Original Article

A Study of Estimated Glomerular Filtration Rate In Chronic Kidney Disease

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ABSTRACT

Background: *Chronic kidney disease is a life threatening disease, which is a common cause of mortality and morbidity. The chronic kidney disease patients are at high risk of developing end stage renal disease, cardiovascular complications and stroke. Therefore, we carried out this study to know the functional status of kidneys in chronic kidney disease cases and to classify the chronic kidney disease into different stages by calculating estimated glomerular filtration rate.*

Material and Methods: *Twenty five cases of chronic kidney disease, between 25-70 years of age of either sex, admitted at R.L.Jalappa Hospital and Research Centre, Kolar, India and twenty five healthy age and gender matched controls were enrolled into the study. For calculating estimated glomerular filtration rate serum creatinine values, age, sex, race, and weight of the patients are considered.*

Results: *The mean estimated glomerular filtration rate in cases was 22.096 and in control group 118.28($p<0.001$) as per Cockcroft Gault Equation and as per Modification of Diet in Renal Disease equation in cases it was 18.176 and in controls 113.796($p<0.001$). The estimated glomerular filtration rate was significantly low in cases when compared with healthy subjects.*

Conclusion: *Estimated glomerular filtration rate better predicts the functional status of kidneys and is more accurate than serum creatinine and can be used to classify chronic kidney disease.*

Key words: *Chronic kidney disease (CKD), Cockcroft Gault Equation (CCG), Estimated Glomerular Filtration Rate (eGFR), End Stage Renal Disease (ESRD), glomerular filtration rate (GFR), Modification of Diet in Renal Disease(MDRD), Serum creatinine.*

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INTRODUCTION

The estimated prevalence of CKD is approximately 10-15% in most countries. As per NHANES III data, the prevalence of chronic kidney disease was 37.8% among patients older than 70 years. The term end stage renal disease represents a stage of CKD, where there is accumulation of fluid, electrolytes, toxins like ammonia, uric acid which are normally excreted by kidney result in uremic syndrome, which ultimately leads to death.[1]

The best known function of kidneys is plasma filtration, and to know the functioning capacity of kidney, and in the management of patients who need clinical assessment of renal function, GFR is of prime importance, and is considered to be the most reliable measure of the functional capacity of the kidneys and thought of as the indicative of the number of functioning nephrons.[2]

Chronic kidney disease is a major cause of morbidity and mortality, particularly at the later stages, and among patients with ESRD aged 65 years and older, the mortality rates are 6 times higher than in the general population. It encompasses a different pathophysiologic processes associated with a progressive decrease in glomerular filtration rate and significant irreversible decrease in nephron number. Risk factors include hypertension, diabetes mellitus, autoimmune disease, older age, African ancestry, family history of renal disease, previous episode of acute kidney injury, and presence of proteinuria, abnormal urinary sediment, or structural abnormalities of the urinary tract.[3]

The various modalities to determine the glomerular status are,

1. Clearance methods (Inulin, creatinine and urea). Creatinine based studies are frequently used.
2. Isotope methods[2].

The most important step to overcome CKD is early detection and evaluation. But the creatinine based studies have many disadvantages like its concentration is directly dependent on muscle mass, which varies with sex (women tend to have less muscle mass as a percent of body weight than men), age (muscle mass decreases with age), and race (African Americans have a higher serum creatinine level for the same GFR than other Americans).[4]

Thus, there is no "normal" value for serum creatinine which applies to all patients. Other factors which can alter the creatinine level without changing the GFR, such as changes in dietary protein intake, exercise[5], and drugs such as cimetidine[6] and fibrates[7].Another important point is that the relationship between the serum creatinine concentration and GFR is parabolic.[8] Therefore, large changes in the GFR are reflected by very small changes in serum creatinine, and cannot diagnose CKD until 50% of kidney functions are lost.[9]

So to overcome these problems, and with the increasing incidence of kidney dysfunction the use of formulas to estimate renal function is implemented more frequently in clinical practice taking age, sex and creatinine values into consideration. The most frequently used formulas are the Cockcroft-Gault and Modification of Diet in Renal Disease (MDRD) equations.[10] The Cockcroft-Gault equation estimates creatinine clearance and Modification of Diet in Renal Disease (MDRD) equation estimates GFR.

OBJECTIVES

1. To calculate and compare eGFR using MDRD and Cockcroft-Gault equation in cases and controls.
2. To classify CKD into different stages using eGFR values of MDRD and Cockcroft-Gault equation.
3. To correlate serum creatinine values with that

of eGFR values.

MATERIAL AND METHODS

The study involved fifty subjects of either sex with age between 25-70 years. Twenty five diagnosed cases of chronic kidney disease admitted at R.L. Jalappa Hospital, Kolar, India were considered. And twenty five age and sex matched healthy controls were considered. Serum samples of cases and controls were analyzed for creatinine by Jaffe's kinetic method and urea levels were analyzed by Urease/GLDH Method. The eGFR was calculated by Cockcroft-Gault Equation, taking the patients age, sex, and weight and serum creatinine values. And eGFR was also calculated using the Modification of Diet in Renal Disease formula (4 variable equation) taking patients age, race (ethnic group), gender and serum creatinine values.

THE ESTIMATING EQUATIONS:

1. MODIFICATION OF DIET IN RENAL DISEASE EQUATION[4].

Estimated GFR (ml/min per 1.73 m^2) = 186 x $(P_{Cr})^{1.154}$ x $(age)^{0.203}$

Multiply by 0.742 for women

Multiply by 1.21 for African Americans

Age - in years

Serum creatinine - in milligrams per decilitre

2. CCR= [(140-AGE) X WEIGHT])/ (72 X SCR) X 0.85 (If the patient is female)

CCR- Creatinine clearance is expressed in millilitres per minute.

Age - in years

Weight - in kilograms

SCR -Serum creatinine- in milligrams per decilitre years.

STATISTICAL ANALYSIS

In the present study, to compare the age distribution, eGFR in both groups we have used Independent t test, for gender distribution and staging of CKD we have used Chi square test and for correlating the serum creatinine levels and blood urea levels we have used Pearson's correlation.

OBSERVATION & RESULTS

In the present study, the mean age in cases was 47.7 and for controls it was 42.56 and there was slight preponderance of females. The mean eGFR was found to be 22.096 and 118.28 in cases and controls respectively according to Cockcroft Gault Equation (Table 1) and 18.176 and 113.796 in cases and controls (Table 2) respectively according to Modification of Diet in Renal Disease equation.

DISCUSSION

In this study we have made an attempt to classify the cases in different stages of chronic kidney disease based on the eGFR value. It was observed that (in Table 6 & 7)16% of cases were in stage 5, while 24% were in stage 4, and 10% in stage 3 according to Cockcroft Gault equation

Table No. 1. eGFR between cases and controls as per CCG equation.

Type	N	Mean	Standard Deviation
Controls	25	118.28	9.560
Cases	25	22.096	7.409

$p < 0.001$

Table No. 2. eGFR between cases and controls as per MDRD equation.

Group	N	Mean	Standard Deviation
Controls	25	113.796	11.030
Cases	25	18.176	7.160

$p < 0.001$

Table No. 3. Comparison of eGFR values in cases using both the equations.

Group	N	Mean	Standard Deviation
CCGE	25	22.10	7.41
MDRD	25	18.18	7.16

Table No. 4. Correlation of serum creatinine with eGFR values

	Value	eGFR (CCGE)	eGFR(MDRD)
Creatinine	R	-0.890	-0.888
	P	0.001	0.001

Table No. 5. Correlation of blood urea with cases

	Value	Cases
Urea	r	-0.72
	p	<0.001

Table No. 6. Staging of CKD as per CCG equation

Group	Stage 1	2	3	4	5	Total
Controls	0	0	0	0	0	0
Cases	0	0	5	12	8	25

Table No. 7. Staging of CKD as per MDRD equation

Group	Stage 1	2	3	4	5	Total
Controls	0	0	0	0	0	0
Cases	0	0	2	12	11	25

and 22% in stage 5, 24% in stage 4, 4% in stage 3 according to MDRD equation. None of the cases could be classified under stage 1& 2. We can see that as the creatinine and urea levels are increasing the eGFR is decreasing. And we found that there is no difference between the eGFR measured by CCG and MDRD equations (Table 3) and we observed that as there is increase in serum creatinine levels (Table 4) there is corresponding decrease in eGFR which is statistically significant and as there is rise in blood urea levels, we observed that there is corresponding worsening of the cases (Table 5) The Kidney Disease Outcome Quality Initiative (KDOQI) of the National Kidney Foundation (NKF) defines chronic kidney disease as either kidney damage or a decreased renal glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2 for 3 or more months. Whatever the underlying etiology, the destruction of renal mass with irreversible sclerosis and loss of nephrons leads to a progressive decline in GFR.

Approximately 1 million nephrons are present in each kidney, each contributing to the total GFR. The pathophysiology of CKD involves two broad sets of mechanisms of damage: (1) initiating mechanisms specific to the underlying aetiology (e.g., genetically determined abnormalities in kidney development or integrity, immune complex deposition and inflammation in certain types of glomerulonephritis, or toxin exposure in certain diseases of the renal tubules and interstitium) and (2) a set of progressive mechanisms, regardless of the aetiology of renal injury, with progressive destruction of nephrons, (the responses to reduction in nephron number are mediated by vasoactive hormones, cytokines, and growth factors) the kidney has an innate ability to maintain GFR by hyper filtration and compensatory hypertrophy of the remaining healthy nephrons. This nephron adaptability allows for continued normal clearance of plasma solutes so that substances such as urea and creatinine start to show significant increases in

plasma levels only after total GFR has decreased to 50%, when the renal reserve has been exhausted. The plasma creatinine value will approximately double with a 50% reduction in GFR. A rise in plasma creatinine from a baseline value of 0.6 mg/dL to 1.2 mg/dL in a patient, although still within the reference range, actually represents a loss of 50% of functioning nephron mass.[3]

eGFR is the estimated glomerular filtration rate. It is used to assess renal function and is a more sensitive measure of renal impairment than serum creatinine clearance measurement .Because as patients can have significant renal impairment even with a serum creatinine in the normal range[4]. It is possible to lose up to 50% of renal function before the creatinine becomes elevated, especially in the elderly. People with CKD may go on to develop end stage renal disease (ESRD) requiring dialysis or transplantation but a much greater problem is the increase in cardiovascular and all cause mortality and morbidity.[12]

In order to stage CKD, it is necessary to estimate the GFR. Two equations commonly used to estimate GFR are CCG and MDRD equation and they incorporate the measured plasma creatinine concentration, age, sex, weight and ethnic origin.

MDRD equation adjusts for 4 variables, body surface area, race, gender and age, but it will not be adjusted for the difference in muscle mass not attributable to intrinsic ageing processes and race, such as pathological muscle wasting and accelerated muscle growth. This equation may be inaccurate in amputees, frail patients, stroke victims, and those with unusual diets like vegetarians, high protein or low protein diet[4]. It has also indicated that the applicability of the Modification of Diet in Renal Disease study equation to many patient groups other than the original MDRD study population has not been determined, specifically this study equation has not been validated as the preferred clinical tool to predict glomerular filtration rate in the broad range of patients requiring routine medication and dosing.[13]

Cockcroft- Gault equation follows the recommendations in the Renal National Service Frame Work (Renal NSF). It is a more sensitive marker of kidney dysfunction than serum creatinine. It will allow earlier identification of patients with chronic kidney disease. This is particularly important as these patients are at increased cardiovascular risk compared with the general population and may benefit from risk factor modification. The use of eGFR will also facilitate identification of patients with more advanced CKD previously not recognized as such (for example an 80 year old with a creatinine of 1.6).[12]

A study done by Khetepal et al, showed that the CockcroftGault formula suffers from the absence of any race-specific measures and the Modification of Diet in Renal Disease formula suffers from the absence of any weight-based measures. They used the Cockcroft-Gault formula for several reasons: (1) It is more accurate across a broad range of renal function.[6] (2) it incorporates weight and the effect of weight on anticipated normal serum creatinine, (3) it is used more widely in pharmacologic dosing practice, and (4) the Modification of Diet in Renal Disease formula is known to

underestimate glomerular filtration rate in patients with normal renal function.[14]

Identifying patients with normal preoperative renal function was the foundation of our methodology and guided us to the use of the Cockcroft Gault formula.[15]

Rostoker G,et al have studied the accuracy of Cockcroft Gault formula to estimate GFR by adjusting body surface area in 269 patients. They compared original and modified Cockcroft Gault and MDRD formulas using Inulin clearance and concluded that adjustment of body surface area [BSA=body weight$^{0.425}$(in kg) X height$^{0.725}$(in cms)X0.007184][13] improves the accuracy of the original Cockcroft Gault formula. Inulin clearance correlated better with BSA-modified Cockcroft Gault formula.[16]

Wieneke M et al, compared estimations of CockcroftGault formula, MDRD and Chronic Kidney Disease-Epidemiology collaboration (CKD-EPI) equations to a gold standard GFR measurement using I^{125} Iothalamate within strata of GFR, gender, age, body weight and body mass index between 2003-2007, and concluded that the absolute bias of all formulas is influenced by age, and Cockcroft Gault formula additionally influenced by body weight and body mass index.[13]

On correlation we have found that as chronic kidney disease increased the creatinine levels increased, the urea levels were also increased and stage of chronic kidney disease increased as the eGFR values significantly decreased. So eGFR calculation indicates the progression of damage to the kidneys in chronic kidney disease. A study done by Macgregor M.S. using MDRD formula also found the same results.[12]

An eGFR >100 ml/min/1.73m^2 is considered normal. An eGFR of 60 to 90 ml/min does not in itself indicate chronic kidney disease for a formal diagnosis of CKD additional markers of damage are required as well like, abnormal urine findings (for example microalbuminuria or microscopic haematuria).

The diagnosis requires the abnormalities to be present for at least three months. People with eGFR over 60 ml/min/1.73m^2 should not be considered to have CKD unless there is other evidence of kidney damage.

CKD is classified into five stages based on eGFR. The lower the eGFR the worse the stage of CKD [4](Table 8).

CONCLUSION

A formula, the Cockcroft Gault and MDRD which are easy to carry out, and convenient, and are based on serum creatinine, sex, age, weight, ethnic group are simple equations for calculating eGFR which are useful to know the functional status of kidneys, for staging the CKD into different grades. Using these we can also detect the onset of renal insufficiency and progression of renal disease.

eGFR values help a clinician to know the progression of disease status and it will help to adjust the dose of drugs excreted by the kidneys, and to evaluate the effectiveness of therapy in various stages of kidney disease.

LIMITATION

1. As creatinine is influenced by many non- renal factors like, body mass index, and partial reabsorption in renal tubules it may affect the eGFR indirectly

2. This formula is not applicable in children less

Table 8: Stages of chronic kidney disease based on eGFR.

Stage	eGFR (ml/min)	Description	Frequent complications	Testing frequency	Prevalence (%)
1.	90-99	Kidney damage with normal GFR	Hypertension	Yearly	3.3
2	60-89	Kidney damage with mild CKD	Hypertension (Parathyroid hormone elevation)	Yearly	3.0
3	30-59	Moderate CKD	Hypertension, Changed in Calcium and phosphate metabolism, renal anaemia, left ventricular hypertrophy	6 months	4.3
4	15-29	Severe CKD	As above, plus hyperkalaemia	3 months; 6 monthly once stable	0.2
5.	<15	Kidney failure	All above plus salt and water retention causing apparent heart failure, anorexia, vomiting, pruritis	3 months	0.2

than 18yrs, pregnant women and elderly persons aged more than 75years.

3. eGFR is not useful in assessing acute renal failure.

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