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Research Article

OBSERVATION OF ESTIMATED GFR IN THE ASSESSMENT OF CHRONIC KIDNEY DISEASE: APPLICATION AND PRACTICE

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ABSTRACT

Staging of Chronic kidney disease (CKD) is important not only for proper evaluation and treatment but also to consider the need for dialysis. This staging depends on GFR value which is measured by radio labeled substances and 24 hours urine creatinine clearance but these have their own limitations. Serum creatinine based estimated GFR (eGFR) is more convenient and cost effective. Therefore this study was undertaken to estimate GFR by using Cockcroft-Gault formula, MDRD equation and MCQE in controls and CKD patients. The study comprised of 123 healthy individuals as control group and 128 patients with evidence of CKD. In control group, MCQE provided a reasonable value of eGFR in all age groups when compared with CG and MDRD formulae. Besides this, MDRD provided a higher value of eGFR than CG in the age group of above 60 years. CG and MDRD placed in, around 50% of the control population under less than<90ml/min/1.73m^2 grading them all as stage 2 mostly and only a few as stage 3. MCQE placed only 10% of healthy individuals under stage 2. Therefore, MCQE more appropriately estimates GFR in control group than CG and MDRD. There is a significant decrease of estimated GFR by three formulae in CKD group when compared with control group. In CKD group, very few cases are under stage 2 whereas stage 3 comprises of 28.2%, 26% and 23% according to CG, MDRD and MCQE respectively. The distribution of stage 4 includes 32%, 28.2% and 27% and stage 5 includes 39%, 45.3% and 48% according to CG, MDRD and MCQE respectively. This reflects the fact that the GFR is underestimated in CKD group and the same might have happened in the controls too. However, with some reservation, MCQE in control and MDRD and MCQE in cases are found to be satisfactory in staging CKD in the present study.

Keywords: CKD, eGFR, Serum Creatinine, CG, MDRD, MCQE.

INTRODUCTION

The epidemiology of chronic Kidney disease (CKD) is a world-wide phenomenon with poor outcome[1]. In CKD, there is a decreased number of functional nephrons and the remaining healthy nephrons maintain the Glomerular Filtration Rate (GFR) by hyperfiltration which consequently leads to compensatory hypertrophy. The Kidney Disease Outcomes Quality Initiative (K/DOQI) defines chronic kidney disease as either kidney damage or a decreased kidney glomerular filtration rate of less than 60 ml/min/1.73m^2 for 3 or more months[2]. Classification is a major step in CKD which is done by quantifying the glomerular filtration. GFR will assess the filtering capacity of nephrons in the kidney[3]. It is an index for renal function and without an awareness of GFR, the clinical features in CKD may remain silent and deceptive[4]. GFR is helpful for early detection of renal impairment and is a good indicator for the need of dialysis. The K/DOQI classified CKD patients based on GFR into five stages. These are stage 1 (GFR ≥ 90 ml/min/1.73 m^2), stage 2 (GFR 60 to 89 ml/min/1.73 m^2), stage 3(GFR 30 to 59 ml/min/1.73 m^2), stage 4 (GFR 15 to 29 ml/min/1.73 m^2) and stage 5 (GFR less than 15 ml/min/1.73 m^2)[5].

CKD staging and thereby, the assessment of renal function is helpful for clinicians for proper diagnosis and to undertake suitable therapeutic measures. After third decade, GFR starts declining around 0.75 ml/min/year in normal people[6, 7]. It may be further aggravated in older age. This may be due to either physiological or pathological processes which include a decline in the vascular elasticity of kidneys with ageing[8], besides diabetes and hypertension which are common associations during senescence [9].

Gold standards for GFR assessment employ Inulin and Radiolabeled substances but both these are not free of adverse effects and hence do not constitute routine investigations. Estimation of serum creatinine is a simple method and commonly used for estimation of GFR. However, serum creatinine based GFR has its own drawbacks like the tubular secretion of creatinine, and variation of serum creatinine from individual to individual based on muscle mass. Additionally, it varies with the assay procedure. Besides this, any significant rise of serum creatinine reflects already a fall of about 50% of GFR. In spite of these shortcomings of serum creatinine as an indicator for CKD, it still serves as an acceptable parameter for diagnosis of CKD in clinical practice[3]. Measured Creatinine clearance by using 24 hours urine has its own disadvantages as it will not be possible to collect accurate 24 hour urine in older people and dialysis patients[10].

Measuring GFR can be done by employing different equations using serum creatinine. These methods are simple, cost effective and less time consuming[11]. The most common formulae are Cockcroft-Gault formula (CG) [12] and Modification of Diet in Renal Disease (MDRD) [13]. Mayo Clinic Quadratic Equation (MCQE) [14] has been brought forth as an alternative. MDRD and MCQE are based on clearance of I^{125} iothalamate where as CG is based on the creatinine clearance. These three formulae too have their own limitations.

The current study was undertaken to estimate and compare the CG, MDRD and MCQE equations in assessing the GFR in control and CKD groups.

MATERIALS AND METHODS

The study comprised of 251 subjects. Of these, control group comprised of 123 age and sex matched healthy individuals who were free of features of kidney disease and were having a normal blood urea and serum creatinine level. The upper limit for serum creatinine levels was 1.2 mg/dl and the corresponding value for blood urea was 45 mg/dl. Individuals suffering from diseases that are likely to alter these parameters were excluded from the study. Likewise, persons with history of drug intake which cause changes in these parameters were also excluded. 128 patients with evidence of CKD were taken as cases. These patients were admitted into Nephrology unit of MIMS hospital, Nellimarla. The CKD cases included both non dialysis group and hemodialysis group. They were included in the study on the basis of clinical signs and symptoms of kidney disease along with elevated blood urea and serum creatinine levels. The hemodialysis patients were undergoing hemodialysis in Nephrology department, 3 to 4 hours per day, 2-3 times in a week for the past 6 to 18 months, but non dialysis patients were under conservative medical therapy.

Informed consent was taken from the patients and controls who participated in the present study. Ethical committee approval has also been obtained.

In all the subjects, Height was measured in centimeters and Weight was recorded in kilogram on standard clinical weighing machine. BMI was calculated as Weight in kilogram divided by Height in

meters squared. Based on BMI they were categorized as underweight (<18.4), normal (18.5-22.9), overweight (23-24.9) and obese (>25) .Individuals with a BMI of 25 to 29.9 were regarded as mildly obese whereas those with a BMI exceeding 30 were considered as moderately obese. Moderately obese subjects were excluded from the study.

In all these groups blood urea and serum creatinine were measured. The blood urea was estimated by GLDH – Urease method[15]. Serum creatinine was estimated by Jaffes method[16]. The eGFR was computed by the following methods:-

1. Cockcroft-Gault Creatinine Clearance (ml/min)[12] = (140 - age) x (weight in kg) / Serum Creatinine (mg/dl) x 72 (Multiply with 0.85 if female)CG formula is adjusted to body surface area (BSA) by using DuBois, DuBois method[17,18] BSA = ($W^{0.425} \times H^{0.725}$) x 0.007184
2. MDRD Creatinine Clearance (ml/min/1.73m^2)[13] = 186 x (Serum Creatinine (mg/dl))$^{-1.154}$ x (age in years)$^{-0.203}$ x 0.742 (Multiply with 0.742 if female)
3. The MCQE estimated GFR (ml/min /1.73 m2)[14] = exp [1.911 + 5.249 / SCr – 2.114 / SCr^2 – (0.00686 x age (years)] (– 0.205 if female). Where SCr is Serum Creatinine in mg/dl. Values <0.8 mg/dl set to 0.8 mg/dl, as per the reported method.

All the data are expressed in Mean and Standard deviation. For the statistical significance, Z test was performed.

RESULTS

Table –I Shows Demographic features and diagnostic parameters in Controls and CKD Patients.

	Control (n=123)	CKD Patients (n=128)
Age (mean±SD) years	44.02±13.76	46.45±11.78
Sex (Males %)	69%	62.5%
(Females %)	31%	37.5%
Body weight(kgs)	66.72±6.64	62.70±6.88
Height (cm)	172.67±5.17	172.04±5.93
Blood urea (mg/dl)	28.55±8.16	99.76±38.13**
Serum Creatinine (mg/dl)	0.90±0.13	4.49±2.51**

****p<0.001**

Table I :The diagnostic criteria for CKD consisting of blood urea and serum creatinine were significantly higher (p<0.001) in CKD patients when compared to control.

Table- II Shows Distribution of Control and Cases according to BMI.

BMI	Control (n=123)	CKD Patients (n=128)
Under weight (<18.4)	05 (4%)	16(12%)
Normal (18.5-22.9)	74 (60%)	83(65%)
Over weight (23-24.9)	29 (24%)	19 (15%)
Mildly Obese (25-29.9)	15 (12%)	10 (8%)

Table II: Most of the subjects in both control and CKD patients had normal BMI. The number of subjects falling under lower and higher spectrum of BMI in both the groups was much less.

Table –III Shows Creatinine Clearance in Controls and CKD Patients.

	Control (n=123) (mean±SD)	CKD patients (n=128) (mean±SD)	p value comparison between control vs. CKD
CG (ml/min/1.73m^2)	92.12±20.41	23.56±14.15	<0.001
MDRD (ml/min/1.73m^2)	92.61±20.52	20.82±14.52	<0.001
MCQE (ml/min/1.73m^2)	114.94±19.11	22.47±16.55	<0.001

Table III: When the creatinine clearance values between control and CKD cases were compared on the basis of CG, MDRD and MCQE equation it was observed that the values were significantly decreased (p<0.001) in the CKD cases as per all the three equations.

In control group, there was no significant variation in creatinine clearance in respect of CG and MDRD equation (p= not significant). However the value of clearance as per the MCQE equation was significantly higher (p<0.001) when compared to CG or MDRD values.

In CKD group, there was no significant difference in creatinine clearance in respect of CG, MDRD and MCQE formulae (p= not significant).

Table –IV Shows Age wise Creatinine clearance in Control by using CG, MDRD and MCQE.

Age in years	CG (ml/min/1.73m^2)	MDRD (ml/min/1.73m^2)	MCQE (ml/min/1.73m^2)
20-29(n=24)	113.89±19.75	108.46±22.24	133.56±15.14**
30-39(n=24)	103.44±16.02	99.50±20.02	124.27±16.67**
40-49(n=28)	89.36±13.47	87.22±18.07	110.23±15.84**
50-59(n=30)	79.08±10.96	84.75±16.16	105.58±14.30**
60-70(n=17)	72.93±9.74	83.28±13.84*	99.77±12.79**

***p<0.05; **p<0.001**

Table IV: When the creatinine clearance was compared age wise in control group, it was noticed that there was no significant difference in the values in 20-29, 30-39, 40-49 and 50-59 years range in respect of CG and MDRD equation (p=not significant).But in the age range of 60-70 years the creatinine clearance was significantly higher (p< 0.05) as per the MDRD equation.

In all the age groups in controls the creatinine clearance as per MCQE method was significantly higher when compared with CG and MDRD ($p<0.001$)

(This is legend for table V, place it under that table only and delete this line) Table V: In control group both CG and MDRD equation included a much higher number of normal individuals as having creatinine clearance value below <90 ml/min/1.73m^2. This constituted 48% and 49.6% in respect of CG and MDRD. Thus many control cases which were apparently healthy with a normal serum creatinine were included as CKD patients under stage 2 and stage 3 of CKD. As per MCQE method, only 10% of control cases were included under stage 2 of CKD and there was not a single case under stage 3. Therefore MCQE appears to be comparatively a better method for assessing GFR in healthy control.

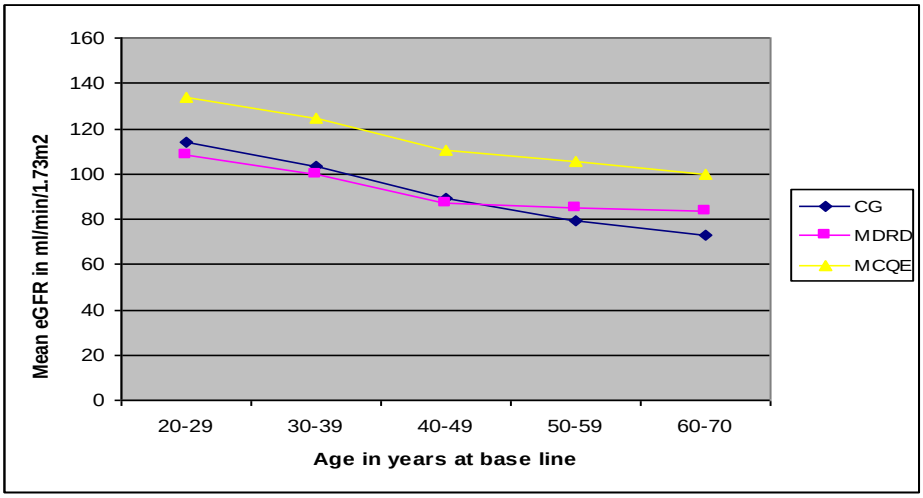

Fig-1: Shows calculated eGFR by CG, MDRD and MCQE versus Age in years.

Table –V Shows Distribution of control in different stages on the basis of Creatinine clearance.

Stages	CG (ml/min/1.73m^2)	MDRD (ml/min/1.73m^2)	MCQE (ml/min/1.73m^2)
50-59 ml/min/1.73m^2 (stage-3)	02 (1.6%)	02 (1.6%)	0 (0%)
60-89 ml/min/1.73m^2 (stage-2)	57 (46.4%)	59 (48%)	12 (10%)
≥ 90 ml/min/1.73m^2 (normal)	64 (52%)	62 (50.4%)	111 (90%)

Table –VI: Shows Stage wise classification of CKD patients by using CG, MDRD and MCQE:

Stages	CG (ml/min/1.73m^2)	MDRD (ml/min/1.73m^2)	MCQE (ml/min/1.73m^2)
Stage 1 >90 ml/min/1.73m^2	0	0	0
Stage 2 60-89 ml/min/1.73m^2	01 (0.8%)	01 (0.8%)	03 (2%)
Stage 3 30-59 ml/min/1.73m^2	36 (28.2%)	33 (26%)	30 (23%)
Stage 4 15-29 ml/min/1.73m^2	41 (32 %)	36 (28.2%)	34 (27%)
Stage 5 <15 ml/min/1.73m^2	50 (39%)	58 (45.3%)	61 (48%)

Table VI: The distribution of CKD into different stages on the basis of CG, MDRD and MCQE does not show any appreciable difference in respect of stages 1 to 4, however for stage 5, there is a closer compatibility between MDRD and MCQE equations. Therefore for assessment of renal function in CKD patients MDRD or MCQE are appear to be almost equally appropriate.

DISCUSSION

Evaluation of renal function by estimating GFR is one of the most important aspects in the management of CKD. Accurate GFR measurement is carried out by infusion of a substance like ^{51}Cr-EDTA or ^{99m}Tc-DTP[19]. But these are neither cost effective, nor free of risk and hence are not suitable for routine clinical practice. Serum Creatinine is also a sensitive marker of GFR associated with changes in renal function[20]. However, serum creatinine alone cannot provide the exact status of the renal impairment because appreciable rise of serum creatinine is required to identify 50% of fall in GFR. Therefore, serum creatinine based estimated GFR (eGFR) was introduced for more accurate results, It does not require utilization of nephrotoxic contrast medium, but this procedure requires timed urine collection (24 hours), which introduces its own inaccuracy and inconvenience[21].

In the year 1976, Cockcroft and Gault formulated CG formula on the basis of observations done on the male hospitalized patients by using 24 hours urine creatinine excretion from two 24 hours urine collections obtained. In the case of women, the eGFR is corrected by multiplying with 0.85. The main purpose of CG is to calculate the Creatinine clearance[12]. But the CG equation is biased because of the body weight parameter in the equation[22]. Based on body weight CG eGFR overestimates GFR in obese and underestimates in lean individuals. However, this can be overcome by adjusting to body surface area. At the same time, there are doubts about the accuracy of CG formula in individuals with normal renal function especially in older age group people [23] because the age in the CG formula is inversely proportional to eGFR.

In the year 2000, Levey introduced a new formula which was referred to as MDRD and this was based on the renal clearance of ^{125}I-iothalamate in patients with moderate CKD. But applicability of MDRD in healthy individuals is not clearly understood[23]. The importance of MDRD formula is, it does not require patient's weight and does not need any correction for body surface area. Johnson[24] and Lamb[25] reported that it can only estimate lower GFR values that is less than 60 ml/min/1.73m^2 with accuracy. Hence it can give better result only when GFR declines. Rule[14] reported that MDRD did not improve in performance even after recalibration of serum creatinine and there is still bias in patients with CKD.

In the year 2002, NFK-K/DQOI published clinical practice guidelines and proposed uniform use of eGFR for grading CKD and recommended the use of CG and MDRD formulae[26]. But the accuracy of these two formulae in staging of CKD patients is still debated[27]. Corsonelo[28] suggested that several drugs cause depression of GFR and therefore detection of CKD in early stages where the serum creatinine is near normal is important for proper therapeutic management. But CG and MDRD formulae have maximum disagreement in the low and normal serum creatinine ranges, thus causing inaccuracy[29, 30]. There exists more controversy around the CG and MDRD accuracy in elderly people[31] and End stage renal disease[32]. Because of various ambiguities in the assay of the eGFR by CG and MDRD methods as highlighted above, the other alternative method i.e. Mayo clinic quadratic equation (MCQE) is taken into consideration for estimating eGFR. In the year 2004, Rule equated new equation MCQE on the basis of ^{125}I-iothalamate clearance in 320 patients with CKD and 580 healthy individuals. Due to mixed population, the result of creatinine dependent MCQE gave intermediate performance[14], though it does not underestimate normal GFR[33]. Hence MCQE is found to be a better alternative to CG and MDRD[34].

In the present study, creatinine clearance values using CG, MDRD and MCQE in CKD patients are significantly lowered when compared with control ($p<0.001$) (Table-III). This is evident by raised serum creatinine in CKD group. As creatinine is the common parameter in all the three formulae, the CG, MDRD and MCQE based eGFR is altered. In control group, there is no significant difference between CG and MDRD equation. But MCQE registered significantly higher value of eGFR ($p<0.001$) when compared with both CG and MDRD. Srinivas[35] studied GFR by using 99mTc-diethylenetriamine penta acetic acid (DTPA) in renal donors of south Asian population and reported that the mean GFR is 95.5 ml/min/1.73 m^2±11.6. In our study mean GFR by CG, MDRD and MCQE was observed to be 92.12 ml/min/1.73 m^2±20.41, 92.61 ml/min/1.73 m^2±20.52 and 114.94 ml/min/1.73 m^2±19.11 respectively in the control group.

In ageing process, there is a decline of muscle mass called sarcopenia which leads to decreased level of muscle creatinine and later the serum creatinine levels. But normally there is an increased level of serum creatinine with ageing which is due to a decline in kidney function, typically seen as age advances, and is associated with decreased level of eGFR[36, 37]. In our study of control subjects, it was observed that there was a progressive decline in GFR as the age advances and it is true by all the methods of estimation of GFR. (Table IV). When a comparison was made between CG and MDRD methods in respect of older age group, it was reported by both Garg[38] and Wieczorowska[39] that older individuals more than 60 years of age showed a higher value for GFR by the MDRD method in comparison to the CG method. Our observations in the present study in respect of GFR in controls over 60 years of age as estimated by MDRD and CG methods are in agreement with the authors mentioned above. Carnevale[40] reported that MCQE provides overestimated value in old subjects compared with 24 hours creatinine clearance. In our study of controls, MCQE provided a significantly ($p<0.001$) higher GFR values in all age groups when compared with CG and MDRD. More or less it is the MCQE method which reasonably approximates to normal GFR values in all age groups.

In our study both CG and MDRD formulae included normal healthy individuals in stage 2 and stage 3 of CKD though there was no apparent evidence of renal impairment and they had a normal serum creatinine level. They comprised 46.4% in stage 2 by CG and 48% by MDRD. In case of stage-3 the inclusion of healthy individuals was to the extent of 1.6% by both the CG and MDRD equations (Table-V). This suggests that CG and MDRD underestimate GFR. In case of MDRD, it generally underestimates GFR at the higher end or within normal ranges and provides inaccurate results[41]. Both the MDRD and Cockcroft-Gault prediction formulae perform poorly in patients with normal or near-normal renal function,[42] The new equation MCQE placed only 10% of healthy individuals in CKD stage 2 and there was not a single case of control in stage 3. Both the CG and MDRD formulae included around 50% of control population under CKD category with a GFR less than <90 ml/min/1.73m^2. Although Barai[43] put forth that normal healthy Indian population has a lesser GFR compared to Western population, a more recent study by Rajeshwari[44] in Indians has reported that CG and MDRD equation classified more than 50% subjects in stage 2 of CKD and 0.8 to 1.4 % under stage 3 of CKD depending on equation. Therefore the observation in our study in healthy control population is in concurrence with the findings of Rajeshwari [44].

In CKD patient's serum creatinine is raised due to an alteration in renal function and is finally reflected in decreased GFR. In clinical practice, staging of CKD is very important because it is essential for management and medication. Generally stage 1 and 2 are asymptomatic, anemia is a common feature in stage 3 to 5 and in stage 5 which involves serious features like neuropathy and pericarditis, dialysis becomes mandatory. The three formulae CG, MDRD and MCQE which are employed to estimate GFR and stage the CKD patients have their own advantages and disadvantages in classifying CKD. There may not be a single equation available for accurate measurement of eGFR in both controls and renal impairment groups[45].

Botev [46] reported that both CG and MDRD formula have certain limitations consequent upon which approximately 60% of the CKD population was classified properly according to K/DOQI. Froissart[47] also reported that both MDRD and CG formulae classified and categorized CKD patients accurately to the extent of only 70.8% and 67.6% respectively and concluded that MDRD provided a more reliable result than the CG Formula although both lacked precision for proper staging. Lamb[25] observed that the in comparison between MDRD and CG equation for estimating GFR in CKD cases, MDRD estimate provides a more accurate result when GFR is less than 60 ml/min, but overestimated GFR in groups like elder people. Poggio[23] likewise corroborated that MDRD gave better result when compared with CG in CKD patients. Kuan[32] also reported that CG formula overestimated the GFR in ESRD when compared with 24 hours creatinine clearance and inulin clearance and suggested that MDRD provided more accurate results in ESRD group. Teruel[48] contradicted the above fact and reported that CG was a better indicator of GFR than MDRD in advanced stages of CKD when compared with golden standard method (mean of urea and creatinine clearance). Buitrago[49] suggested that MDRD formula has to be excluded from consideration in elderly subjects and males with cardiovascular risk. Bostom [29] also suggested that CG is more reliable than MDRD in CKD patients with normal serum creatinine. Melloni [50] preferred CG formula for classification of CKD patients in Acute Coronary syndrome. Kuzminskis[51] noted that CG and MDRD both gave accurate results for classifying early and moderate CKD. Kuan[32] reported that MDRD was more accurate than CG in end-stage renal disease.

Fontsere[52] deduced from the results obtained from stages 3 and 4 of CKD cases that there was no superiority of MCQE equation over the MDRD and CG equation. Marsik[53] was of the opinion that both MDRD and MCQE showed comparable results in stage 4 and 5.

In our study in CKD groups (Table-VI) the three formulae did not include any subject under stage 1. This could be due to the reason that the subjects might not have sought any medical assistance as they did not manifest any clinical features of CKD with a normal or near normal GFR. In stage 2, CG, MDRD and MCQE included only 0.8%, 0.8% and 2% of CKD cases respectively. As the features of the diseases are not very severe to demand attention, the patients in this category do not usually visit a hospital nor seek medical attention

accounting for their lack of awareness. The other reason for only a few number of subjects falling under stage 1 and stage 2 in CKD may be due to that, the three formulae underestimated GFR as they might have also done in controls. Therefore staging becomes inappropriate.

Most of the patients of CKD in our study belonged to Stages 3 to 5 with a higher preponderance in stage 5 as the data obtained were from the dialysis unit of the hospital. In respect of stages 3 and 4, there is no significant difference in the distribution of CKD cases with reference to all the equations. Stage 3 comprises of 28.2%, 26% and 23% of CKD cases according to CG, MDRD and MCQE respectively. Likewise stage 4 includes 32%, 28.2% and 27% of total CKD patients according to CG, MDRD and MCQE respectively. Therefore it can be inferred that with regard to stages 3 and 4 of CKD, the difference according to the 3 methods employed to assess GFR is not significant. The distribution of CKD cases in stage 5 is almost similar according to MDRD and MCQE methods and comprise 45.3% and 48% respectively. It is the CG equation which gives a lower value of 39%.Thus there exists an incompatibility in grading patients in stage 5.Therefore taking into account the whole gamut of CKD patients, it can only be stated with some reservation that either MDRD or MCQE equation can be used to assess GFR as both of them have close resemblance. Thus our observations in CKD cases are in concurrence with the observations of Marsik[53].

In view of various conflicting and ambiguous reports in the literature regarding the assessment and acceptability of GFR values in CKD patients it has become practically a very intricate and complicated predicament on the part of medical professionals to categories the patients in different stages and institute appropriate treatment. However the present study infers with some degree of reservation that MCQE formula is acceptable for normal controls and MDRD and MCQE are both satisfactory for CKD patients.

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