

Original Article

A New Biochemical Marker For Determination of Glomerular Filtration Rate in Pediatric Renal Diseases

Mervat Hesham, Zeinab Dosouky, Doaa Tawfeek
and Somayya Abd-Alla*

Departments of Pediatrics and Biochemistry, Faculty of Medicine, Zagazig University, Egypt*

ABSTRACT

Background: The estimation of the glomerular filtration rate (GFR) is an important part of the clinical evaluation of renal function. In clinical practice serum creatinine and creatinine clearance are the most commonly used methods for estimating GFR, but their use as a markers of GFR is connected with several problems. Cystatin C is a basic protein produced by nucleated cells. The low molecular mass and the basic nature of cystatin C, in combination with its stable production rate, suggested that the glomerular filtration rate (GFR) is the major determinant of cystatin C concentration in the peripheral circulation.

Objectives: The aim of the study was to evaluate serum cystatin C as a new marker of the glomerular filtration rate (GFR) in children with various renal diseases in comparison with serum creatinine and β 2-microglobulin, the most commonly used markers of the GFR.

Methods: Fifty subjects were included in this study and were divided into a control group and a patient group. The control group comprised 20 healthy infants and children with normal renal functions. The patient group comprised 30 patients with various renal diseases. The two groups were subjected to full clinical history, thorough clinical examination, routine investigations to confirm the etiology of renal diseases, kidney function tests (serum urea and creatinine levels), serum β 2-microglobulin level, isotope renogram using ^{99m}Tc -DTPA-clearance (for measuring GFR) and estimation of serum cystatin C level by particle-enhanced turbidimetric assay.

Results: The levels of serum creatinine, β 2-microglobulin and serum cystatin C were significantly higher with the reduction of GFR in patients than control group. There was highly significant negative correlation of GFR with serum creatinine, serum β 2-microglobulin and serum cystatin C ($r = -0.69, -0.71, -0.89$ respectively) and a highly significant positive correlation between serum cystatin C and both of serum creatinine and serum β 2-microglobulin ($r = 0.81, 0.67$ respectively). Serum creatinine showed significant positive correlation with age and body mass index but no significant correlation with gender of patients, while no correlation was found between serum cystatin C and serum β 2-microglobulin and age, gender and body mass index. This study showed that serum cystatin C was more sensitive and specific (90.9% and 88.8% respectively) than serum creatinine (54.5% and 75% respectively) and serum β 2-microglobulin (86.7%, 75% respectively) as markers of GFR. Serum cystatin C level started to increase to greater than normal values when GFR value was (90 ml/min/1.73 m²), while serum β 2-microglobulin and serum creatinine levels began to increase when GFR value was (80.1 ml/min/1.73 m² and 76.7 ml/min/1.73 m² respectively).

Conclusions: These data suggest that measurement of serum cystatin C is superior to serum creatinine and serum β 2-microglobulin to detect mild reduction of GFR in children, and therefore may be important in the detection of early renal insufficiency in a variety of renal diseases for which early treatment is critical.

INTRODUCTION

The estimation of the glomerular filtration rate (GFR) is an important part of the clinical evaluation of renal function and of

the management of renal diseases in children.

In clinical practice serum creatinine and creatinine clearance are the most commonly used methods for estimating GFR.

Measurements of creatinine are fast and cheap, but its use as a marker of GFR is connected with several problems⁽¹⁾. The serum creatinine concentration is correlated to the muscle mass, which declines with increasing age and several substances such as ketoacids, glucose, bilirubin and drugs can interfere with the measurements of serum and urine creatinine⁽²⁾. GFR may be halved before the concentration of serum creatinine rises significantly, thus delaying the diagnosis of progressive renal disease⁽³⁾.

The measurement of creatinine clearance eliminates some of the problems with serum creatinine level and also improves the assessment of GFR, but it presents some disadvantages. One of the major problems is related to 24 hours urine collection, which is connected with a high rate of error due to incomplete urine collection especially in children⁽⁴⁾, moreover, true GFR could also be disturbed by the variability of tubular secretion of creatinine, and this factor greatly diminishes the reliability of creatinine clearance⁽⁵⁾.

However, data from several studies demonstrated good agreement between creatinine clearance and "true filtration markers" and reported a close correlation between creatinine clearance and inulin and creatinine clearance and ^{99m}Tc-DTPA at all levels of renal function⁽⁶⁾.

Other measurements using the infusion of external substances such as inulin, radio-nuclides or iohexol have been proposed for determining GFR, but they are difficult to perform, costly, in some cases require

radiation exposure, have difficult and time-consuming methods for analysis and are impractical for routine GFR assessment⁽⁷⁾.

Several low molecular weight proteins as β 2-microglobulin, retinol binding protein and cystatin C have been proposed as replacement for creatinine as a biochemical marker of GFR⁽⁸⁾. β 2-microglobulin is filtered by the glomeruli and reabsorbed by the proximal tubular cells where it is metabolized. Its plasma concentration increases with decreasing renal function⁽⁹⁾.

Cystatin C is a non-glycated 13-kilodalton basic protein produced by nucleated cells. It is freely filtered in the renal glomeruli and reabsorbed and catabolised in the proximal tubules. The low molecular mass and the basic nature of cystatin C, in combination with its stable production rate, suggested that the glomerular filtration rate (GFR) is the major determinant of cystatin C concentration in the peripheral circulation⁽¹⁰⁾.

Moreover, cystatin C is not influenced by renal factors such as inflammation, infections and liver disease or by dietary or constitutional factors that could influence the production rate⁽⁷⁾.

AIM OF THE WORK

This study aimed at determining the diagnostic validity of cystatin C in childhood renal diseases and to elucidate the applicability of it as a new marker of GFR in children with various kidney diseases in comparison with serum creatinine and serum β 2-microglobulin, the most commonly used markers of the GFR.

SUBJECTS AND METHODS

This study was carried out in the Pediatrics and Biochemistry Departments of the Faculty of Medicine, Zagazig University.

Subjects:

Fifty subjects were included in this study. They were divided into the following two groups.

A- Group I (control group):

It comprised 20 healthy infants and children (10 males and 10 females). Their ages ranged from 1.5 to 15 years with a mean \pm SD of 4.04 ± 3.7 years. All control subjects had normal renal functions.

B- Group II (patient group):

It comprised 30 patients (18 males and 12 females) with different renal diseases (6 patients with nephrotic syndrome, 6 with obstructive uropathy, 7 with malignant diseases, 5 with acute glomerulonephritis, 4 with end stage renal disease and 2 with unexplained acute renal failure). Their ages ranged from 0.7 to 15 years with a mean \pm SD of 7.7 ± 5.2 years. They were admitted to our department during a period from January 2001 to November 2001.

Methods:

The above-mentioned groups were subjected to the following:

1. Full clinical history.
2. Thorough clinical examination.
3. Routine investigations for all patients to confirm the etiology of renal disease including blood picture, urine analysis, ESR, ASO, C3 and C4, anti-nuclear antibody (ANA), cholesterol and

Radiologic! investigations (plain X-ray - ultrasonography - I.V.P.).

4. Isotope renogram using ^{99m}Tc -diethylene triamine penta-acetic acid (DTPA) single injection technique for measurement of GFR.
5. Estimation of serum urea⁽¹¹⁾ and creatinine level⁽¹²⁾. Kits were obtained from Randox Laboratories Ltd., U.K.
6. Estimation of serum β 2-microglobulin was assayed by immunometric enzyme immunoassay. Kit was obtained from Orgen Tec Diagnostika GmPh. Mainz, Germany.
7. Estimation of serum cystatin C level by particle enhanced turbidimetric assay as described by Newman et al.⁽¹³⁾. Kit was obtained from DAKO A\ S, Produktionsve, Denmark.

Sampling:

Venous blood samples (2 ml) were withdrawn from all subjects and were incubated at 37 degrees till clot retraction and then were centrifuged at 4000 rpm for 15 minutes and sera were separated and collected in clean disposable epindorf tubes and stored at -20 degrees till time of analysis.

Statistical Analysis:

Data were entered, checked and analyzed using Epi-Info version 6⁽¹⁴⁾. The diagnostic validity of cystatin C, β 2-microglobulin and creatinine for detecting reduced GFR in comparison with ^{99m}Tc -DTPA clearance was evaluated by the receiver operating characteristics (ROC) curve analysis (SPSS for windows, version 8). The reference cut off value for GFR was 90 ml/min/1.73 m².

RESULTS

Table 1: Comparison between group I and group II as regards serum creatinine, serum β 2-microglobulin and serum cystatin C and GFR (measured by ^{99m}Tc -DTPA-clearance method).

	Control No. = 20 Median (Range)	Patients No. = 30 Median (Range)	Kruskal-Wallis	p
Serum creatinine (mg/dl)	0.5 (0.4 - 0.8)	0.8 (0.5 - 11.3)	18.61	0.0001 (HS)*
Serum β2-microglobulin (mg/L)	1.01 (0.7 - 2.5)	3.02 (1 - 10.5)	27.72	0.0001 (HS)*
Serum cystatin C (mg/L)	1.2 (0.14 - 2.156)	3.1 (0.19 - 9.6)	9.54	0.002 (HS)*
GFR by ^{99m}Tc-DTPA clearance method	88.5 (63 - 130)	65.5 (4.5 - 135.6)	9.4	0.002 (HS)*

* HS = Highly Significant

Table 2: Correlation of GFR (measured by ^{99m}Tc -DTPA-clearance) with serum creatinine, Serum β 2-microglobulin and serum cystatin C in-group II (patients group).

Variables	GFR (^{99m}Tc-DTPA-Clearance)		
	r	p	Sig
Serum creatinine	- 0.69	< 0.001	HS*
Serum β2-microglobulin	- 0.71	< 0.001	HS*
Serum cystatin C	- 0.89	< 0.001	HS*

Sig = significance

* HS = Highly significant

Table 3: Correlation between serum cystatin C and both serum β 2-microglobulin and serum creatinine.

Variables	r	p	Sig
Serum cystatin C with serum creatinine	0.81	< 0.001	HS
Serum cystatin C with serum β 2-microglobulin	0.67	< 0.001	HS

Table 4: Correlation between serum creatinine, serum β 2-microglobulin and serum cystatin C and age and body mass index of patients.

Variables	AGE		Body mass index		Sig
	r	p	r	p	
Serum creatinine	0.47	< 0.001	0.46	< 0.01	HS
Serum β 2-microglobulin	0.27	> 0.05	0.31	> 0.05	NS
Serum cystatin C	0.23	> 0.05	0.26	> 0.05	NS

BMI = (weight) / (height)² [kg/m²]

Table 5: Validity of serum creatinine, serum β 2-microglobulin and serum cystatin C as confirmed by ^{99m}Tc-DTPA-clearance.

Variables	Sensitivity %	Specificity %	Negative Predictive Value %	Positive Predictive Value %	Accuracy
Serum creatinine	54.5	75.0	85.7	37.5	60.0
Serum β 2-microglobulin	86.7	75.0	83.9	78.9	82.0
Serum Cystatin C	90.9	88.8	95.2	80.0	93.3

Table 6: GFR values associated with beginning of rise of serum cystatin C, serum β 2-microglobulin and serum creatinine above the mean values for both.

	GFR (ml/min./1.73 m ²) ^{99m} TC-DTPA-Clearance
Serum cystatin C	90
Serum β 2-microglobulin	80.1
Serum creatinine	76.7

Table 6 shows that the GFR value of 90 ml/min/1.73 m² was associated with the beginning of rise of serum cystatin C above the mean value, while the GFR values of 80.1 ml/min/1.73 m² and 76.7 ml/min/1.73 m² were associated with the beginning of rise of serum β 2-microglobulin and serum creatinine above the mean value, respectively.

DISCUSSION

Cystatin C, a cysteine protease inhibitor, is a low molecular weight basic protein produced at a stable rate by all nucleated cells⁽¹⁵⁾. It is freely filtered through the renal glomeruli and primarily catabolised in the proximal tubules⁽¹⁰⁾. There is no known extra-renal route of elimination with clearance from circulation only by glomerular filtration⁽¹⁶⁾.

Several studies including adults and children with different renal diseases with various kidney functions have suggested serum cystatin C to be a better marker of GFR than serum creatinine⁽¹⁷⁾.

So, the aim of this study was to evaluate serum cystatin C as a new marker for GFR in children with various kidney diseases in comparison with serum creatinine and serum β 2-microglobulin. Their variation were analyzed based on ^{99m}Tc-DTPA clearance as a standard marker of GFR.

Our study showed that a decrease in ^{99m}Tc-DTPA clearance was accompanied by an increase in the serum levels of cystatin C, β 2-microglobulin and creatinine in the patient group and this inverse relationship was significant in patients compared to control group.

These data are in agreement with

Donadio et al.⁽⁶⁾ and Randers et al.⁽¹⁸⁾ who reported that serum concentration of cystatin C increased progressively with the reduction of GFR. Correlation of GFR (measured by ^{99m}Tc-DTPA clearance) with serum cystatin C, serum β 2-microglobulin and serum creatinine showed a highly significant negative correlation of GFR with all, but GFR correlated with serum cystatin C ($r = -0.89$) more than serum β 2-microglobulin and creatinine ($r = -0.71$ and -0.69 respectively). These data are in accordance with Elisa et al.⁽¹⁰⁾ and Helin et al.⁽¹⁹⁾ who reported that the correlation between GFR and cystatin C ($r = -0.90$) tended to be stronger than that between GFR and serum creatinine ($r = -0.75$). Also, Tamba et al.⁽²⁰⁾ reported that cystatin C level correlated inversely with creatinine clearance more than β 2-microglobulin. Our results showed a significant positive correlation between serum cystatin C and both serum β 2-microglobulin and creatinine ($r = 0.67$ and 0.81 respectively). The same result was found by Sildova et al.⁽¹⁶⁾. In contrast, Bokenkamp et al.⁽²¹⁾ reported that correlation between cystatin C and creatinine concentrations was poor and suggested that this was due to the age dependency of serum creatinine in contrast to cystatin C.

As regards correlation between serum cystatin C, serum β 2-microglobulin and serum creatinine and age and gender of our patients we found that serum creatinine showed a highly significant positive correlation with age, while serum cystatin C and β 2-microglobulin showed a non-significant correlation with age. This is in accordance with Filler et al.⁽²²⁾

who demonstrated age independency for serum concentrations of both cystatin C and β 2-microglobulin. Also there was no significant difference between mean levels of serum cystatin C and serum creatinine and gender of patients. This is in agreement with Filler et al.⁽²³⁾ who found that creatinine concentration was positively correlated with age, whereas cystatin C was neither age- nor sex-dependent and this age independence makes cystatin C a new tool for detecting impaired GFR in children. Newman et al.⁽¹³⁾ and Norlund et al.⁽²⁴⁾ reported that gender and extra-renal diseases did not alter serum cystatin C concentration. However, Pergande and Jung⁽²⁵⁾ found higher levels in males. In our study serum creatinine showed highly significant positive correlation with the body mass index, while serum cystatin C and β 2-microglobulin showed non-significant correlation with the body mass index. This is in agreement with Bokenkamp et al.⁽²¹⁾ who found that serum concentration of cystatin C was independent of patient age, weight, height, gender and body mass index in contrast to creatinine. Also, Coll et al.⁽⁷⁾ suggested that serum cystatin C was independent of age, sex and muscle mass.

For a screening test, on the one hand, high sensitivity is important, as the test should ideally identify all diseased patients. On the other hand a high negative predictive value is required as the disease should be absent in the case of negative test results. In our study, cystatin C fulfills both criteria with its high sensitivity of 90.9% and high negative predictive value of 95.2%, also it has

a greater specificity (88.8%), positive predictive value (80%) and diagnostic accuracy (93.3%) than serum β 2-microglobulin (75%, 78.9% and 82% respectively) and serum creatinine (75%, 37.5% and 60% respectively).

These data are in accordance with Elisa et al.⁽¹⁰⁾ who showed that serum cystatin C had a greater sensitivity (100%), specificity (97%) and diagnostic accuracy (98%) than serum creatinine (74%, 86% and 88% respectively). Also, Coll et al.⁽⁷⁾ and Hergret et al.⁽²⁶⁾ reported that sensitivity of cystatin C was greater than creatinine (97% and 83% respectively). In contrast, Chantrel et al.⁽²⁷⁾ suggested that serum cystatin C was not more sensitive than serum creatinine for detecting renal failure. However, it could be proposed as a confirmatory test for patients with elevated serum creatinine. Another study done by Donadio et al.⁽⁸⁾ suggested that cystatin C and beta-2 microglobulin had a diagnostic accuracy very similar to that of creatinine. A third study done by Oddoze et al.⁽²⁸⁾ suggested that serum cystatin C was not better than serum creatinine or serum beta-2 microglobulin for estimating GFR in patients with steady state diabetes.

In our study serum cystatin C level started to increase to greater than the mean value (1.39 mg/l) when GFR was 90 ml/min/1.73 m², while serum β 2-microglobulin and serum creatinine began to increase when GFR was 80.1 ml/min/1.73 m² and 76.7 ml/min/1.73 m² respectively. In our study the reference cut off level for GFR was 90 ml/min/1.73 m² on the basis of the non-

parametric approach. This means that serum cystatin C started to increase to greater than the mean value when GFR started to decrease below the reference cut off level. These data suggest that measurement of serum cystatin C is useful to estimate GFR especially to detect mild reductions in GFR and therefore may be important in the detection of early renal insufficiency in a variety of renal diseases for which early treatment is critical.

The same results were found by Coll et al.⁽⁷⁾ where serum cystatin C level started to increase to greater than normal values when GFR was 88 ml/min/1.73 m², whereas serum creatinine level began to increase when GFR was 75 ml/min/1.73 m². Also, Bianchi et al.⁽⁹⁾

reported that with decreasing GFR, the increase of serum β 2-microglobulin occurs before than that of serum creatinine.

Finally we can conclude that serum cystatin C offers a more efficient diagnostic tool than serum β 2-microglobulin and serum creatinine in children with various renal diseases. Also, cystatin C may be useful for the identification of mildly impaired GFR without need to correct for age dependency as has to be done with serum creatinine. So, we recommend the use of serum cystatin C in routine laboratory work to facilitate early identification of the patients with early renal impairment specially in localized areas where there are no radiological facilities.

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