measured and compared to endogeneus cretainine clearense.
There were 104 patients testid in total with various etiology of kidney disease. Mean age of patients receiving conservative treatment was 68, 4 ± 5, 06 years and controls 69 ± 3, 66 years. Significant correlation have established between creatinine clearence and creatinine r = 0, 663 p < 0, 001, and between creatinine clearence and cystatin C r = 0, 765, p < 0, 001 in patients will different degrees of chronic kidney failure (CKF). Correlation between creatinine clearence and cystatin C was significantly better than between serum creatinine p < 0, 05.
According to results from our study the level of cystatin C in serum is better marker of kidney function than the level of creatinine in serum.
Hering in mind that this is faster and cheaper method it could find wider application in every day clinical practtise, especially in elderly where is often impossible to accurately collect 24 - hour - urine (inconontinence)

Key words: serum cystatin C, chronic kidney failure, clearence creatinin

Introduction

In clinical practice the glomerular filtration rate (GFR) is assessed with various methods. The most accurate method is the radioisotopic measurement of inulin clearance (1). However, in everyday clinical practice radioisotopic methods are expensive, time-consuming and they expose patients to radiation, the reason of their substitution with cheaper and quicker methods such as the measurement of creatinine and creatinine clearance levels in serum (2). As of recent many studies have evaluated the use of cystatin C in the assessment of GFR in elderly and children, especially in group of pre-dialysis patients because the cystatin C value does not depend on age, gender of muscle weight.
Cystatin C is a cystatin protease inhibitor and is a part of intracellular protein catabolism. It is non-glycolysed, low-molecular protein (133kD) which comprises 120 amino acids. Protein is created in each nucleus, freely passes glomerular membrane and almost completely is reabsorbed and catabolised in proximal tubular cells (3). Due to these facts concentration of serum cystatine C primarily depends on the glomerular filtration rate (GFR), and cystatin C concentration in serum can be used as an endogenous marker of kidney function (4). Many authors, (Schuck O, Teplan V *et al*., 2003) agree that cystatin C, as a new endogenous marker, can have advantages in early recognition of damaged kidney function (5-7).
The aim of this study was to compare both serum markers: creatinine and cystatin C with creatinine clearance in elderly, and to evaluate the use of cystain C as a renal marker of the glomerular filtration rate (GFS) in patients with various degrees of kidney failure.

Patients and methods

The study included the total of 104 patients (various etiology of kidney disease), with different degrees of kidney failure. All of them were on conservative treatment (I degree of creatinine clearance – mean value 72.48 ± 17.62 ml/min – 42 patients, II degree – creatinine clearance 34.53 ± 9.92 ml/min – 44 patients, III degree 11.63 ± 3.71ml/min – 18 patients) and 10 healthy patients which comprised the control group.
Mean values of cystatin C and creatinine in serum had been measured and compared to endogenous creatinine clearance.
Dade Behring nephelometer has been used for cystatin C measurement by immunonephelometric method, urea with uresis method, creatinine with kinetic method on the same machine, and creatinine clearance had been calculated using formula: urine creatinine x diuresis / serum creatinine x f (f = 84.400).
Patients were divided according to the values of creatinine clearance in three groups. During the study they were under the standard treatment of a kidney disease: antihypertensives, drugs lowering fat, vitamins, and Fe preparations.
Manuel statistical data processing has been used: percentages, arithmetic mean, standard deviation, Chi-square test, t-test, differentiation and correlation coefficients.

Results

There were 104 patients tested in total with various etiology of kidney disease: 46 patients – Chronic Pyelonephritis (CP);

Correspodence to: H. Resic, Center for Haemodialysis, Clinical Center, Sarajevo, Bosnia and Herzegovina

25 patients – Obstructive nephropathy (ON); 27 patients – Polycystic kidneys (PK); 6 patients – Other etiology: Nephrectomy, unknown etiology (Other).

Discussion

Accurate measurement of kidney function on daily basis in clinical practice is essential in order to be able to continually follow up differential treatments aimed to maintain or improve kidney function, and in time set to begin with kidney function replacement therapy in pre-dialysis patients (1). Accurate methods such as inulin clearance, radioisotopic contrast techniques are often expensive, time-consuming and inaccessible, therefore in routine clinical practice more suitable are measurement of creatinine concentration in serum and creatinine clearance (2). These methods have their disadvantages in pre-dialysis patients and in elderly because they are not absolute indicators of the GFR (4,5). The creatinine level is actually lower because a part of creatinine is eliminated by intestinal degradation, then in uremia with lower ingestion of proteins occur muscle degradation, which in turn lowers the production of creatinine and its level in serum. Many substances such as keto acids, glucose, and bilirubin can interfere with measurement of creatinine in serum (6). Thus the serum level of creatinine is lower than it is expected according to the decrease of the GFR. On the other hand, the creatinine clearance measurement depends on muscle weight of a patient, on the feasibility of adequate 24-hour urine collection and tubular secretion which makes the method deficient (7).

As of recent cystatin C has proven to be not only better, but ideal, endogenous marker of kidney function since it is a constant value that does not depend on gender, patient's muscle weight, accompanying infections or malignancies (3-6). It is produced in every nucleus as a constant value, freely passes glomerular membrane and it is reabsorbed and completely metabolized in proximal tubules. Its plasma level linearly correlates with the GFR, i.e. its plasma level increases proportionally to the decrease of the GFR which makes it more sensitive marker than creatinine (6-10). Besides, it does not take long time to prepare 24-hour urine for the cystatin C measurement. It is believed to show the kidney function damage much earlier than creatinine.

Serum cystatin C has been measured with immunoassay technique which is fast, accurate and suitable for use in clinical practice (3,10-12). There are not any drugs yet known to affect the serum level of cystatin C in clinical settings, as the available literature suggests (11-14).

In our study we have established significant correlation between creatinine clearance and creatinine $r = - 0,663$, $p<0.001$, and between creatinine clearance and cystatin C $r = - 0,765$, $p<0,001$ in patients with different degrees of chronic kidney failure (CKF). Correlation between creatinine clearance and cystatin C was significantly better than between creatinine clearance and serum creatinine $p<0,05$.

Fig 1. Distribution of patients according to age and gender

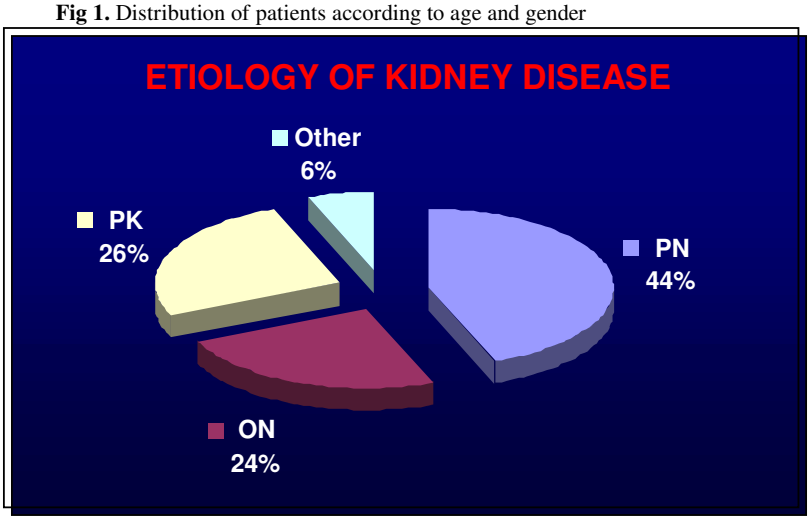

Table 1. Distribution of patients according to age and gender

	Gender	Number of patients (n)	Mean age (x) years	Standard deviation (SD)
Conservative treatment				
I Degree	M	22	69,7	5,72
	F	22	67,4	5,05
Total		**44**	**68,5**	**5,55**
II Degree	M	22	69,8	5,04
	F	20	66,3	3,96
Total		**42**	**68,1**	**4,86**
III Degree	M	8	66,1	2,47
	F	10	70,3	4,98
Total		**18**	**68,4**	**4,67**
TOTAL	M	52	69,2	5,25
	F	52	67,5	4,85
Total		**104**	**68,4**	**5,06**
Control group	M	4	59,8	3,42
	F	6	58,5	3,73
Total		**10**	**69**	**3,66**

Mean age of patients receiving conservative treatment was 68.4 ± 5.06 years, and controls 69 ± 3.66 years

Fig 2a Control group – distribution according to gender

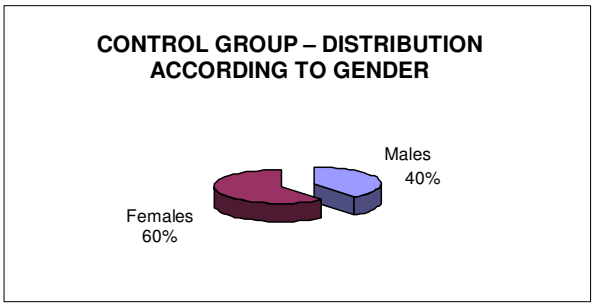

Fig 2b Conservative treatment according to gender

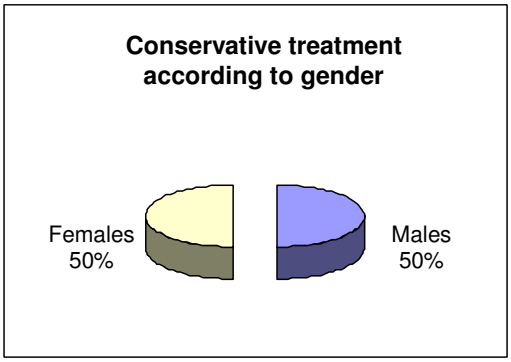

Table 2. Mean creatinine value (umol/l) in various groups of patients

	Number of patients (n)	Arithmetic mean x	Standard deviation (SD)
CONSERVATIVE TREATMENT			
I DEGREE	42	108,07	27,79
II DEGREE	44	164,32	49,45
III DEGREE	18	437	113,06
TOTAL	**104**	**188,8**	**130,79**
CONTROL GROUP	10	70,6	8,27

Test results of significant differencies in mean creatinine values, according to the type of treatment compared to control group

	I DEGREE	II DEGREE	III DEGREE
CONTROL GROUP	7,459	11,862	13,683
SIGNIFICANCE	p<0,001	p<0,001	p<0,001

Fig 3. Mean creatinine in serum of studied patients

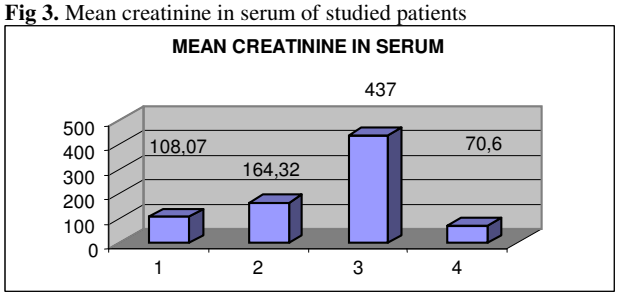

Table 3. Mean cystatin C values (mg/l)

	Number of patients (n)	Arithmetic mean x	Standard deviation SD
CONSERVATIVE TREATMENT			
I DEGREE	42	1,015	0,279
II DEGREE	44	1,898	0,677
III DEGREE	18	3,931	0,897
TOTAL	**104**	**1,893**	**1,181**
CONTROL GROUP	10	0,648	0,131

Test results of significant differencies in mean creatinine values, according to the type of treatment compared to control group

	I DEGREE	II DEGREE	III DEGREE
CONTROL GROUP	5,495	11,351	15,239
SIGNIFICANCE	p<0,001	p<0,001	p<0,001

Fig 4. Mean cystatin C values

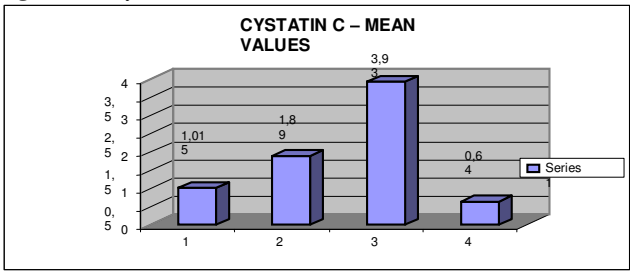

Table 4. Creatinine clearance (ml/min)

	Number of patients (n)	Arithmetic mean x	Standard deviation SD
CONSERVATIVE TREATMENT			
I DEGREE	42	72,48	17,62
II DEGREE	44	34,53	7,92
III DEGREE	18	11,63	3,71
TOTAL	**104**	**45,89**	**26,41**
CONTROL GROUP	10	70,6	10,77

Test results of significant differencies

	I DEGREE	II DEGREE	III DEGREE
CONTROL GROUP	0.432	9.995	16.772
SIGNIFICANCE	NS	p<0,001	p<0,0001

Fig 5. Mean values of creatinine clearance

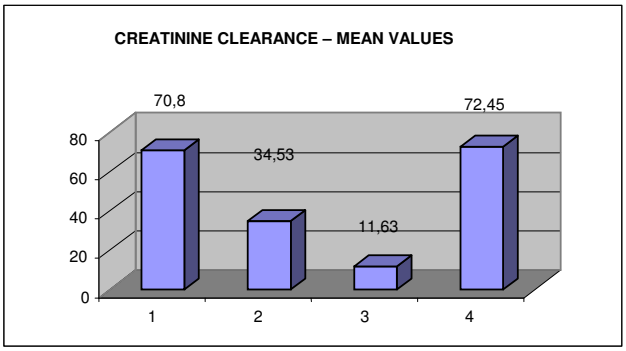

Table 5. Coefficients of linear correlation between creatinine and creatinine clearance

	COEFIFCENT OF LINEAR CORREALATION (r)	SIGNIFICANCE
CONSERVATIVE TREATMENT		
I DEGREE	r= -0,302	p<0,05
II DEGREE	r= -0 ,452	p<0,01
III DEGREE	r= -0,439	NS
TOTAL (n=104)	**r= -0,663**	**p<0,001**

Table 6. Coefficients of linear correlation between creatinine clearance and cystatin C in studied and control groups

	COEFFICENT OF LINEAR CORREALATION (r)	SIGNIFICANCE
CONSERVATIVE TREATMENT		
I DEGREE	r= -0,391	p<0,001
II DEGREE	r= -0,599	p<0,001
III DEGREE	r= - 0,327	NS
TOTAL (n=104)	**r= -0,765**	**sign. p<0,001**

Conclusions

According to results from our study the level of cystatin C in serum is better marker of kidney function than the level of creatinine in serum. Having in mind that this is faster and cheaper method it could find wider application in everyday clinical practice, especially in elderly (or in children) where it is often impossible to accurately collect 24-hour urine (incontinence).

References

1. Perrone RD, Madias NE, Levey AS. Serum creatinine as an index of renal function: new insights into old concepts. *Clin Chem* 1992; 38: 1933-53
2. Swan SK. The search continues – an ideal marker of GFR. *Clin Chem* 1997; 43: 913-4
3. Abrahamson M, Olafsson I, Palsdottir A, Ulvsbäck M, Lundwall A, Jensson O *et al*. Structure and expression of the human cystatin C gene. *Biochem J* 1990; 268: 287-94
4. Kyhse-Anderson J, Schmidt C, Nordin G, Andersson B, Nilsson-Ehle P, Lindström V *et al*. Serum cystatin C, determined by a rapid, automated particle-enhanced turbidimetric method, is a better marker than serum creatinine for glomerular filtration rate. *Clin Chem* 1994; 40:1921-6
5. Finney H, Newman DJ, Gruber W, Merle P, Price CP. Initial evaluation of cystatin C measurement by particle-enhanced immunonephelometry on the Behring nephelometer systems (BNA, BN II). *Clin Chem* 1997; 43: 1016-22
6. Filler G, Witt I, Priem F, Ehrich JHH, Jung K. Are cyststin C and β2-microglobulinbetter markers than serum creatinine for prediction of normal glomerular filtration rate in pediatric subjects? *Clin Chem* 1997; 43: 1077-8
7. Newman DJ, Thakkar H, Edwards RG, Wilkie M, White T, Grubb AO *et al*. Serum cystatin C measured by automated immunoassay: a more sensitive marker of changes in GFR than serum creatinine. *Kidney Int* 1995; 47: 312-8
8. Weber JA, van Zanten AP. Interferences in current methods for measurements of creatinine. *Clin Chem* 1991; 37: 695-700
9. Shemes O, Golbetz H, Kriss JP, Myers BD. Limitations of creatinine as a filtration marker in glomerulopathic patients. *Kidney Int* 1985; 28: 830-8
10. Giovanetti S, Barsotti G. In defense of creatinine clearance. *Nephron* 1991; 59: 11-4
11. Rehling M, Rabol A. Measurement of glomerular filtration rate in adults: accuracy of five single-sample plasma clearance methods. *Clin Physiol* 1989; 9: 171-82
12. Tian S, Kusano E, Ohara T, Tabei K, ItohY, Kawai T, *et al.* Cystatin C measurement and its practical use in patients with various disease. *Clin Nephrol* 1997; 48: 104-8
13. Erlandsen EJ, Randers E, Kristensen JH. Reference intervals for serum cystatin C and serum creatinine in adults. *Clin Chem Lab Med* 1998; 36: 393-7
14. Norlund L, Fex G, Lanke J, von Schenck H, Nilsson J-E, Leksell H *et al*. Reference intervals for the glomerular filtration rate and cell-proliferation markers: serum cystatin C and serum β2-microglobulin/cystatin C - ratio. *Sca J Clin Lab Invest* 1997; 57: 463-70