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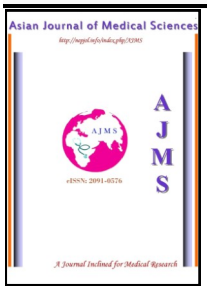

Assessing Renal Function Using Cockcroft-Gault and Modification of Diet in Renal Disease Equations in Healthy South Indian Males – A pilot study

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Abstract

Objective: To compare the estimated GFR (eGFR) calculated by CG and MDRD formulae and to study the correlation between body mass index (BMI) and eGFR in healthy South Indian men.

Material & Methods: Healthy male volunteers were enrolled. eGFR was estimated by CG and MDRD equation and categorized as normal, mild, moderate, severe renal impairment and renal failure. Estimated clearance by these two methods was compared using paired student's t test. Correlations were performed with pearson's correlation test.

Results: A total of 491 subjects were enrolled. Mean (±SD) eGFR was 91.05 (± 15.04) and 86.43 (± 13.61) by CG and MDRD equations respectively; this difference though statistically significant (p=0.01), was clinically insignificant. A reduced renal function (<90ml/min) was found in 50.9% and 63.1% of population by CG and MDRD formulae respectively. BMI positively correlated with CG-GFR (r=0.471, p<0.001), and negatively correlated with MDRD-GFR (r=-0.268, p<0.001). Serum creatinine positively correlated with BMI (r=0.19, p<0.001).

Conclusion: The normal eGFR seems to be lower in the South Indian population compared to the western standards. CG and MDRD formulae may need to be validated before these can be applied for staging of kidney function in a healthy Indian population.

Key Words: *Cockcroft-Gault formula; Modification of Diet in Renal disease (MDRD) equation; renal function*

1. Introduction

Chronic kidney disease (CKD) is an increasing public health problem in India. Proper population based epidemiological studies on the exact prevalence of CKD in India are lacking.[1] The National Kidney Foundation, through its Kidney Disease quality Outcome Initiative (K/DODI) and other National institutions recommend glomerular filtration rate (GFR) estimates for the diagnosis, classification, screening, and monitoring of CKD.[2,3] Without GFR measurements the clinical manifestations of kidney failure remain largely silent until renal function is so low that the patient may be in end stage renal disease.[4] Measuring serum creatinine is easier but this test cannot detect early kidney disease. In many clinical settings where creatinine clearance is not available decisions concerning drug dosing must be made based on estimations of creatinine clearance.[5] Accurate determinations of GFR can be done using inulin clearance or radionuclide-labeled markers. Since GFR determinations by inulin or radioisotope studies on large numbers of patients are impractical, cumbersome, and expensive, clinicians also rely on GFR prediction equations on a daily basis. Cockcroft-Gault (CG) and Modification of Diet in Renal Disease (MDRD) formulae are the most widely used and recommended by K/DOQI guidelines to estimate kidney function.[6] Though both these formulae have been validated in Western populations, and in patients with renal dysfunction, there is still a need to validate them in Asian populations.[7,8] The issue of obtaining an accurate estimate of CKD prevalence is further limited by this lack of GFR estimating equations validated for the Indian population.[9] Just as the proposed cut-offs for defining overweight and obesity are not appropriate for Asian Indians,[10] eGFR calculated by CG/MDRD equation which were developed primarily

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based on Western data may not be appropriate in the Indian population. Hence this pilot study to assess the renal function in healthy South Indian males was done. This would also add to the limited medical literature on the reference ranges of eGFR in this population.

This study compares these two - the CG formula and the MDRD study equation, in young healthy South Indian males. Obesity has been shown to be a strong predictor of CKD.[11-13] Therefore we estimated the correlation between body mass index with serum creatinine and eGFR by CG and MDRD formulae. Hence this study was conducted to compare the estimated GFR calculated by the CG and the MDRD formulae in healthy South Indian males, to study the correlation between BMI and eGFR by CG and MDRD formulae and to study the correlation between BMI and serum creatinine.

2. Material and Methods

The study was conducted at a tertiary care teaching hospital at Mangalore, Karnataka. It was a cross sectional study conducted over a period of six months in healthy male volunteers aged between 18 and 60 years. Subjects with any intercurrent illness or chronic systemic diseases like diabetes mellitus, hypertension or renal impairment and any chronic drug therapy were excluded. Before inclusion to the study, these subjects were screened for the absence of hypertension, diabetes, cardiovascular disease, and microalbuminuria. The study protocol was approved by the Institutional Ethics Committee. Written informed consent was taken from all the subjects. All the subjects who were willing to give the written informed consent during the study period were included in the study. Sample size was not calculated as this pilot study was a first of its kind in the light of lack of similar previous data in our setup. Demographic characteristics – age, height, and weight of all the subjects were recorded. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Based on BMI, subjects were categorized as underweight (< 18.4), normal (18.5 – 22.9), overweight (23 – 24.9) and obese (>25).[10] All subjects were investigated for serum creatinine and blood urea. GFR was estimated by the CG formula (CG–GFR) and the 4-variable MDRD study equation (MDRD–GFR). Based on eGFR volunteers were categorized as normal (>90ml/min), mild renal impairment (60-89ml/min), moderate renal impairment (30-59ml/min), severe renal impairment (15-29ml/min) and renal failure (<15ml/min).[14]

Statistical analysis: Estimated creatinine clearance obtained by the two methods was compared using student's t test. Correlations were performed with the Pearson's correlation test. A p-value less than 0.05 was considered statistically significant.

3. Results

A total of 491 healthy male subjects were enrolled. Clinical and laboratory characteristics of the study population are summarized in Table 1.

Table-1: Demographic data and performance of estimated GFR (eGFR)

Characteristics	Mean ± SD
N	491
Age (years)	23.82 ± 5.51
Weight (kgs)	60.26 ± 8.48
Height (meters)	1.69 ± 0.06
BMI	21.02 ± 2.65
S. creatinine (mg/dl)	1.08 ± 0.14
S. urea (mg/dl)	10 ± 2.5
CG - GFR	91.05 ± 15.04
MDRD - GFR	86.43 ± 13.61

Student's t-test showed a significant difference between the mean eGFR by CG formula (91.05±15.04) and MDRD study equation (86.43±13.61) (p=0.01), however it was clinically not significant.

Table 2 shows distribution of healthy volunteers according to BMI categorization.

Table-2: Distribution according to BMI

BMI	Number of subjects (%); N=491
Underweight (<18.4)	82 (16.7)
Normal (18.5 – 22.9)	299 (60.9)
Overweight (23 – 24.9)	61 (12.4)
Obese (>25)	49 (10)

Table 3 shows distribution of subjects according to CG and MDRD-GFR.

Table-3: Degree of renal impairment according to CG-GFR and MDRD - GFR

Creatinine clearance grading	CG (%)	MDRD (%)	X^2 value	p value
Normal (≥90ml/min) (stage 1)	241 (49.1)	181 (36.9)	14.46	0.0001
Mild (60 – 89 ml/min) (stage 2)	246 (50.1)	303 (61.7)	12.95	0.0003
Moderate (30 – 59 ml/min) (stage 3)	04 (0.8)	07 (1.4)	0.36	0.54

Of the 491 subjects, four (0.82%) had serum creatinine values above the normal reference range (0.8 – 1.4 mg/dl). Table 4 shows characteristics of these four patients whose serum creatinine value was above the reference range.

Table-4: Characteristics of subjects with increased serum creatinine levels

Characteris-tics	Volunteer 1	Volunteer 2	Volunteer 3	Volunteer 4
Age (years)	20	23	24	26
Weight (kgs)	81.72	55.04	70.42	70.54
BMI	23.62	19.5	22.73	23.30
Serum creatinine (mg/dl)	1.5	1.9	2.2	1.5
CG-GFR (ml/ min)	90.80	47.07	51.57	74.46
MDRD-GFR(ml/ min/1.73m^2)	60	44	37	57

Table 5. Correlation of BMI *vs* age, serum creatinine, CG and MDRD-GFR

Characteristics	BMI	
	r value	p value
Age	0.31	<0.01
Serum creatinine	0.19	<0.01
CG-GFR	0.47	<0.001
MDRD-GFR	-0.27	<0.001

We found that the relationships between body mass index (BMI) and GFR were different, depending on the equation used. While BMI positively correlated with CG-estimated GFR (r=0.471, p<0.001), it showed a negative correlation with MDRD-GFR (r=-0.268, p<0.001). Age (r=0.31, p<0.01) and serum creatinine (r=0.19, p<0.001) positively correlated with BMI (Table-5).

4. Discussion

This pilot study compared CG and MDRD estimated GFR in 491 healthy subjects who enrolled for the study during the six month study period. GFR estimating equations provide a more accurate assessment of the level of kidney function than serum creatinine alone. International organizations recommend that clinical laboratories report estimated GFR and that clinicians use these to evaluate kidney function for all patients.[5,6] However, this recommendation has been debated by many centers. This is further complicated by the availability of more than one equation for GFR estimation and previous studies showing that none of these are optimal for clinical use in an Indian setting.[3]

The present study was done on young male healthy individuals with normal serum creatinine values. The CG -GFR and MDRD–GFR showed statistically significant difference in GFR values but it was clinically insignificant. The difference between GFR estimates can be explained partly by their non-validation in Indian population and lack of an Indian subgroup in the original study population from which these equations were derived. In some studies, the MDRD study equation has been reported to be more accurate than CG formula [15-17] where as other studies have found that the two yield similar results.[6,18-20] In our study too both CG formula and MDRD equations have shown similar eGFR.

It is well recognized that Indian population has a lower normal range of GFR than western population.[21] Srinivas et al, evaluated the performance of serum creatinine based equations to estimate GFR in South Asian healthy renal donors and found that the mean GFR was 95.5±11.6 ml/min.[22] Our study too is comparable with earlier reports and the mean eGFR by CG and MDRD equations was found to be 91.05±15.04 and 86.43±13.61 respectively.

More than 50% of subjects had mild chronic kidney disease (stage 2) estimated by both the formulae, which is a staggering revelation. The prevalence of moderate renal impairment (< 60 ml/min) averages from 0.8 to 1.4%, depending on the estimating equation. It seems unlikely that an otherwise healthy population having a mean age of 23.82 $\pm$ 5.51 has such a high prevalence of mild CKD. This suggests that both the CG and MDRD equations may be underestimating GFR at least in healthy Indian subjects. Further studies with both genders and more number of subjects are required to confirm the true prevalence of CKD and whether eGFR by CG and MDRD equations are underestimating renal impairment in south Indian population. CG–GFR was directly proportional to BMI whereas MDRD-GFR was inversely proportional to BMI. Obviously, in the CG formula the presence of weight as a factor influences these findings. Body weight is one of the parameter for calculating BMI and estimated GFR by CG formula hence body weight must be positively related by mathematical coupling. On the other hand inverse association between BMI and MDRD- GFR though seemingly paradoxical, can be explained by the observation that BMI increases with age (upto the age of 60 years) and MDRD-GFR decreases with age, hence BMI is expected to be inversely related to MDRD-GFR.

As far as the authors' knowledge goes, there is no community based study which compares the GFR estimates derived from these two equations in south Indian population. GFR estimating equations validated for south Indian populations are needed before reliable studies of CKD prevalence are done.

The classification of CKD is based on GFR, so a reproducible and accurate method is needed for correct

staging. This study shows that south Indian population has a lower normal GFR compared to western population. From our study we conclude that CG and MDRD equations may be underestimating GFR at least in healthy south Indian subjects. However further studies with both genders, more number of subjects and comparison of eGFR with gold standard urinary clearance of inulin are required to confirm these findings. This is one of the grass root level research and needs further community based programs as a main pillar for confirmation.

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