Accuracy of commonly used equations for estimating glomerular filtration rate in Nepalese population

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ABSTRACT

Introduction - *Estimation of glomerular filtration is of utmost importance in clinical practice. Various equations have been developed in different populations based on serum creatinine. These equations have not yet been validated in the Nepalese population. This study was conducted to compare the accuracy Cockcroft Gault and Modification of Diet in Renal Disease equations for estimating the glomerular filtration rate in Nepalese population.*

Methods - *A total of 100 patients with chronic kidney disease were included in the study. Fifty patients had serum creatinine less than 1.5 mg/dl and 50 patients had serum creatinine more than or equal to 1.5 mg/dl. Glomerular Filtration Rate was measured as creatinine clearance from 24 hour timed urinary collections and estimated using both the Cockcroft-Gault and Modification of Diet in Renal Disease equations for all the patients. The degree of accuracy of each equation was calculated by the coefficient of determination(R^2).*

Results - *The mean glomerular filtration rate estimated from the Cockcroft Gault equation was 51.29 ml/min/1.73sqm and mean glomerular filtration rate estimated from the Modification of Diet in Renal Disease equation was 48.41 ml/min/1.73sqm whereas the mean measured GFR was 53.30ml/min/1.73sqm. The coefficient of determination (R^2) was calculated for both the equations. The Cockcroft Gault equation was more accurate in the Nepalese population (R^2=0.88) than the Modification of Diet in Renal Disease equation whose coefficient of determination was 0.84.*

Conclusions - *In the Nepalese population the Cockcroft Gault equation was more accurate in estimating the glomerular filtration rate in comparison to the Modification of Diet in Renal Disease equation .*

INTRODUCTION

Glomerular filtration rate (GFR) is defined as the rate at which an ultrafiltrate of plasma is produced per unit time. It is the best estimate of the number of functioning renal mass.[1] Normal value of GFR is related to age, sex, and body size and it is approximately 130 ml per minute per 1.73 sq m in young men and 120 ml per minute per 1.73 sq m in young women. Mean values decline as persons age.[2] Estimation of the GFR is of utmost importance in clinical practice as it is used in detection of Chronic Kidney disease, monitoring progression of chronic kidney disease (CKD), evaluation and management of complications in patients with CKD. It is also used by general practitioners to refer patients to Nephrologists, adjust the medication doses in renal impairment, assessment of risk for cardiovascular disease,medicolegal reimbursement.[3]

GFR is estimated from the urinary clearance of an ideal filtration marker, defined by $C_i = U_iV/P_i$ where Ci is the clearance of ideal filtration marker, Ui is the urinary concentration and Pi the plasma concentration of the substance and V is the urine flow rate.

Inulin fulfills the criteria as an ideal filtration marker, and its urinary clearance has long been considered the “gold standard” in measuring GFR however the availability of inulin is limited and the protocols for measurement of inulin clearance are inconvenient.[4] Exogenous filtration markers, such as iothalamate sodium and technetium Tc 99m DPTA, are simpler and have been used in clinical trials but they are also inconvenient and expensive because of the use of radioactive material, the requirement that multiple blood and urine measurements be taken over 3 to 4 hours, and the need for trained personnel to perform the procedure.

Clearance of creatinine is also used in clinical practice as it is endogenously produced, has a relatively constatnt rate of production. There is some degree of tubular secretion but it is minimal in patients with normal kidney functions.[5]

Creatinine Clearance (CrCl) = UV/P where U and P are urinary and plasma concentrations of creatinine and urine and V is the urine flow rate . Various clinical equations have been developed for estimating GFR from serum creatinine .

The first of these is the CCG equation described first by Cockcroft and Gault in 1976.[6]

$$\text{CrCl} = \frac{(140\text{-age}) \times \text{body wt(Kg)}}{72 \times \text{serum Creatinine(mg/dl)}}$$

The Cockcroft-Gault equation was derived from an investigation of 249 men with creatinine in a steady state; the subsequent companion equation for women was based on their 15% lower muscle mass. In one study of 394 subjects (208 men and 186 women), the correlation between estimated creatinine clearance and measured GFR was excellent (R^2 = 84%).[7] More recently, an equation was developed to predict GFR using data from

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1,628 patients enrolled in the baseline period of the Modification of Diet in Renal Disease (MDRD) study.[8] GFR = 170 x (S.Cr)-0.999 x (age)-0.176 x (BUN)-0.170 x (Serum albumin) 0.318, the obtained value is multiplied by 0.762 in females and by 1.18 in people of darker skin tone.

The correlation of GFR predicted from the "six-variable equation" with measured GFR was outstanding (R^2 = 90.3%).[9] Till date there are no records of the study of these prediction equations being tested for their accuracy in Nepalese patients. The aim of the present study was to compare the estimated GFR using above prediction formulae with 24-hour urine CrCl in Nepalese population

METHODS

The present study was a cross sectional comparative study. Study was done in patients attending Bir Hospital and Shree Birendra Hospital, Chhauni, Nepal. The study was approved by the institutional review board (IRB) of National Academy of Medical Sciences. An informed consent was taken from each study participant.

A total of 100 patients with diagnosis of CKD according to Kidney Disease Outcomes Quality Initiative (NKF/KDOQI) definitions were included in the study. Patients were excluded if they had any of the following conditions, not willing to give consent, acute renal failure and acute on chronic renal failure, urine output less than 500 ml / 24 hours, undergoing maintenance hemodialysis, patients with edema, liver cirrhosis, amputation, muscle wasting, significant pleural effusion or ascites and patients whose body weights were rapidly changing and age less than 18 years and more than 85 years.

The participants were asked to follow their normal daily activities and were asked to report to the laboratory next morning with the 24 hour urine in a container provided to them. Urine flow rate in ml/min was calculated using the total volume of urine. This urine was also used for measurement of urine creatinine levels. At the same time participants were asked to give a blood sample which was used to measure the hemoglobin, total leukocyte count, blood sugar level, serum creatinine level, blood urea level and serum albumin levels. The serum creatinine was measured by kinetic Jaffe test. The reagents used were picric acid and sodium hydroxide. Urine creatinine was also measured using the same principles. The blood urea was measured using the urease method. Serum albumin was measured using the bromocresol green method.

The GFR was measured using the creatinine clearance method of 24 hour urine collection. The GFR was also estimated using the two study equations ie the CCG equation and MDRD 7 equation. The means for the measured GFR and the GFR obtained by each of the study equations were compared using the student's paired t test. Linear regression analysis was done and the coefficients of determination (R^2) for each of the study equations were calculated.

Table 1(a). Baseline characteristics of the study participants.

Characteristics		Value
Total number of patients		100
Age in years	Mean±SD	53.90±15.22
Gender	M/F	66/34
Height (cm)	Mean±SD	159.00±7.00
Weight (kg)	Mean±SD	59.21±11.33
Body Mass Index (kg/m^2)	Mean±SD	23.51±3.77
Body surface area in m^2	Mean±SD	1.61±0.15
Existing illness	Diabetes	77
	Hypertension	78
Etiology of CKD	Diabetes	77
	Hypertension	6
	SLE	6
	CGN	6
	Others/unknown	12
Mean arterial pressure in mmHg	Mean±SD	101±15
Hemoglobin in g/dl	Mean±SD	11.20
Total leukocyte count per cumm	Mean±SD	8807±3330
Blood urea levels in mg/dl	Mean±SD	82.12±8.99
Serum creatinine level in mg/dl	Mean±SD	2.02±0.26
Random blood sugar in mg/dl	Mean±SD	179.54±61.13
Serum albumin in g/dl	Mean±SD	3.97±0.52
24 hour urinary volume in ml	Mean±SD	1678±773.61
Urinary creatinine level in mg/dl	Mean±SD	67.71±20.25
Measured GFR in ml/min	Mean±SD	53.37±33.58
CCG GFR in ml/min	Mean±SD	51.22±31.64
MDRD 7 GFR in ml/min	Mean±SD	51.22±31.64

CKD - Chrinic Kidney Disease, SLE - Systemic lupus erythematosus, MDRD - Modification of Diet in Renal Disease, CGN - Chronic Glomerulo Nephritis,

Table 1(b). Baseline characteristics of the study participants.

Characteristics		Number of participants
Ethnicity	Brahmin	18
	Chhetri	32
	Gurung	7
	Newar	17
	Magar	7
	Others	19

Table 2. Performance of the study equations according to various stages of CKD

Stages of CKD	N	Measured GFR	CCG GFR	R^2	MDRD 7 GFR	R^2
		Mean±SD	Mean±SD		Mean±SD	
Stage 1	13	114.41±15.73	104.92±23.32	0.55	104.55±33.17	0.26
Stage 2	29	72.44±8.11	68.32±17.37	0.22	61.24±13.16	0.16
Stage 3	27	45.61±9.23	43.74±11.45	0.62	44.31±13.22	0.69
Stage 4	19	20.82±4.60	23.98±6.02	0.16	20.33±5.91	0.20
Stage 5	12	9.32±3.82	12.44±5.63	0.66	10.18±4.06	0.53

Table 3. Performance of the study equations according to gender

Gender	N	Measured GFR	CCG GFR	R^2	MDRD 7 GFR	R^2
		Mean±SD	Mean±SD		Mean±SD	
Male	66	49.95±34.33	48.74±32.71	0.93	48.18±34.87	0.89
Female	34	59.80±31.42	56.25±29.20	0.75	48.86±26.46	0.75

Table 4. Performance of the study equations according to serum creatinine

Serum Creatinine	N	Measured GFR	CCG GFR	R^2	MDRD7 GFR	R^2
		Mean±SD	Mean±SD		Mean±SD	
Group 1 ≤1.5mg/dl	50	79.73±24.49	75.41±25.82	0.70	72.32±27.33	0.60
Group 2 ≥1.5mg/dl	50	79.72±24.46	27.21±12.90	0.84	24.52±13.24	0.83
Total	100	53.30±32.21	51.29±24.67	0.88	48.41±27.20	0.84

RESULTS

During the study period of one year a total of 100 participants were included in the study. The total number of male participants were 66 and females were 34. Out of the total participants Chhetris were the maximum (32%) in terms of ethnic groups. They were followed by Brahmins (18%), Newars (17%), Magar and Gurung communities were equally represented (7% each) and other ethnic groups comprised 19 % of the total study population. The mean age of the study population was 53.9 years with a standard deviation of 15.2 years. The mean body weight of the study population was 59.2 (±11.3)Kg. The mean height was 159.3(±7.8) Cm. The mean Body Mass Index (BMI) was 23.51(±3.77) Kg/m^2. The mean of the mean arterial pressure was 101±15 mmHg. Total number of patients with Hypertension was 78. Seventy seven out of the 100 study participants had diabetes. Other study variables along with baseline characteristics are shown in the following table.(Table 1)

The mean estimated GFR from the CCG equation was 51.2±31.64ml/min and that from the MDRD7 equation was 48.4±32.1ml/min. The mean measured GFR was 53.3±33.58. The coefficient of determination(R^2) for the CCG equation was 0.88 and for the MDRD 7 equation was 0.84.
The results of the study were further analyzed in various subgroups according to the various stages of CKD and the results are shown in the following table (Table 2). The study population was stratified according to sex and the performances of both the equations were analyzed. The results are shown as in the following table (Table 3). The study participants were divided in two groups according to the serum creatinine. The following results were observed. (Table 4)

DISCUSSION

GFR determined by inulin or radioisotope studies, is widely considered as the best way to evaluate renal function. Unfortunately, this method is impractical to perform and available in only a small number of hospitals. To circumvent this problem, a number of predictive equations have been developed for a bedside assessment of GFR.[10] The recent K/DOQI guidelines,[11] advocate use of the formulae proposed by either Cockcroft and Gault (CCG) or the Modification of Diet in Renal Disease (MDRD) equations to predict GFR in adults.[12] Most clinicians throughout the world, utilize them to identify and stratify patients at risk of renal disease. These equations are also used to estimate GFR in individuals who had normal Serum creatinine (Scr) level for certain situations such as in evaluating living kidney donors. However, several recent studies showed that both equations were much less accurate and precise in those who are otherwise healthy with normal Scr levels.[13] Furthermore, both equations were derived primarily from a Caucasian population thus it may not be directly applicable to other racial groups. The validity of these prediction equations need to be tested before their application in clinical practice in other people.

An important characteristics of the present study population cohort is that it included subjects whose measured GFR ranged from 3.15 to 145.5 ml/min per 1.73 m^2 . Thus, the performances of the CCG and MDRD7 formulas could be assessed over a wide range of kidney function. All of the subjects included in this study were Nepalese, the performances of the MDRD and CCG formulas could be assessed in a group of subjects whose anthropometric characteristics are slightly different from those of Americans. For example, when compared with the MDRD cohort, the mean weight of our study population was 20% lower (59kg Vs 79.6 kg) and the mean BSA was 13% lower (1.63 versus 1.91 kg/m^2), whereas, on average, our patients were only 3.3 yr older than those included in the MDRD cohort (53.9yr versus 50.6 yr) and a similar percentage of subjects were male in both cohorts (66 versus 60%). The study with similar objective and methodology was done in Thailand by Charoen Kaitwatcharachai.[14] The sample size was less than in the present study (100 Vs 60). The mean measured GFR in the Thai study was 105 ml/min/1.73m^2. The study results were very contrasting to the present study. The presented data demonstrated that prediction equations using either the CCG or MDRD performed poorly in subjects of Thai origin (R^2 = 0.1, 0.18 respectively). Whereas the finding in the present study showed the R^2 of 0.887 and 0.843 for the CCG and MDRD 7 equations respectively.

Studies by Tazeen HJ et al in Pakistan had a total of 332 patients (higher than in the present study) and were significantly older as the study included people of more than 40 years of age.[15] The mean BMI was comparable to our population (23.4). Twenty eight percent of the study population had diabetes. The coefficient of determination for measured GFR on the logarithmic scale was 0.667 and 0.555 for the CCG and MDRD Study equations, respectively.

There are some limitations to the present study. The sample size was small and all ethnic groups of Nepal were not represented in the study. The 24 hour urine collection may not have been accurate and methods of measuring the various laboratory parameters were not standardized across laboratories. Further studies are required to fully validate these equations in the Nepalese population.

CONCLUSION

In the Nepalese population both the CCG and MDRD 7 equations had high coefficient of differentiation. CCG equation was more accurate in estimating the GFR in comparison to the MDRD 7 equation when measured creatinine clearance was used as the control. This finding was true irrespective of the serum creatinine levels, in both sexes and across all stages of CKD.

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