ESTIMATION OF GLOMERULAR FILTRATION RATE IN HEALTHY ADULT PAKISTANI POPULATION: A COMPARISON OF COCKCROFT GAULT AND MODIFIED DIET IN RENAL DISEASE

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ABSTRACT

Objective: To compare the Cockcroft-Gault (CG) and Modification of Diet in Renal Disease (MDRD) equations of Glomerular filtration rate (GFR) estimation with 24 hours urine creatinine clearance so as to assess their application in clinical practice as a suitable alternative.

Study Design: Cross sectional study.

Place and Duration of Study: This study was carried out at CMH Pano Aqil in 2013.

Material and Methods: This was a cross sectional study conducted to compare results of GFR estimation using 24 hour urine with that of prediction equations based on samples obtained from healthy young adult volunteers. Urine creatinine clearance was measured (mGFR) from 24 hours collected urine sample and serum creatinine of the study subjects. GFR was estimated (eGFR) using standard 4 variable MDRD equation, CG creatinine clearance and CG GFR. The performance of these equations was compared with reference to measured GFR.

Results: Out of 480 persons who consented for evaluation, 426 were included in the study. The subjects were healthy male adults with mean age of 27.86 ± 5.97 years. Mean measured 24 hours urine creatinine clearance was 93.38 ± 13.21 (ml/min/1.73m2). Results showed that MDRD and Cockcroft Gault's GFR equation underestimated GFR as compared to 24 hour urine evaluation (-0.7 ml/min/1.73m^2 and -4.2 ml/min/1.73m^2 respectively), while Cockcroft–Gault creatinine clearance equation over estimated by 12.2 ml/min/1.73m^2. Overall, MDRD equation fared better with 24 hours urine creatinine clearance than the rest, having a strong correlation (r 0.8795, p<0.0001 and 95% CI of r 0.8561 to 0.8994) and least difference of mean (-0.7 ml/min/1.73m^2) by Bland Altman Plots.

Conclusion: We recommend MDRD equation in preference to Cockcroft Gault's equations to be used for estimation of GFR in clinical practice in young adult Pakistani population. The mean GFR of Pakistani population as of other south Asian is lower than the western population likely due to the racial difference between the two.

Keywords: Cockcroft Gault equation, Creatinine clearance, GFR, MDRD equation, Pakistani population.

INTRODUCTION

The burden of end stage renal disease (ESRD) is causing a lot of impact on the health care system throughout the globe. The exact incidence of chronic kidney disease (CKD) in Pakistan is lacking but data from community based studies reveal alarmingly high burden of the disease[1]. Thus rigorous screening for major risk factors like hypertension and diabetes mellitus, application of preventive measures and early detection and treatment of CKD can help reduce this burden[2].

For the early detection of renal disease, accurate assessment of renal functions is required. Renal inulin clearance is regarded as the gold standard test for estimation of glomerular filtration rate (GFR), but it is cumbersome, costly and not readily available[3,4]. The 99mTcdiethylenetriamine penta-acetic acid (DTPA) and iothalamate clearance correlate well with the results of inulin clearance and are being used in clinical practice[5-7]. These tests are also expensive, not widely available and these cannot be used repeatedly and for screening of large population. Urinary creatinine clearance is often used for estimation of GFR but it is time

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consuming and there can be errors in urine collection[8]. Serum creatinine (SCr) is the most commonly used biochemical marker of renal functions. However several factors other than GFR can affect SCr including its generation from muscle metabolism, tubular secretion and the creatinine assay method used. In addition, SCr is insensitive for detection of mild to moderate reduction in GFR[9]. To overcome this deficiency several SCr based equations for predictingGFR were created in the past[10]. The most frequently used ones are Cockcroft-Gault (CG) equation and the Modification of Diet in Renal Disease (MDRD) study prediction equation. These equations have now also been validated in renal transplant recipients for estimation of GFR[11].

The aim of this study was to compare the GFR prediction equation with 24 hours urine creatinine clearance to assess their application in clinical practice as a suitable alternative. 24 hours urine creatinine clearance is currently being used in most peripheral hospitals of Pakistan for measuring GFR, as DTPA scan is not widely available.

MATERIAL AND METHODS

This cross sectional study was conducted at CMH PanoAqil in 2013. Informed consent was taken from all the individuals who reported for routine medical examination and wanted to participate in this study. Subjects with any co-morbidity including hypertension, diabetes mellitus or any renal disease were excluded. The subject's identity, age and residence were recorded on proformas. Weight and height were measured to calculate body surface area (BSA). Detailed verbal and written instructions were provided about 24 hour urine collection. Blood sample was taken for SCr and collected urine stored for measurement of urine volume and urinary creatinine.

a**. Measurement of BSA:** BSA was calculated using the following formula:

Body surface area =(Weight in Kgs x Height in cms / 3600)$^{0.5}$.

b. **Measurement of serum and urine creatinine:** The serum and urine creatinine was determined by Jaffe's colorimetric-kinetic method. In this method creatinine present in the sample reacts with alkaline picrate forming a reddish complex and the intensity of the color thus produced is measured at the wavelength of 510nm which is proportional to the creatinine concentration present in the sample. Creatinine analysis was performed on Metrolab DR-1600, a semi-automated chemistry analyzer by using a company manufactured kit for creatinine provided by Linear Chemicals, BarcelonaSpain. As per the kit literature the detection limit of the kit is 0.02 mg / dl while the linearity of the kit is upto 20 mg / dl. As the urine creatinine concentration is very high, a urine sample diltution of 1 / 50 with normal saline was made and the result obtained was multiplied by 50 (dilution factor). To ensure the quality control, preassayed human control sera (Randox Company) of both normal and abnormal levels were run before the actual analysis of the test samples. The equipment was calibrated daily and quality control check was carried out regularly. The normal reference range for Scr was 53 to 120 umol / L.

c. **Measurement of urinary creatinine clearance** The soldiers were counselled regarding urine collection and were also given written instructions in Urdu language. The collection that was not considered adequate was discarded. 24 hours urine creatinine clearance was calculated using following formulas:

24 hours urine Cr Cl (L / day)

$$= \frac{\text{Urinary Creatinine x Urinary volume (L / day)}}{\text{Serum Creatinine}}$$

Converting to Cr Cl (ml / min)

$$= \frac{\text{Cr Cl x 1000 (ml / min)}}{1440}$$

Normalized to 1.73 m2 BSA

$$= \frac{\text{Cr Cl (ml / min) x 1.73}}{\text{BSA}}$$

d. **Estimation of GFR by prediction equations:** Three prediction equations for estimation of creatinine clearance / GFR were used:

CG CrCl equation

$$= \frac{(140\text{-age}) \times \text{Weight (Kg)} \times 1.23}{\text{Serum creatinine (umol / L)}}$$

As all were males so constant of 1.23 used for males was used.

CG GFR= 0.84 x Cockcroft Gault's CrCl[12]

MDRD equation

$$= 175 \times \left[\frac{Cr(umol/L)}{88.4}\right]^{-1.154} \times (Age)^{-0.203}$$

As all were males and Pakistanis no constant for females of 0.742 and for African Americans 1.212 were not used.

Statistical analysis: Descriptive analysis was done to determine values of mean creatinine clearance and GFR with expression of their standard deviations, standard error of means and range. Statistical comparison between results of 24 hour urine creatinine clearance and prediction equations was performed in pairs by calculating Correlation Coefficient (r). A *p* value <0.05 was considered as significant. Bland Altman Plots[13,14,15] was used to assess differences of Means (Bias) with Limits of Agreement for each pair. Data had been analyzed using MedCalc version 12.7.0.0 (Mariakerke, Belgium)

RESULTS

Out of 910 soldiers who reported for medical examination, 480 consented for the study, of which 426 were included in the study. Of the excluded 54 soldiers, 12 had co-morbid conditions, and the rest had errors in urine collection.

Table-1: Demographic and Laboratory characteristics (n=426).

Variables	Mean ± SD	95% CI	SEM	Min	Max
Age (yrs)	27.86 ± 5.97	27.29 - 28.43	0.28	18	45
Height (cms)	171.96 ± 4.23	171.56 - 172.37	0.20	161	184
Weight (kgs)	65.92 ± 7.49	65.20 - 66.63	0.36	49	85
BSA	1.77 ± 0.11	1.76 - 1.78	0.0055	1.52	2.07
Serum Cr(umol / l)	87.28 ± 11.06	86.22 - 88.33	0.53	68	111
Urine Cr (umol / l)	6809.65 ± 892.80	6724.62 – 6894.67	43.25	4640	9200
Urine Vol (l / day)	1.76 ± 0.23	1.73 - 1.78	0.011	1.2	2.3
24hr Urine CrCl	93.38 ± 13.21	92.12 - 94.64	0.64	65.77	126.91

(BSA-Body Surface Area; Cr- Creatinine; CrCl- Creatinine Clearance).

Table-2: Correlation coefficients for 24 hour Urine Creatinine Clearance with prediction equations (n=426).

Variable X-Y	Correlation Coefficient (r)	Significance Level (*p*)	95% Confidence Interval for r
24hr Urine CrCl CG CrCl	0.7684	*p*<0.0001	0.7264 to 0.8047
24hr Urine CrCl CG GFR	0.7684	*p*<0.0001	0.7264 to 0.8047
24hr Urine CrCl MDRD	0.8795	*p*<0.0001	0.8561 to 0.8994

(CG Cockcroft Gault; CrCl Creatinine Clearance).

Table-1 shows the demographics of the studied population. All subjects were healthy male adults. Mean age was 27.86 ± 5.97 years. The study population represented all areas of Pakistan, out of which 48.4% belonged to Punjab, 36.8% from Sind, 4.2% from KPK, 1.5% from Azad Kashmir and 0.1% from Baluchistan. Mean measured 24 hours urine creatinine clearance (mGFR) was 93.38 + 13.21 (ml/min/1.73m2). Mean estimated creatinine clearance by Cockcroft

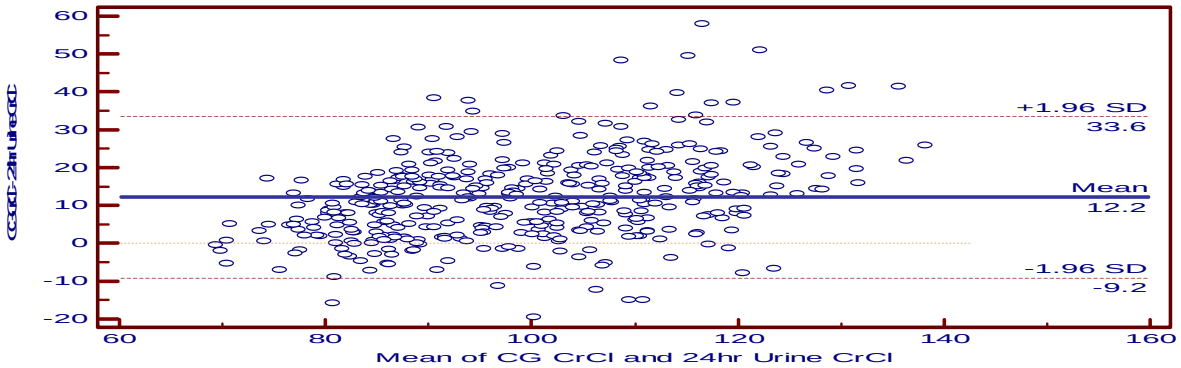

Figure-1a: Bland–Altman plot describing agreement between Cockcroft Gault's CrCl and 24 hour Urine Creatinine Clearance. Difference of Means=12.2 ml/min/1.73m²; Upper limit of agreement =33.6 ml/min/1.73m²; Lower limit of agreement= -9.2 ml/min/1.73m².

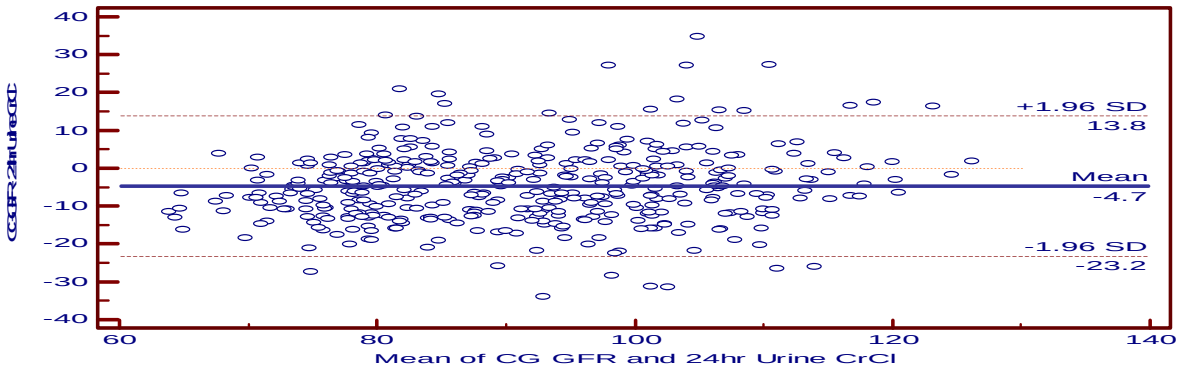

Figure-1b: Bland–Altman plot describing agreement between Cockcroft Gault's GFR equation and 24 hour Urine Creatinine Clearance. Difference of Means=-4.7 ml/min/1.73m2; Upper limit of agreement =13.8 ml/min/1.73m2; Lower limit of agreement= -23.2 ml/min/1.73m2.

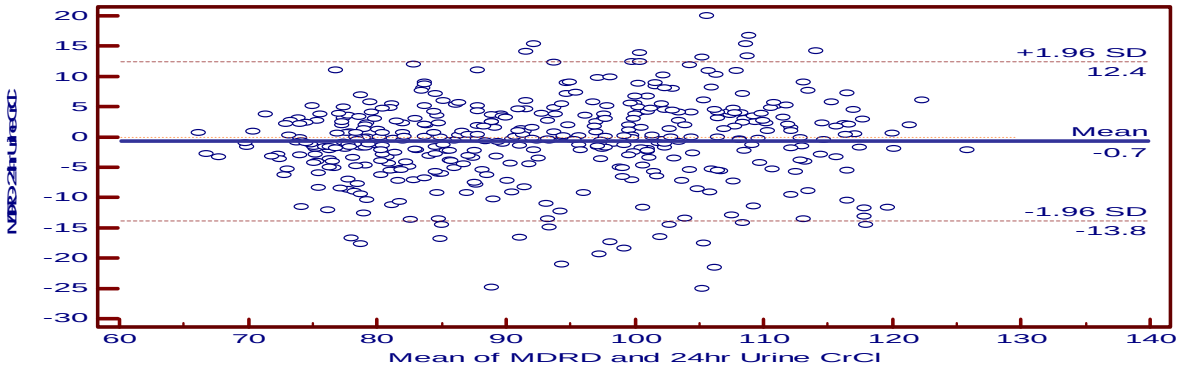

Figure-1c: Bland–Altman plot describing agreement between MDRD equation and 24 hour Urine Creatinine Clearance. Difference of Means=-0.7 ml/min/1.73m2; Upper limit of agreement =12.4 ml/min/1.73m2; Lower limit of agreement= -13.8 ml/min/1.73m2

Gault CrCl equation was 105.55+17.06 (ml/min); 88.66+14.33 (ml/min) by Cockcroft Gault GFR equation; and 92.66+13.87 (ml/min) by MDRD formula.

Table-2 shows the correlation coefficient for each pair. A very high correlation was found between MDRD and 24 hours urine creatinine clearance (r 0.8795, *p*=0.0001)

Bland Altman Plots for each pair are shown in Figures 1a-c. Differences of Means (Bias) with Limits of agreement have been highlighted. MDRD equation had the least difference of mean (-0.7 ml/min/1.73m^2) whereas Cockcroft Gault's creatinine clearance showed the maximum difference of mean (12.2 ml/min/1.73m^2). The plots also show increase scatter at higher GFR values depicting reduced precision of the prediction equations at higher GFR

DISCUSSION

Our study compared the commonly used method of GFR calculation in Pakistan i.e. 24 hour urine with the equations used for calculating estimated GFR in a group of young healthy Pakistani adult males. The mean mGFR in the studied population was calculated to be 93.38 ± 13.21 ml/min per 1.73m^2.

The adult creatinine–based formulas were developed in middle-aged or aged populations of patients with various pathologic conditions and were not designed to study renal function in young adults or adolescents. The Cockcroft Gault's CrCl formula was developed in 1976 by using the mean 24-hour urine creatinine excretion from two urine collections obtained in 249 adult men aged from 18 to 92 years. MDRD study prediction equation was developed in 1628 patients (males and females) with a mean age of 50.6 ± 12.7 years and a mean GFR of 39.8 ± 21.2 ml/min per 1.73m^2 and included age, sex, and race to account for average differences in muscle mass in subgroups[16]. The anthropometrics of our study population were quiet different when compared with the MDRD study population, from which the original MDRD formula was derived. The mean age of our subjects was 27.86 ± 5.97 years versus 50.6 ± 12.7 years of MDRD study population, mean weight was 65.92 ± 7.49 versus 79.6 ± 16.8, mean BSA (1.77 ± 0.11 versus 1.91 ± 0.23) and mean GFR was (93.38 ± 13.21 versus 39.8 ± 21.2).

Studies have reported a higher mGFR in western population (106–125 mL/ min per 1.73 m^2)[17], but our results are comparable to that reported by Selistre et al[18] for the same age group in French population. Other studies on South Asian populations have also reported a similar mGFR[19,20]. Srinivas et al reported that low GFR of South Asians (95.5+11.6 mL/min per 1.73 m2) as compared to western has two possible causes, low protein diet and low birth weight[12]. These factors may be operative in our study as well but here population are not strict vegetarians and this difference from Western population might be racial.

In regard to the predictive ability of Cockcroft Gault's and MDRD based equations in healthy subjects the opinion has been divided with evidence in favour of Cockcroft Gault's equations[21,22] and other in favour of MDRD[23,24]while some have reported that both MDRD and Cockcroft Gault's equations performed poorly in estimating GFR in healthy renal donors[25]. Analysis of our data show linear correlation of prediction equations with 24 hour urine creatinine clearance. Correlation was found to be strong in case of MDRD formula and weak in case of Cockcroft Gault's CrCl equation. Calculating Cockcroft Gault's GFR improved the correlation with reduction in bias between eGFR and mGFR methods (table-2, fig-1a and 1b). Shaikh GM etal conducted a study in Pakistan and reported that MDRD equation is a suitable and valid equation for estimating GFR in CKD patients of Rawalpindi[26].

Studies show that the prediction equations have lower precision in high GFR populations and GFR estimates are less useful in the normal range of GFR[27]. Results of our study show a similar increase in scatter of observations at higher mGFR levels (fig-1a-c).

Studies have also revealed that the prediction equations overestimate or underestimate GFR in healthy renal donors, especially Cockcroft Gault's CrCl which usually over estimates creatinine clearance probably due to anthropometry[28]. Our results noted an overestimation of creatinine clearance by Cockcroft Gault's CrCl by a mean of 12.2 ml/min /1.73m^2 (fig-1a). On the contrary, our analysis showed an underestimation of GFR by Cockcroft Gault's GFR equation by a mean of 4.2 ml/min/1.73m^2 (fig- 1b) and MDRD formula by a mean of 0.7 ml/min/1.73m^2 (fig-1c). These findings have also been supported by previous evidence[15] that showed an underestimation of GFR by MDRD formula by a mean of 9–29 mL/min per 1.73 m^2.

CONCLUSION

Our results fall in favour of MDRD equations that show better estimation, narrow limits of agreement and good correlation to measured creatinine clearance, than Cockcroft Gault's equations. So we recommend MDRD equation in preference to Cockcroft Gault's CrCl equation to be used for estimation of GFR in clinical practice in young healthy Pakistani population. Cockcroft Gault's CrCl equation can also be used, keeping in mind the overestimation of GFR of around 10 ml/min/1.73m^2.

The mean GFR of Pakistani population (80 to 107 ml/min per 1.73m^2) as of other south Asian is lower than the western population (106 to 125 mL/ min). This might be due to the racial difference between us.

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CONFLICT OF INTEREST

This study has no conflict of interest to declare. No funding was received from any agency or institution.

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