

EVALUATION OF THE THREE METHODS AVAILABLE FOR THE ESTIMATION OF CREATININE CLEARANCE

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ABSTRACT:

Background: The Glomerular filtration rate (GFR) is considered to be the most reliable measure of the functional capacity of the kidneys and it has proved to be the most sensitive and specific marker of changes in overall renal function. The accurate measurement of the GFR is time consuming, expensive, and not practical for routine clinical use.¹ Though Inulin clearance is considered to be the gold standard test, it has not been used widely because it time consuming, expensive, requires continuous infusion, and constraining for the patient.^{2,3,4} Creatinine clearance is most commonly used for the estimation of GFR. The need to collect a urine sample remains a major limitation of the creatinine clearance test.⁵ Many formulae have been developed to transform serum creatinine so that it may accurately reflect, GFR.⁶ Variations in creatinine production owing to age and sex related differences in muscle mass have been measured and incorporated into the formulas to improve the GFR.⁷ In adults, the most commonly used formulae are those derived from the Modification of Diet in Renal Disease (MDRD) and the Cockcroft-Gault (CG), which have not been validated in Indian population.⁸ This study was aimed to compare the diagnostic performance of the MDRD Cockcroft-Gault formulae, and Measured Creatinine Clearance in Indian population.

Materials and Methods: In 370 subjects Creatinine Clearance was calculated by Routine Creatinine Clearance test using serum and urine Creatinine and also through MDRD and the Cockcroft-Gault formulae. Subjects were divided into two groups based on the Measured Creatinine Clearance values.

Group A consisted of subjects with Measured Creatinine Clearance >60 ml/min.

Group B consisted of subjects with Measured Creatinine Clearance <60 ml/min

Statistical analysis: Correlation (Pearsons correlation) between the values of Clearance obtained through the three methods in the above two groups was analyzed using SPSS-16 version.

Results:

Group A (Measured Creatinine Clearance >60 ml/min) The Cockcroft-Gault formula showed strong positive correlation (r value 0.756, p value <0.001) with the Measured Creatinine Clearance than the MDRD formula. (r value 0.684, p value <0.001)

Group B (Measured Creatinine Clearance <60 ml/min) both Cockcroft and MDRD showed weak positive correlation with Measured Creatinine Clearance. Cockcroft ((r value 0.617, p value <0.001) MDRD (r value 0.613, p value <0.001)

Conclusion: The present study shows weak positive correlation between the Measured Creatinine Clearance, MDRD and Cockcroft formulae at Clearance values <60 ml/min and strong positive correlation between Measured Creatinine Clearance and Cockcroft formula at Clearance values >60 ml/min. Since MDRD formula includes age, gender, and race and developed for the western population with chronic renal insufficiency, further research is needed in our population, to establish and incorporate adjustment & Correction factors in the formula, so that it can be used for a wider range of renal function, in our population to give reliable results and therefore can replace the traditional Measured Creatinine Clearance test.

Keywords: eGFR, Modification of Diet in Renal Disease (MDRD), Cockcroft-Gault (CG) Measured Creatinine clearance.

BACKGROUND

The Glomerular filtration rate (GFR) is considered to be the most reliable measure of the functional capacity of the kidneys and is often thought of as indicative of the number of functioning nephrons. It has been proved to be the most sensitive and specific marker of changes in overall renal function.⁹ A low or decreasing GFR is a good index of chronic kidney disease. Since the total kidney GFR is equal to the sum of the filtration rates in each of the functioning nephrons, the total GFR can be used as an index of functioning renal mass.¹⁰ A decrease in GFR precedes kidney failure in all forms of progressive kidney disease. Monitoring changes in GFR can delineate progression of kidney disease. The level of GFR is a strong predictor of the time to onset of kidney failure as well as the risk of complications

of chronic kidney disease. Additionally, estimation of GFR in clinical practice allows proper dosing of drugs excreted by glomerular filtration to avoid potential drug toxicity.

Glomerular filtration rate cannot be measured directly. If a substance in stable concentration in the plasma is physiologically inert, freely filtered at the glomerulus, and neither secreted, reabsorbed, synthesized, nor metabolized by the kidney, the amount of that substance filtered at the glomerulus is equal to the amount excreted in the urine.¹¹ The fructose polysaccharide inulin has each of the above properties and has long been considered an ideal substance to estimate GFR. The classic method of inulin clearance requires an intravenous infusion and timed urine collections over a period of several hours making it costly and cumbersome.¹¹ As

a result a number of alternative measures for estimating GFR have been devised.

The urinary clearance of exogenous radioactive markers (^{125}I -iothalamate and $^{99\text{m}}\text{Tc}$ -DTPA) provides excellent measures of GFR¹² but are not readily available.

The most widely used measure of GFR in clinical practice is based on the 24-hour creatinine clearance or serum creatinine concentration. Creatinine is an endogenous product. It is an excretory product derived from creatine phosphate. The excretion of creatinine is rather constant and is not influenced by body metabolism and dietary factor. The value of creatinine clearance is close to GFR; hence its measurement is a sensitive and good approach to assess the renal glomerular function.⁹

The need to collect a urine sample remains a major limitation of the creatinine clearance test. Therefore, many attempts have been made to mathematically transform or correct serum creatinine so that it may more accurately reflect GFR.¹³ Variations in creatinine production owing to age and sex related differences in muscle mass have been measured and incorporated into the formulas to improve the GFR.¹⁴ The K-DOQI (Kidney Diseases Outcomes Quality Initiative) clinical practice guidelines and the European Best Practice guidelines recommended for the use of predictive equations to estimate GFR.¹⁵ In adults, the most commonly used formulae are those derived from the Modification of Diet in Renal Disease (MDRD) study population and that of Cockcroft and Gault.

The Cockcroft and Gault formula was developed in 1973 using data from 249 men with creatinine clearance from approximately 30-130 ml/min.^{15, 16}

It is not adjusted for body surface area (BSA). $C_{Cr} = \{((140 - \text{age}) \times \text{weight}) / (72 \times S_{Cr})\} \times 0.85$ if **female** where C_{Cr} is expressed in milliliters per minute, age in years, weight in kilograms, and serum creatinine (S_{Cr}) in milligrams per deciliter.

The Modification of Diet in Renal Disease (MDRD) equation, was published in 1999 and later simplified.¹⁸ This equation was proposed by Levey et al to estimate GFR. In its original form, the MDRD formula used six variables (serum creatinine, albumin and urea nitrogen, gender, age and ethnicity). A simplified version requiring only serum creatinine value, age, race and gender was found to correlate with measured GFR. $\text{GFR (ml/min per } 1.73\text{m}^2) = 186 \times \text{Pcr}^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if female).¹⁹ This equation automatically estimated GFR from serum creatinine for most laboratories.²⁰ The MDRD

equation has now been evaluated in numerous populations, including African Americans, Europeans, and Asians with non-diabetic kidney diseases, diabetic patients with or without kidney diseases.

In this study, we compared the values of conventional creatinine clearance using serum and urinary creatinine with the creatinine clearance obtained through Cockcroft and Gault formula and MDRD formula.

Objectives of the study is to estimate

- Measured Creatinine clearance by conventional creatinine clearance test using serum and urine creatinine;
- Calculation of Creatinine Clearance through Cockcroft and Gault formula and MDRD formula using serum creatinine;
- Finding the correlation between the Measured Creatinine Clearance values with the Clearance values obtained through the formulae.

METHODS

The study was approved by the ethical committee of St. John's Medical College, Bangalore. The study group consisted of 370 subjects in the age group of 20-50 years of both sexes from the inpatient and outpatient departments of St. John's Medical college Hospital, Bangalore.

Blood samples were collected under aseptic precautions. 24hrs urine sample was collected in a clean 5L plastic can. Demographic details (age, sex, height, weight of the patient) were also collected. Serum and urine Creatinine were measured by modification of the kinetic Jaffe reaction using Siemens Dimension automated analyser^{21, 22}

The creatinine clearance was calculated

- By Routine creatinine clearance test using serum and urine creatinine.
- By Cockcroft and Gault formula using serum creatinine.
- By MDRD formula using serum creatinine.

Subjects were divided into two groups based on the measured creatinine clearance values.

Group A consisted of subjects with Measured Creatinine Clearance >60 ml/min.

Group B consisted of subjects with Measured Creatinine Clearance <60 ml/min.

Comparison of the Creatinine clearance values obtained by the above three methods in the above mentioned groups were done.

RESULTS

Table 1: Mean of study variables according to gender

Variables	Male	Female	Total	P Value
Age in Years	40.40±9.18	51.36±9.50	50.91±9.72	<0.001**
BMI	22.41±2.63	23.76±4.88	2374±4.81	0.287
24 hours urine	2506.67±909.84	2374.37±998.98	2379.73±994.73	0.615
Serum Creatinine	0.87±0.47	0.80±0.37	0.81±0.38	0.481
Urine Creatinine	41.32±7.69	36.72±17.24	36.91±16.97	0.305
MDRD formula	112.74±47.35	88.66±29.44	89.64±30.65	0.003**
Cockcroft and Gault formula	95.26±35.29	79.53±27.19	80.17±27.68	0.031*
Corrected Creatinine clearance	94.71±38.85	81.89±28.02	82.41±28.58	0.089+

Serum Creatinine-mg/dl; Urine Creatinine mg/ dl; Creatinine clearance ml/min 24 hour urine-ml.

Table 2: Group Statistics

	Group	N	Mean	Std. Deviation	Std. Error Mean
MDRDFORMULA	<60	78	60.1072	21.02094	2.38015
	>60	292	97.5260	27.89007	1.63214
COCKCROFTFORMULA	<60	78	50.8332	15.86068	1.79587
	>60	292	88.0087	24.75592	1.44873
CORRECTEDCREATININECLEARANCE	<60	78	45.5851	9.65354	1.09305
	>60	292	92.2420	23.45986	1.37288

Table-3: Independent Samples Test

	Levene's Test for Equality of Variances					t-test for Equality of Means				
		F	Sig.	t	df	p value	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
MDRD Formula	Equal variances assumed	5.828	.016	-11.037	368	<.001	-37.41885	3.39034	-44.08571	-30.75199
	Equal variances not assumed			-12.966	157.241	.000	-37.41885	2.88600	-43.11918	-31.71851
Cockcroft formula	Equal variances assumed	17.467	.000	-12.584	368	<.001	-37.17553	2.95430	-42.98495	-31.36611
	Equal variances not assumed			-16.112	188.684	.000	-37.17553	2.30737	-41.72709	-32.62397
Measured Creatinine clearance	Equal variances assumed	43.741	.000	-17.167	368	<.001	-46.65686	2.71786	-52.00135	-41.31237
	Equal variances not assumed			-26.587	308.453	.000	-46.65686	1.75487	-50.10989	-43.20383

Table 4: Pearson correlation of the Creatinine clearance using different methods (MDRD, Cockcroft – Gault and Measured Creatinine clearance.)

Pair	Pearson correlation	
	r value	P value
Measured Creatinine Clearance VS MDRD Formula	.684**	<.001
Measured Creatinine Clearance VS Cockcroft – Gault Formula	.756**	<.001
MDRD VS Cockcroft –Gault Formula	.604**	<.001

** . Correlation is significant at the 0.01 level (2-tailed).

Table 5: Pearson correlation of the Creatinine clearance using different methods (MDRD, Cockcroft – Gault and Measured Creatinine clearance.)

Pair	Pearson correlation	
	r value	P value
Measured Creatinine Clearance VS MDRD Formula	.613**	<.001
Measured Creatinine Clearance VS Cockcroft – Gault Formula	.617**	<.001
MDRD VS Cockcroft –Gault Formula	.668**	<.001

** . Correlation is significant at the 0.01 level (2-tailed).

STATISTICAL ANALYSIS

The results were expressed as Mean \pm SD. To evaluate the differences between groups, the student 't'-test was used. Pearson correlation coefficient is used for comparison. Statistical analysis was done using the statistical software: SPSS-16.

DISCUSSION

In this study we used the traditional 24 hour urine collection to calculate Creatinine Clearance and compared it with Clearance values obtained through Cockcroft-Gault and MDRD formulae. The subjects were given proper written instructions for collecting 24 hour urine sample. Our study showed in group A (Creatinine Clearance >60 ml/min), Cockcroft – Gault formula showed strong positive correlation with Measured Creatinine Clearance than with eGFR obtained through MDRD formula.

The results of group A is similar to the results of studies which showed that the values from Cockcroft – Gault formula are much closer to the 24hour creatinine clearance compared with the MDRD formula.^{23,24,25} In group B (Creatinine Clearance <60 ml/min) both Cockcroft and MDRD showed weak positive correlation with Measured Creatinine Clearance. Measuring GFR is widely accepted as the best overall index of kidney function by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) in 2002. It is especially important when GFR reaches near stage 3 and 4. It is performed using inulin or ¹²⁵I-iothalamate clearance methods. However, these tests are technically impractical and expensive for everyday clinical use. The most common method for

assessing GFR is performing a timed urine collection (24hour) for evaluation of Creatinine Clearance. The need to collect a urine sample remains a major limitation of the Creatinine Clearance test.²⁶ Among the formulae available to estimate GFR, Cockcroft-Gault formula and the modification of diet in renal disease (MDRD) study equation have been recommended by the KDOQI practice guidelines to be used for the estimation of GFR. These equations depend upon the relation between serum creatinine and GFR and variations in creatinine production owing to age and sex related differences in muscle mass have been measured and incorporated into the formulas to improve the GFR.^{7, 23}

The MDRD equation was derived from a study of 1628 middle-aged, nondiabetic, chronic renal insufficiency patients that used a directly measured GFR by urinary clearance of ¹²⁵I-Iothalamate. The equation has not been validated for GFR >60 ml/min x 1.73 m² because the study did not include healthy persons. The most widely used equation is the abbreviated (four-variable) MDRD equation. This equation directly relates the accounted variables (e.g., serum creatinine, age, gender, and race) to GFR adjusted for BSA—that is, the determinants of body size are prepackaged in the equation and thus additional adjustment is not required.²⁶ The Cockcroft-Gault formula was developed in 1976 with data from 249 men, primarily in an inpatient setting, with a wide range of renal function. This uses age, the inverse of serum creatinine, and lean body weight to estimate creatinine clearance in milliliters per minute. For women, the equation should be multiplied by 0.85

It was not originally intended to be adjusted for body surface area (BSA). The inclusion of the weight factor is intended to adjust for muscle mass, a determinant of serum creatinine concentration. This implies that in clinical situations in which a change in weight is not the result of a similar change in muscle mass (e.g., edematous states, pregnancy, third spacing, overweight, obesity), the weight factor will adversely affect the performance of this formula²⁷

The above results showed that at low GFR levels (<60 ml/min) there is only weak positive correlation between the three methods available for estimation of Creatinine Clearance and at normal levels of GFR (>60ml/min) Cockcroft formula had strong positive correlation with the Measured Creatinine Clearance than the MDRD formula.

This could be due to the fact that the MDRD formula was developed mainly in CKD patients from the western population including whites and black but not been validated in Asian setting. It can under estimate or overestimate the renal function at low and normal GFR level. The biological variations of creatinine metabolism, as well as different cultural and social habits (e.g., different diets), affect serum creatinine levels, thus requiring an adjustment & Correction factors that are needed for other ethnic populations, such as Asians.²⁵ Studies need to be undertaken in Indian population to establish and incorporate adjustment & correction factors in the formulae so that it can be used for a wider range of renal function, in our population to give reliable results and therefore can replace the traditional Measured Creatinine Clearance test.

CONCLUSION

The present study shows weak positive correlation between the Measured Creatinine Clearance, MDRD and Cockcroft formulae at Clearance values <60 ml/min and strong positive correlation between Measured Creatinine Clearance and Cockcroft formula at Clearance values >60 ml/min. Since MDRD formula includes age, gender, and race and developed for the western population with chronic renal insufficiency, further research is needed in our population, to establish and incorporate adjustment & Correction factors in the formula, so that it can be used for a wider range of renal function, in our population to give reliable results and therefore can replace the traditional Measured Creatinine Clearance test.

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