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Serum cystatin C an early indicator of renal function decline in type 2 diabetes

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Abstract: Objectives: evaluation of cystatin C level in the serum as a predictor of early renal impairment in type 2 diabetic patients. Background: the glomerular filtration rate (GFR) is often estimated from plasma creatinine. Several studies have shown that cystatin C (Cys C) can be used as a better marker for the early detection of renal function decline. Methods: patients were classified according to the urine albumin/creatinine ratio (ACR).Plasma samples were obtained from 20 healthy persons and from 40 patients with diabetes mellitus type 2 for determination of the level of creatinine and cystatin C. Results: There were no significant differences in age and sex between the three groups. However, There was a significant positive correlation between cystatin C and age, A/C ratio, HbA1c, FBS, 2HPP, DM duration and serum creatinine, and there was a significant negative correlation between cystatin C and glomerular filtration rate. eGFR was significantly lower in the macroalbuminuric group than in the micro-albuminuric and normo-albuminuric groups, and cystatin C showed the highest sensitivity and specificity in detecting micro and macro-albuminuria and accordingly early renal function decline in diabetic patients. Conclusion: from this study we concluded that serum cystatin C is a useful, practical, and non-invasive tool for early detection of renal impairment in the course of diabetes.

Keywords: Creatinine, Cystatin C, Glomerular Filtration Rate, Diabetes Mellitus

1. Introduction

Diabetes mellitus (DM) is a syndrome of chronic hyperglycaemia due to relative insulin deficiency, resistance, or both. It affects more than 120 million people world-wide, and it is estimated that it will affect 370 million by the year 2030. Diabetes is usually irreversible, its late complications result in reduced life expectancy and major health costs. These include macrovascular disease, leading to an increased prevalence of coronary artery disease, peripheral vascular disease and stroke, and microvascular damage causing diabetic retinopathy and nephropathy [(1)].

Chronic kidney disease (CKD) is a progressive and irreversible loss of renal function. The appearance of proteinuria and elevated serum creatinine, representing a decrease in the glomerular filtration rate (GFR), and finally complete loss of kidney function, that is, end-stage renal disease (2).

Higher proportion of individuals with type 2 diabetes are found to have diabetic nephropathy shortly after the diagnosis of their diabetes, because diabetes is actually present for many years before the diagnosis is made (3).

Glomerular filtration rate (GFR) is considered the best marker of renal function, and serum creatinine is the most commonly used biochemical parameter to estimate GFR in routine practice. However, there are some shortcomings to the use of this parameter. Factors such as gender, age, muscle mass and protein intake can influence serum creatinine, leading to an inaccurate estimation of GFR. Normal serum creatinine may be observed in individuals with significantly impaired GFR(4).

The presence of albuminuria may be less specific for the presence of diabetic nephropathy, about 20–40% of type 2 diabetic patients with microalbuminuria progress to overt nephropathy, and most of patients will have progressed to end stage renal diseasethe first appeared abbreviation need to present at ref (2)(3).

Cystatin C is a small 13–kDa protein that is a member of the cysteine proteinase inhibitor family that is produced at a constant rate by all nucleated cells. Due to its small size it is freely filtered by the glomerulus, and is not secreted but is fully reabsorbed and broken down by the renal tubules. This

means the primary determinate of blood cystatin C levels is the rate at which it is filtered at the glomerulus making it an excellent GFR marker. A recent meta-analysis demonstrated that serum cystatin C is a better marker for GFR than serum creatinine (5).

Cystatin C is an alternative and more sensitive endogenous marker for the estimation of GFR than serum creatinine and serum creatinine based GFR estimations (6).

New immunoassay methods from several different manufacturers measure cystatin C and this has made it more practical and clinically useful to estimate GFR. These methods are automated and results are rapidly available. Standardization of testing by clinical laboratories will be important to derive accurate GFR estimates (7).

2. Patients and Methods

The present study was carried out on 20 healthy persons and 40 patients with type 2 diabetes mellitus, who were collected from outpatient clinic and inpatient of Internal Medicine Department, in El-mogama El-Tebby Hospital in the period between 2012 and 2013.

They were classified into

- Control group:

Consist of 20 healthy persons (14 male and 6 female) were used as the control group. The rest of patients were classified according to urinary albumin/Creatinine ratio (A/C) into:

- Normo-albuminuria:

Consist of 16 patients (12 males 4 females) with normo-albuminuria, urinary (A/C) ≤ 30 mg/g.

- Micro-albuminuria:

Consist of 10 patients (7 malesand3 females space) with micro-albuminuria, urinary (A/C) 30 - 300 mg/g.

- Macro-albuminuria:

Consist of 14 patients (5 malesand9 females space) with macro-albuminuria, urinary (A/C) ≥ 300 mg/g.

The following patients were excluded from this study:

1. Patients have urinary tract infection.
2. Patients have Malignancy.
3. Patients have liver disease.
4. Patients have thyroid gland dysfunctions.
5. Patients have congestive heart failure.

All patients and controls were subjected to the followings wrong spelling:

- Full history taking :

Including age, sex, previous medications and duration of diabetes mellitus.

- Clinical examination:

Stressing on blood pressure, neurological and cardiac examination

- Electrocardiogram
- Abdominal Ultrasound:

It was done for all patients to see any abnormalities in the kidney.

- Laboratory investigations Include:

- Albumin/Creatinine ratio (A/C).
- Fasting and post- prandial blood glucose.
- Complete urine analysis.
- Glycated hemoglobin (HbA1c).
- Complete blood count.
- Blood Urea.
- Serum creatinine: (modified rate Jaffe method).
- Serum cystatin C (mg/dl) by ELISA technique.
- Measurement of glomerular filtration rate (GFR) by:

Modification of Diet in Renal Disease (MDRD):

eGFR= 186 X s.Cr –1.154 (mg/dl) X age–0.203(years).

X 1.212 (if African American).

X 0.742 (if female).

Determination of Serum Cystatin C concentration space:

Principle of the test:

This assay employs the quantitative sandwich enzyme immunoassay (ELISA technique). Surface of wells in microtitration plate is coated with polyclonal anti-human cystatin C specific antibody. Diluted standards, diluted quality controls (QC) and diluted samples were pipetted into the n wells. Any human cystatin C present was captured by immobilized antibody and unbound protein is washed away after the first incubation period. Then, a horseradish peroxidase (HRP) conjugated polyclonal antihuman cystatin C antibody was added to the wells and incubated. This is followed by another washing step, to remove unbound antibody- HRP conjugate. A substrate solution (H_20_2) is added to the wells. The enzymatic reaction yields a blue product that turns yellow when acidic stop solution is added.

The intensity of the wrong spellingmeasured spectrophotochemically at 450 nm is directly proportional to the amount of the human cystatin C bound in the initial step.

Concentrations of unknown samples are then read off the standard curve. It is constructed by plotting the absorbance values against each respective human cystatin C standard level using a four-parameter function.

Quality controls and samples:

High and low quality control and samples were diluted just prior to the assay at the same ratio as standards.

Results were collected, tabulated, statistically analyzed by IBM personal computer and statistical package SPSS version 11. Two types of statistics were done:

Descriptive statistics: e.g. percentage (%), mean (x) and standard deviation (SD).

Analytic statistics:

1. Chi-square test (x2):was used to study association between two qualitative variables.
2. Student t-test: is a test of significance used for comparison between two groups having quantitative variables.
3. Mann-Whitney test (nonparametric test): is a test of significance used or comparison between two groups not normally distributed having quantitative variables.
4. ANOVA (f) test: is a test of significance used for comparison between three or more groups having quantitative variables.
5. Kruskal-Wallis test (nonparametric test):is a test of significance used for comparison between three or

more groups not normally distributed having quantitative variables.

6. Pearson correlation (r): is a test used to measure the association between two quantitative variables.
7. The ROC (receiver operating characteristic) curves: This procedure used to evaluate the performance of classification schemes in which there is one variable of two categories by which subjects are classified. They were constructed by calculating the sensitivities and specificities of the variable. The cutoff value with the highest accuracy was selected as the diagnostic cutoff points.
8. Sensitivity, specificity, positive and negative predictive values and diagnostic accuracy were calculated according to the following formulas:
    1. Sensitivity= a/(a + c)
    2. Specificity= d/(b + d)
    3. Accuracy= (a + d)/(a + b+ c + d)
    4. Negative predictive value (NBV) = d/ (c + d)
    5. Positive predictive value (PPV) = a/ (a + b)

Where a = true positive cases; b = false positive cases; c = false negative cases; d = true negative cases.

1. Pvalue< 0.05 was considered statistically significant.
2. P value> 0.05 was considered statistically non-significant.
3. P value< 0.001 was considered statistically highly significant. short of statistic analysis describtion

3. Results

The present study was carried out on 40 patients with type 2 diabetes mellitus and 20 apparently healthy persons.

They were classified into:

Control group: Consist of 20 apparently healthy persons "14 male and 6 female", their mean age of 51.4±12.4 years, and mean weight of 77.2±10.7 Kg.

The rest of patients (24 male and 16 female) were classified according to urinary albumin/Creatinine ratio (A/C) into:

Normo-albuminuria: Consist of 16 patients "12 males 4 females" with normo-albuminuria, A/C <30mg/g ranged (8-28), their mean age of 51.7±8.7 years, and mean weight of 100.1±28.5 Kg, they were included 10 patients with GFR≥90 ml/min and 6 patients with GFR 89-60 ml/min.

Micro-albuminuria: Consist of 10 patients "7 males 3 females" with micro-albuminuria, A/C 30-299mg/g ranged (50-292), their mean age of 53.9±5.8 years, and mean weight of 90±16.6 Kg, they were included 4 patients with GFR ≥90 ml/min, 4 patients with GFR 89-60 ml/min and 2 patients with GFR <60 ml/min.

Macro-albuminuria: Consist of 14 patients "5 males 9 females" with macro-albuminuria, A/C ≥300mg/g ranged (352-1240), their mean age of 54.1±6 years, and their mean weight of 84.4±24 kg, they were included 4 patients with GFR ≥90 ml/min, 2 patients with GFR 89-60 ml/min and 8 patients with GFR <60 ml/min.

Comparison of mean values of different Sociodemographic characteristics and laboratory results of the studied patients and controls shows a high significant difference between different groups of patients and controls regarding body weight ,HbA1c, FBS, 2HPP, DM duration , A/C ratio ,serum creatinine blood urea , glomerular filtration rate and cystatin C (Table 1).

Table 1. *Comparison of mean values of different Sociodemographic characteristics and Laboratory results of the studied patients and controls.*

		Normo-alb. N=16	Micro-alb. N=10	Macro-alb. N=14	Control N=20	Test of significance	p. value
Age	Range	33-63	42-60	43-62	43-62	F test	0.783
	M ±SD	51.7±8.7	53.9±5.8	54.1±6	51.4±12.4	0.359	
Sex	Male	12(75%)	7(70%)	5(35.7%)	14(70%)	X^2	0.106
	Female	4(25%)	3(30%)	9(64.3%)	6(30%)	6.1	
Weight	Range	61-162	60-112	65-109	60-95	F test	0.017
	M ±SD	100.1±28.5	90±16.6	84.4±24	77.2±10.7	3.7	
FBG	Range	98-180	120-320	128-330	73-116	F test	0.001*
	M ±SD	124.5±24.3	192.2±61.3	226.2±63.6	90.8±10.9	34.3	
2HPP	Range	112-322	198-440	210-494	75 - 182	F test	0.001*
	M ±SD	197.3±51.6	293.2±83.7	368.3±90.2	124.4±23.9	46.6	
HbA1c	Range	5.5 - 10%	6-11%	7.5-13%	4.8 - 6.8%	F test	0.001*
	M ±SD	7.05±1.43	7.7±1.6	9.3±1.8	5.7±0.53	19.9	
DM duration	Range	1-7 years	1-12	9-20	------	K test	0.001*
	M ±SD	2.81±2.06	6.40±3.65	13.14±3.75	------	40.6	
A/C ratio	Range	8-28	50-292	352-1240	8-26	K test	0.001*
	M ±SD	17.87±6.60	215.6±92.7	714.3±114.2	16±5.80	70.48	
Blood Urea	Range	17.6-250	17-132	36.7-250	15-47	K test	0.032*
	M ±SD	62.8±14.8	79.5±12.33	103.3±20.96	28.8±5.66	3.14	
S.creatinine	Range	0.5-2.8	0.5-2.7	0.88-5.5	0.6-1.2	K test	0.001*
	M ±SD	1.46±0.6	1.48±0.7	3.3±1.5	0.9±0.2	24.65	
GFR	Range	58.3-178	36.2-132	20.1-119.9	72-127	K test	0.001*
	M ±SD	91±43.9	71.3±29.8	38.7±27.8	99.1±13.6	15.8	
Cystatin C	Range	0.5-1.40	0.48-1.41	1.07-4.8	0.24-0.92	K test	0.001*
	Mean ±SD	0.7±0.2	0.99±0.35	2.9±1.04	0.6±0.20	57.6	

There was a significant positive correlation between cystatin C and age, A/C ratio, HbA1c, FBS, 2HPP, DM duration and serum creatinine, and there was a significant negative correlation between cystatin C and glomerular filtration rate (Table 2).

Table 2. *Correlation coefficient (r) between Cystatin C and different studied patients parameters.*

	Cystatin C	
	r.	**p. value**
Age	0.089	0.5
A/C ratio	0.78	0.001
HbA1c	0.56	0.001
FBS	0.49	0.001
2HPP	0.56	0.001
S. urea	0.169	0.197
Weight	- 0.07	0.593
DM duration	0.72	0.001
S. Creatinine	0.75	0.001
GFR	- 0.65	0.001

There was a significant positive correlation between serum creatinine and A/C ratio, HbA1c, FBS, 2HPP, weight and DM duration, and there was a significant negative correlation between serum creatinine and glomerular filtration rate glomerular filtration rate (Table 3). Tables **(**4,5 and6**)** show Sensitivity, Specificity, PPV, NPV, AUC for detecting different stages of albuminuria in diabetic patients as regard serum cystatin C, GFR and serum creatinine.

Table 3. *Correlation coefficient (r) between S. creatinine and different studied patients parameters.*

	S. Creatinine	
	r.	**p. value**
Age	- 0.113	0.858
A/C ratio	0.704	0.001
HbA1c	0.536	0.006
FBS	0.51	0.001
2HPP	0.58	0.001
S. urea	0.115	0.382
Weight	0.289	0.025
DM duration	0.588	0.001
GFR	- 0.80	0.001

Table 4. *shows Sensitivity, Specificity, PPV, NPV, AUC of detecting normo-albuminuria in diabetic patients as regard serum cystatin C, GFR and serum creatinine.*

	Sensitivity	**Specificity**	**PPV**	**NPV**	**AUC**
S. Cystatin C	93.7	87.2	95.2%	89.7%	0.922
GFR	68.7	83.4	71.4%	82.2%	0.818
S.creatinine	75	87.5	60%	78%	0.668

PPV (positive predictive value), NPV (negative predictive value), AUC (area under the curve)

Table 5. *shows Sensitivity, Specificity, PPV, NPV, AUC of detecting micro-albuminuria in diabetic patients as regard serum cystatin C, GFR and serum creatinine.*

	Sensitivity	**Specificity**	**PPV**	**NPV**	**AUC**
S. Cystatin C	95%	97%	86%	84%	0.930
GFR	80%	90%	82%	80%	0.906
S. creatinine	78%	89%	72%	68%	0.609

PPV (positive predictive value), NPV (negative predictive value), AUC (area under the curve)

Table 6. *shows Sensitivity, Specificity, PPV, NPV, AUC of detecting macro-albuminuria in diabetic patients as regard serum cystatin C, GFR and serum creatinine.*

	Sensitivity	**Specificity**	**PPV**	**NPV**	**AUC**
S. Cystatin C	92.7%	78.6%	81%	80.6%	0.854
GFR	91%	64.3%	76%	78.4%	0.813
S.creatinine	78.6%	64%	72%	68%	0.686

PPV (positive predictive value), NPV (negative predictive value), AUC (area under the curve)

Receiver-operating characteristic curve (ROC) for cystatin C, GFR, S.creatinine as a test for predicting different stages of albuminuria in type 2 diabetic patients, the area under the curve for cystatin C is 0.922 in normo-albuminuric group (figure1),0.930 in micro-albuminuric group (figure2) and 0.854 in macro-albuminuric group (figure3),indicating that serum cystatin C has the best sensitivity and specificity and is a better marker than serum creatinine and GFR for detecting early renal function decline in type 2 diabetes patients.

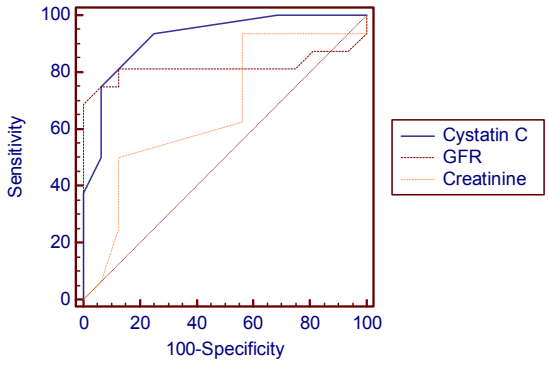

Figure 1. *Receiver-operating characteristic curve (ROC) for cystatin C, GFR, S. creatinine as a test for predicting normo-albuminuria group in diabetic patients, the area under the curve for cystatin C is 0.922.*

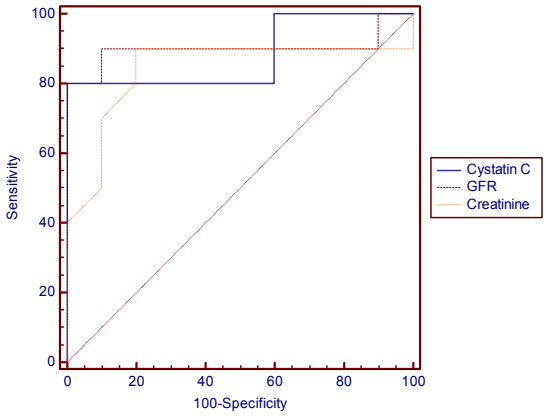

Figure 2. *Receiver-operating characteristic curve (ROC) for cystatin C, GFR, S.creatinine as a test for predicting micro-albuminuria group in diabetic patients, the area under the curve for cystatin C is 0.930.*

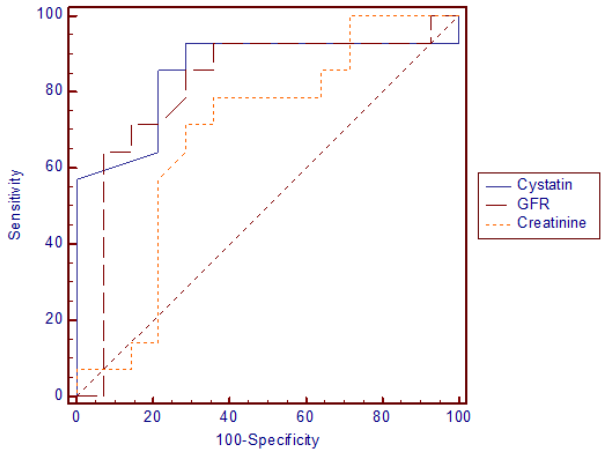

Figure 3. *Receiver-operating characteristic curve for cystatin C, GFR, S.creatinine as a test for predicting macro-albuminuria group in diabetic patients, the area under the curve for cystatin C is 0.854.*

4. Discussion

Chronic kidney disease is increasing worldwide, with higher prevalence in developing countries; diabetic nephropathy (DN) is a common underlying cause (8).

Diabetic nephropathy develops due to a complex interaction between metabolic and haemodynamic pathophysiological factors, which lead to renal damage, It can affect 20remove-30% of the diabetic population, who present with an increase in urinary albumin excretion, microalbuminuria in the earliest stage, This may progress to macroalbuminuria and later renal insufficiency and ESRD (9).

The GFR is considered the most accurate measurement of kidney disease and is reduced before the onset of clinical symptoms; GFR is measured or predicted according to different methods (10).

The primary limitation of creatinine is that levels are determined not only by GFR, but also by muscle mass and dietary intake, lower serum creatinine levels may less reliably detect impaired GFR in patients with certain characters like older age, female sex, chronic illness with muscle wasting, amputation, or a vegetarian diet (11).

There are several factors that may interfere with the accuracy of creatinine clearance such as: incomplete urine collection, pregnancy, vigorous exercise and drugs (12).

Several new biochemical markers have the potential to be markers of CKD progression, these new markers might reflect the early diminished glomerular filtration than the tradional markers, these include: Kidney Injury Molecule-1 (KIM-1), N -acetyl-β-glucosaminidase, β2 -microglobulin, α1-microglobulin, and retinol binding protein, human neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), clusterin, fatty acid binding protein, and cystatin C (13).

Cystatin C is a small (13-kDa) protein that is a member of the cysteine proteinase inhibitor family that is produced at a constant rate by all nucleated cells, due to its small size it is freely filtered by the glomerulus, and is not secreted but is fully reabsorbed and broken down by the renal tubules, this means the primary determinate of blood cystatin C levels is the rate at which it is filtered at the glomerulus making it an excellent GFR marker (14).

Cystatin C is considered as a good marker of GFR as it not influenced by gender, muscle mass, age, protein intake, cystatin C is preferable to creatinine and creatinine clearance (15).

The aim of this study is to evaluate serum cystatin C as an early marker of renal dysfunction in type 2 diabetes mellitus, our study was carried out on 60 persons, 40 patients with type 2 diabetes mellitus and 20 as a health control group, according to albumin/creatinine ratio patients were divided them into normo-albuminuric group, micro-albuminuric group and macroalbuminuric group.

Redundant as result partIn our work we found a significant higher concentration of serum cystatin C in macro-albuminuria more than normo-albuminuria and micro-albuminuria and all are higher than the control group, the sensitivity was 92.7% and the specificity was 78.6% and these results were better than that of creatinine which showed sensitivity of 78.8% and specificity of 64%.

The major advantage of cystatin C over creatinine is its ability to detect mild reduction in GFR to which creatinine is insensitive, since there are no specific therapies, early detection of impaired renal functions is crucial to prevent the progression of renal disease and to improve the patient outcome, the main disadvantage of cystatin C being high cost of its immunoassay.

5. Conclusion

Measurement of GFR is considering a very helpful method for assessment of renal function especially in type 2 diabetes, 20 to 40% of those with type 2 diabetes will eventually develop diabetic nephropathy, and later on they need to receive renal replacement therapy.

It is well known that serum creatinine is an insensitive measure of renal function, moreover, serum creatinine is not

an accurate reflection of GFR as it influenced by many factors, including muscle mass, gender, diet, liver function, age and tubular secretion which can result in an overestimation of GFR up to 20%, so it's better to look for an alternative, non-invasive methods particularly in diabetic nephropathy.

From this study, we can conclude that serum cystatin C is a better marker for GFR than serum creatinine in type 2 diabetes patients with reduced GFR specially in "creatinine blind area", cystatin C may detect mild to moderate decreases in GFR that are not evident with serum creatinine-based measurements

New immunoassay methods from several different manufacturers measure cystatin C and this has made it more practical and clinically useful to estimate GFR, these methods are automated and results are rapidly available, therefore it may be recommended in the routine investigations in assessment of diabetic patients for measuring GFR.

Finally the use of cystatin C to measure renal function will optimize early detection, prevention, and treatment strategies for diabetic nephropathy, serum cystatin C is practical and can detect early decline of renal function in T2DM.

References

[1] AKyhse-Andersen, J., Schmidt, C., Nordin, G., Andersson, B., Nilsson-Ehle, P., Lindström, V., and Grubb A, 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.

[2] Bakris GL, Williams M, Dworkin L, Elliott WJ, Epstein M, Toto R, Tuttle K, Douglas J, Hsueh W and Sowers J: Preserving renal function in adults with hypertension and diabetes: a consensus approach. Am J Kid Dis 36:646–661, 2000.

[3] Bazari H. Approach to the patient with renal disease. In Goldman L, Ausiello D, editors. Cecil Medicine. 23rd ed. Philadelphia, Pa: Saunders Elsevier, 2007: chap 115.

[4] Bruno RM and Gross JL: Prognostic factors in Brazilian diabetic patients starting dialysis: a 3.6-year follow-up study. J Diabetes Complications 2000, 14:266-271.

[5] Caramori ML, Fioretto P and Mauer M: Low glomerular filtration rate in normoalbuminuric type 1 diabetic patients: an indicator of more advanced glomerular lesions. Diabetes 2003, 52:1036-1040.

[6] Filler G, Bokenkamp A, Hofmann W, Le Bricon T, Martinez-Bru C and Grubb A. Cystatin C as a marker of GFR-history, indications, and future research. Clin Biochem 2005;38:1–8.

[7] Finney H, Newman DJ and Price CP: Adult reference for serum cystatin C, creatinine and predicted spacecreatinine clearance. Ann Clin Biochem 2000, 37:49-59.

[8] Alebiosu CO, Ayodele OE. The global burden of chronic kidney disease and the way forward. Ethn Dis 2005; 15: 418-423 [PMID: 16108301].

[9] Forbes JM, Fukami K, Cooper ME. Diabetic nephropathy: where hemodynamics meets metabolism. Exp Clin Endocrinol Diabetes 2007; 115: 69-84 [PMID: 17318765 DOI: 10.1055/ s-2007-949721].

[10] Thomas, L., and Huber,A.R. 2006, Renal function – estimation of glomerular filtration rate. ClinChem Lab Med, 44(11), 1295.1302.

[11] Haase-Fielitz A, Bellomo R, Devarajan P, et al. Novel and conventional serum biomarkers predicting acute kidney injury in adult cardiac surgery—a prospective cohort study. Crit Care Med. 2009. E-pub ahead of print.

[12] Bazari H. Approach to the patient with renal disease. In Goldman L, Ausiello D, editors. Cecil Medicine. 23rd ed. Philadelphia, Pa: Saunders Elsevier, 2007: chap 115.

[13] Wagener G, Jan M, Kim M, Mori K, Barasch JM, Sladen RN, et al. Association between increases in urinary neutrophil gelatinase associated lipocalin and acute renal dysfunction after adult cardiac surgery. Anesthesiology. Sep 2006;105(3):485-91.

[14] Larson A, Malm J, Grubb A, Hanson LO: Calculation of glomerular filtration rate express in ml/min from plasma cyctatin C values in mg/l. Chemistry Scand I Clin Lab Invest 2004;64: 25-30.

[15] levey AS, Eckardt KU, Tsukamoto Y, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Intl. 2005; 67:2089-2100.