Original Article

The Glomerular Filtration Rate: Comparison of various predictive equations based on Serum Creatinine with Conventional Creatinine Clearance test in Pakistani Population

Adnan Mustafa Zubairi, Arif Hussain
Department of Chemical Pathology, Ziauddin University, Karachi.

Abstract

Introduction: To compare the conventional creatinine clearance measured on 24-h urine collection with the estimated Glomerular Filtration Rate by Cockcroft & Gault (CG) and Modification of Diet in Renal Disease (MDRD) prediction equations in adults aged 20 years and above in Pakistani population.

Methods: All the patients, including inpatient admitted in hospital and outpatients, more than 20 years of age, reporting for the test of creatinine clearance in clinical chemistry department of Dr. Ziauddin Hospital clinical laboratory from 1st January to 31st December 2006 were studied.

Results: Comparison was made between conventional creatinine clearance and Cockcroft & Gault (CG) and Modification of Diet in Renal Disease (MDRD) prediction equations on 369 cases which revealed strong correlation with conventional creatinine clearance, MDRD equation has better correlation as compared with Cockcroft- Gault creatinine clearance. Statistical correlation was better in cases where serum creatinine was more than 1.50 mg/dl (r = 0.625 for Cockcroft- Gault creatinine clearance and r = 0.724 for MDRD equation) as compared when serum creatinine levels were less than 1.50 mg/dl (r = 0.608 for Cockcroft- Gault creatinine clearance and r = 0.596 for MDRD equation). There was positive bias in both calculated GFRs from conventional creatinine clearance in healthy as well as diseased population.

Conclusion: The creatinine based formulas with their inherent property of convenience and cost effectiveness can be a useful tool for monitoring the progression of disease. They can be applied in clinical practice on our population but they should be interpreted with caution as they over estimate the GFR (JPMA 58:182;2008).

Introduction

Chronic renal failure (CRF) is a significant public health problem as it causes a substantial burden on the health services. Apart from its financial impacts on the individual or health care providers, it is associated with numerous social and psychological implications.[1] There is progressive loss of renal function in CRF. The causes include hypertension, diabetes, glomerulonephritis, pyelonephritis, renal vascular diseases, analgesic nephropathy and in a substantial number of cases the cause remains unknown. The clinical features of CRF are due to uraemia, which develops very late and insidiously. In the effort of maintaining the quality of life, patients of CRF are advised various renal replacement treatments like dialysis or renal transplantation.

The incidence of Chronic Kidney Disease (CKD) is higher in South Asians than in European population.[2,3] If remained undiagnosed and untreated it may progress into CRF. There are a number of potential complications associated with CRF including cardiovascular diseases.[4] Some of these can be prevented or at least delayed by early detection and treatment of CKD.[5-7]

There could be damage to glomerular or tubular function by diseases affecting the kidney, but isolated tubular defects are rare. In all sorts of renal diseases there is loss of nephron function and since the process of filtration is essential for formation of urine, tests of glomerular function are always required for diagnosis and management of renal disorders. The renal function can best be evaluated by determining the glomerular filtration rate (GFR).[8] The results of GFR should be interpreted carefully as it decreases with age, more so in males than in females.[9] Early detection of CKD requires identification of patients with reduced GFR for the age and sex. A GFR level of <60 ml/min per 1.73 m^2 represents loss of half or more of the adult level of normal kidney function and is classified as CKD.[10] The severity of the renal failure can be classified by clinical conditions and proportion of renal function lost as, mild (GFR, 30-50 ml/min), moderate (GFR 10-29 ml/min), severe (GFR <10 ml/min) and

end stage (GFR <5 ml/min).[11]

GFR can be estimated by measuring the clearance of certain substances by the kidney. The renal clearance of a substance is defined as the volume of plasma from which the substance is completely cleared by the kidney per unit of time. The renal clearance is measured by using the exogenous (radioisotopic and nonradioisotopic) and endogenous filtration markers like, inuline, 125-iothalamate, 51 Cr-ethylene diamine tetra acetic acid (EDTA), 99mTc- diethylene triamine penta acetic acid (DTPA) and iohexol.[12] Unfortunately these methods are expensive, time consuming, cumbersome, not free of risks for patient and above all over estimate the GFR, they cannot be easily implemented in routine clinical practice.[13] In routine clinical practice, creatinine (an endogenous marker) is widely estimated as a marker of GFR. Creatinine (molecular mass 113 Da) is freely filtered at the glomerulus. It is convenient and cheap to measure but is affected by age, sex, exercise, certain drugs (cimetidine, trimethoprim etc), muscle mass, nutritional status and meat intake.[14] Furthermore, a small but significant and variable amount of creatinine appearing in urine is derived from tubular secretion. Estimating GFR, by creatinine clearance requires timed urine specimen, which introduces its own inaccuracies, is inconvenient and unpleasant. To compensate for these shortcomings, several investigators have made successful attempts to construct GFR prediction equations that include creatinine and additional variables. More than 25 different formulas have been derived for estimating GFR using plasma creatinine corrected for a combination of factors like gender, body size, race and age. The most widely used GFR prediction equations for adults are those proposed by Cockcroft and Gault (CG), which produce absolute GFR values in ml/min, and the Modification of Diet in Renal Disease (MDRD) equation, which produces relative GFR values in ml/min/1.73m^2.[15, 16] Automatic laboratory reporting of estimated GFR calculated from serum creatinine measurements can help to identify asymptomatic kidney dysfunction at an earlier stage. None of the equations mentioned above have been validated in Pakistani population.

We conducted this study to compare the conventional creatinine clearance measured in 24-h urine collection with the performance of CG and MDRD equations in adults aged 20 years and above in Karachi, Pakistan

Patients and Methods

All the patients, both inpatients admitted in hospital as well as outpatients reported for the test of creatinine clearance in clinical chemistry department of Dr. Ziauddin Hospital clinical laboratory from 1st January to 31st December 2006 were studied. Patients less than 20 years of age and those patients where height and weight were not possible were excluded from the study. Patients were explained the 24 hour urine sample collection protocol in the language they understood. Height was measured in centimeters and weight was recorded in kilograms on standard clinical height and weight balance.

Venous blood was aseptically collected in yellow top, gel separator BD Vacutainer. After separation of serum, the serum creatinine was estimated by alkaline picrate, rate kinetic method using Roche reagent Cat. No. 1489291 on Hitachi 902 automated clinical chemistry analyzer. 24 hour urine was collected in containers without any additive / preservative. Volume of the urine passed in 24 hours was measured in milliliters in volumetric flasks. After thorough mixing of urine sample, 1:10 dilutions were prepared manually with deionized water. The diluted urine samples were also analyzed by alkaline picrate, rate kinetic method using Roche reagent Cat. No. 1489291 on Hitachi 902 automated clinical chemistry analyzer and the results were multiplied by 11 to get creatinine concentration in urine samples.

The following were calculated,

1. Creatinine clearance (ml/min/1.73m^2) = U x V x 1.73 / P x 1440 x BSA

Where U is urinary creatinine (mg/dl), V is urinary volume in 24 hours (ml), P is serum creatinine (mg/dl) and BSA is body surface area.

BSA = weight (kg) $^{0.425}$ x height (cm) $^{0.725}$ x 7.1 x 10^{-3}

2. Cockcroft- Gault estimated creatinine clearance (ml/min) = (140-age) x (weight in Kg) / serum creatinine (mg/dl) x 72 x (0.85 if female).
3. MDRD estimated creatinine clearance (ml/min/1.73m^2) = 186 x [serum creatinine (mg/dl)] $^{-1.154}$ x (age in years) $^{-0.203}$ x (0.742 if female).

Statistical analysis

The data was analyzed through the SPSS version 10.0 (SPSS Inc, Chicago, US). Results are expressed as mean and standard deviation (SD). Pearson correlation coefficient (r) was used to assess the association between the results of conventional creatinine clearance on 24 hour urine collection and GFR calculated by Cockcroft- Gault creatinine clearance (ml/min) and MDRD creatinine clearance (ml/min/1.73m2) equations. Statistical significance was considered when $p<0.01$. Bias is defined as the mean difference between estimated and measured GFR.

Results

A total of 369 cases were included in the study, 161 (43.6%) were inpatients admitted in the hospital and 208 (56.6%) were outpatients, 168(45.5%) were females and 201(54.5%) were males. Creatinine clearance as calculated on 24 hours urine collection, ranged from 2 to 187 ml/min/1.73m^2. Mean age of the cases was 55.58 ± 14.02 years and they were ranging from 20 to 91 years. Demographic and clinical

characteristics of the study population are given in Table 1.

Comparison of means and standard deviations between creatinine clearance calculated on 24 hour urine collection, Cockcroft- Gault creatinine clearance (ml/min) and MDRD creatinine clearance (ml/min/1.73m^2) is given in Table 2, which reveals better correlation between the three when serum creatinine was more than 1.50 mg/dl. A low significance value for the t test (typically less than 0.05) indicates that there is a significant difference when creatinine clearance was compared with Cockcroft- Gault or MDRD creatinine clearance.

Statistical correlation between creatinine clearance calculated on 24 hour urine collection and MDRD creatinine clearance (ml/min/1.73m^2) revealed strong correlation (r = .788), and statistical correlation between creatinine clearance calculated on 24 hour urine collection and Cockcroft- Gault creatinine clearance (ml/min) revealed strong correlation (r = .775), as shown in Table 2.

Although statistically both equations are showing strong correlation with conventional 24 hour creatinine clearance, MDRD equation has better correlation as compared with Cockcroft- Gault creatinine clearance. Statistical correlation was better in cases where serum creatinine was more than 1.50 mg/dl (r = 0.625 for Cockcroft- Gault creatinine clearance and r = 0.724 for MDRD equation) as compared when serum creatinine levels were less than 1.50 mg/dl (r = 0.608 for Cockcroft- Gault creatinine clearance and r = 0.596 for MDRD equation).

Table 1. Demographic and clinical characteristics of study population.[a]

	Overall (n = 369)	Females (n = 168)	Males (n = 201)
Serum creatinine(mg/dl)	1.94 ± 1.55	1.66 ± 1.33	2.18 ±1.68
Creatinine clearance (ml/min/1.73m^2)	43.85 ± 33.57	43.33 ± 32.35	44.28 ± 36.64
Age (years)	55.58 ± 14.02	53.31 ± 14.07	57.48 ± 13.72
Weight (Kg)	67.69 ± 12.62	64.09 ± 16.42	70.70 ± 14.28
Height (cm)	161.63 ± 11.16	155.21 ± 10.19	166.99 ± 8.87
BMI (Kg/m^2)	26.07 ± 6.58	26.80 ± 7.80	25.45 ± 5.29
24 Hour Urine Volume (ml)	1951.9 ± 1104.5	1831.0 ± 1023.7	2052.9 ± 1160.6

[a]Data are given as mean + SD
BMI; Body Mass Index

Table 3. Bias in the means of calculated GFR from conventional 24 hr creatinine clearance in various stages of renal function.

	24 Hr creatinine clearance		C&G creatinine clearance (ml/min)		MDRD creatinine clearance (ml/min/1.73m^2)	
	Mean + SD	Range	Mean	Bias	Mean	Bias
Overall (n = 369)	43.85 + 33.57	2 - 185	60.15	16.30	59.07	15.22
End stage renal \failure (GFR <5 ml/min) (n = 15)	3.73 + 0.96	2 - 5	20.27	16.54	15.13	11.40
Severe renal failure (GFR 5 - 10 ml/min) (n = 32)	8.31 + 1.38	6 - 10	19.81	11.50	17.13	8.82
Moderate renal failure (GFR 10-30 ml/min) (n = 116)	19.80 + 5.63	11 - 30	33.20	13.40	32.75	12.95
Mild renal failure (GFR 30-50 ml/min) (n = 88)	40.78 + 5.75	31 - 50	62.65	21.87	63.13	22.35
Minimal renal function impairment (GFR 50-60 ml/min) (n = 18)	54.39 + 2.99	51 - 60	72.28	17.89	75.83	21.44
Normal renal function (GFR > 60 ml/min) (n = 100)	89.94 + 24.85	61 -187	105.92	15.98	103.01	13.07

Bias is defined as the mean difference between calculated and measured GFR. There is positive bias in both calculated GFRs from conventional 24 hours creatinine clearance in healthy as well as diseased population Table 3.

Discussion

Repeated evaluation of renal function is very important aspect in the management of many metabolic disorders. Especially in patients with diabetes mellitus to preempt possible renal complications, which if detected early can be halted or reverted back to normal with modification of management.[5-7] In this study, we evaluated the performances of the CG and MDRD

Table2. Comparison between creatinine clearance and other estimated equations.

	Overall (n = 369)		Serum creatinine >1.50mg/dl (n = 176)		Serum creatinine <1.50mg/dl (n = 193)	
	Mean+SD	Correlation / sig	Mean+SD	Correlation / sig	Mean+SD	Correlation / sig
Creatinine clearance (ml/min/1.73m2)	43.8+33.5	r = .775 p = .000	21.1+14.5	r = .625 p = .000	64.5+32.6	r = .608 p = .000
Cockcroft- Gault creatinine clearance (ml/min)	60.1+45.0		29.1+14.9		88.4+44.7	
MDRD creatinine clearance (ml/min/1.73m2)	59.0+43.4		25.9+12.1	r = .724 p = .000	89.9+39.3	
24 Hour Urine Volume (ml)	1951.9 + 1104.5	r = .788 p = .000	1987.3 + 1142.1		1919.5 + 1071.0	
Age (Years)	55.58 + 14.02		58.35 + 13.72		53.06 + 13.84	
Male : Female	54.5:45.5		60.8:39.2		48.7:51.3	

formulas for estimating GFR in a cohort of 369 subjects. An important characteristics of our cohort is that it included subjects whose measured GFR ranged from 2 to 187 ml/min per 1.73 m^2, with sufficient numbers of subjects having measured GFR values $\geq$ and <60 ml/min per 1.73 m^2 (101 and 268 subjects, respectively). Thus, the performances of the CG and MDRD formulas could be assessed over a wide range of kidney function. Furthermore, because the patients included in this study were Pakistani, the performances of the MDRD and CG formulas could be assessed in a group of subjects whose anthropometric characteristics are different from those of Americans. For example, when compared with the MDRD cohort[16], the mean weight of our study population was 14.9% lower (67.7 ± 15.6 versus 79.6 ± 16.8 kg), whereas, on average, our patients were 5 years older than those included in the MDRD cohort (55.6 ± 14.2 versus 50.6 ± 12.7 yr) and a similar percentage of subjects were male in both cohorts (55 versus 60%).

There are advantages in using the calculated GFR by MDRD formula or CG prediction equation, based on its relative simplicity, ease of reporting and low cost. However it tends to overestimate GFR i.e. positive bias, in healthy as well as diseased population, which is 16.57 ml/min in CG prediction equation and 15.49 ml/min/1.73m^2 in MDRD equation, which is much higher than a study conducted on 262 subjects where the bias in these prediction equations was 6.1 and 8.2 ml / min / 1.73m^2 respectively.[17] Whereas in another study which was conducted on 122 renal donors i.e. normal healthy population, the bias in CG prediction equation and MDRD equation, compared with 9mTC-DTPA GFR was -14.14 and 17.70 ml / min / 1.73m^2 respectively.[18] Similarly the performance of these prediction equations with near normal serum creatinine yielded inconsistent results in another study.[19] This overestimation of calculated GFR may possibly be due to variation in characteristics, for example ethnicity, muscle mass, height, weight and diet intake in our cases and in the population where these formulae has been validated.

Conclusion

Plasma creatinine concentration is affected by age, sex, exercise, certain drugs, muscle mass, nutritional status and meat intake. The analytical interferences by other analytes present in the sample also add in inaccuracies in its estimation. And most importantly the plasma creatinine remains within reference limits until significant renal function is lost, therefore plasma creatinine may not detect mild to moderate renal function impairment (GFR 30 ml/min/1.73m2 or above). Thus although an elevated plasma creatinine concentration does generally equates with impaired renal function, a normal plasma creatinine does not necessarily equate with normal renal function. Various formulae are used to calculate GFR on the basis of serum creatinine levels. These formulae have fairly good correlation with conventional 24 hours creatinine clearance in the subject studied. The creatinine based formulae with their inherent property of convenience and cost effectiveness can be a useful tool for monitoring the progression of disease. They can be applied in clinical practice on our population but they should be interpreted with caution as they over estimate the GFR. Furthermore it is recommended that a study may be conducted on a large population including all segments of ethnic groups and these formulae should be redefined for our population.

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