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ESTIMATED GLOMERULAR FILTRATION RATE AS AN EARLY MARKER OF RENAL FUNCTION IMPAIRMENT IN APPARENTLY HEALTHY INDIVIDUALS WITH NORMAL SERUM CREATININE LEVELS: A COMPARISON OF VARIOUS EQUATIONS

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ABSTRACT

This study was done to assess the renal function in normal healthy individuals with normal serum creatinine levels, on the basis of estimated glomerular filtration rate (eGFR) and to compare and correlate eGFR obtained by various formulae. The mean eGFR reduced with an increase in age. There was a reduction in eGFR in 44.5% of subjects as calculated by Modification of Diet in Renal Disease study (MDRD) equation. The eGFR values calculated by MDRD, Chronic Kidney Disease Epidemiology equation (CKD EPI) and Mayo Clinic Quadratic equation (MCQ) were comparable. Stage 3 chronic kidney disease by both MDRD and CKD EPI formula was 5.2%, whereas by MCQ formula it was 0.4%. eGFR appears to be a predictive diagnostic marker of early stages of renal dysfunction in otherwise normal apparently healthy individuals with normal serum creatinine.

KEY WORDS: Estimated glomerular filtration rate, Modification of Diet in Renal Disease study, renal function

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INTRODUCTION

The Glomerular Filtration Rate (GFR) is considered the best marker for renal function[1]. The early stages of renal function impairment are clinically silent and are diagnosed by measuring GFR. Once GFR has decreased to <60 mL/min/1.73m^2, functional impairments can be detected by determining internal filtration markers[1]. The goal of GFR determination is to detect chronic kidney disease (CKD) in its early stages in order to slow its progress. To assess the renal function using estimated GFR (eGFR) from the endogenous markers, various formulae have been derived and applied. One such commonly used equation is the Modification of Diet in Renal Disease study (MDRD) equation. MDRD Study equation has been considered to be more accurate than the Cockcroft–Gault equation and measured urinary creatinine clearance[2]. Studies have however, shown that the MDRD equation underestimated GFR by 29% in healthy subjects when compared to Mayo Clinic Quadratic (MCQ) equation [2, 3]. Hence there is a confusion regarding the formula to be clinically used for the healthy subjects as all the formulae were derived for CKD patients. Based on data from major tertiary care centres the presumptive estimates of incidence of end stage renal disease (ESRD) in India are about 100/ million polulation[4]. Population based studies in India estimated the prevalence of overt CKD ESRD to be about 0.79 – 1.39%[4]. Very few studies have been conducted in India to determine the incidence of kidney impairment in healthy individuals. The present study has made an attempt to assess renal function in healthy individuals by estimating GFR and to correlate eGFR values derived from various equations.

METHODS AND METHODOLOGY

This hospital-based study was conducted with the approval of the Institutional Ethics Committee. Voluntary informed consent was obtained from all the study subjects. Subjects selected for our study were apparently healthy normal individuals (n=211) aged ≥ 18 years, who visited the Father Muller Medical College hospital outpatient department for routine health check up. They did not have any obvious symptoms or clinical manifestations of chronic kidney disease as per the clinical and biochemical examinations (serum creatinine being within normal range). Chronic alcoholics, smokers, and individuals with chronic illness, systemic diseases such as diabetes, hypertension, liver disorders, malignancy, and infections were excluded from the study. Blood samples of the subjects were collected taking aseptic precautions, and sera separated. Serum creatinine was estimated by Jaffe's kinetic method in Automated Chemistry Analyzer (Cobas c 311; Roche Diagnostics). GFR was calculated using various equations as follows: [2, 5,6]

a. Modification of Diet in Renal Disease study (MDRD Study equation) MDRD=186 × (SCr) $^{1.154}$ × [age (years)] $^{0.203}$ × (0.742 if female) ×(1.210 if African–American)
b. CKD EPI = 141 ×min(SCr/k,1)^a ×max (SCr/k,1)$^{-1.209}$× 0.993 ^{age}×[1.018 if female]×[1.159 if black]

k is 0.7 for females and 0.9 for males, a is -0.329 for females and -0.411 for males, min indicates the minimum of SCr/k or 1 and maximum of SCr/k or 1

c. Mayo Clinic Quadratic (MCQ) equation (MCQ) = exp [1.911+ 5.249/SCr - 2.114/SCr2- 0.00686 × age (years) -0.205 if female] Where SCr is serum creatinine in mg/dL

The data was tabulated and statistically analysed using Students t test, intraclass correlation and Karl Pearsons Correlation Analysis.

RESULTS

The study group consisted of 211 individuals of whom 82 were females and 129 were males. The mean serum creatinine level was 0.88 mg/dl with a standard deviation of 0.183 (Normal reference range for males and females being 0.8- 1.5 and 0.5- 1.2mg/dL). The mean age of the subjects was 50.78 years with a standard deviation of 14.84. The mean e GFR values as per MDRD, CKD EPI and MCQ equation were 90.89, 91.73 and 107.06 ml/min/1.73 m^2 respectively (table 1).

Males had marginally higher GFR values when compared to females, but the difference was statistically not significant. The eGFR showed variations (graph -1) and a significant decrease with age (graph -1,2). Interclass correlation done to find the agreement between the formulae which was found to be statistically significant. The correlation among various equations of e GFR was significant (table -2) The eGFR values computed by the MCQ equation were consistenly on the higher side as compared to the other two equations.

Interquartile ranges of eGFR (table -3) when taken into consideration for the various formulae; there was difference in the number of population catagorised in each quartile. MCQ had the highest population in the last quartile (graph-3), showing that the GFR calculated by the formula gives a higher value in the healthy individuals. Moderate reduction in the eGFR by both MDRD and CKD EPI formula was 5.2%, whereas by MCQ formula it was 0.4%.

Table 1

GFR values calculated from MDRD, CKD EPI and MCQ equations. (Values are mean ± S.D.)

	MDRD	CKD EPI	MCQ
GFR ml/min/1.73 m^2	90.89 ± 18.92	91.73 ± 17.74	107.06 ± 18.92

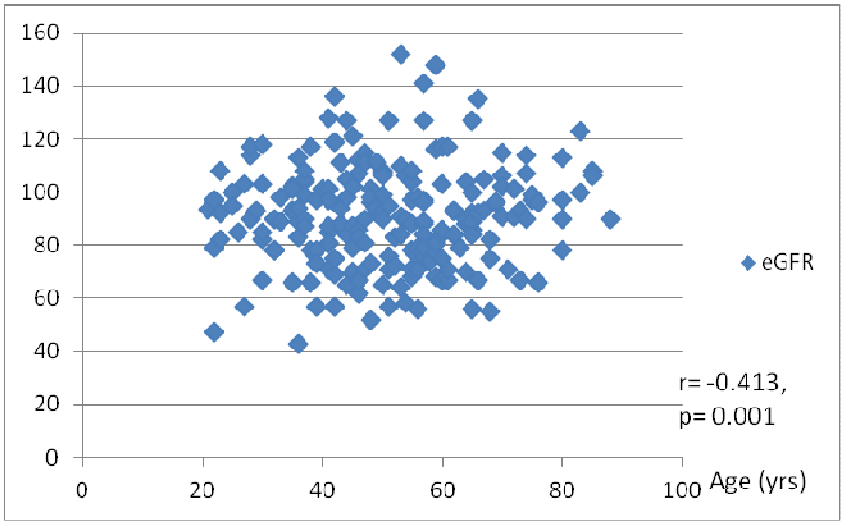
Table 2

Correlation among the GFR values obtained from MDRD, CKD EPI and MCQ equations.

Correlation	Interclass Correlation	Karl Pearson's Correlation
MDRD -CKD EPI	r = 0.959 ; P < 0.001	r = 0.923 ; P < 0.001
MDRD- MCQ	r = 0.680 ; P < 0.001	r = 0.707 ; P < 0.001
CKD EPI-MCQ	r = 0.769 ; P < 0.001	r = 0.848 ; P < 0.001

Graph 1

Variation of MDRD GFR with age.



Graph 2
showing the difference in the GFR by the formulae with respect to the age groups

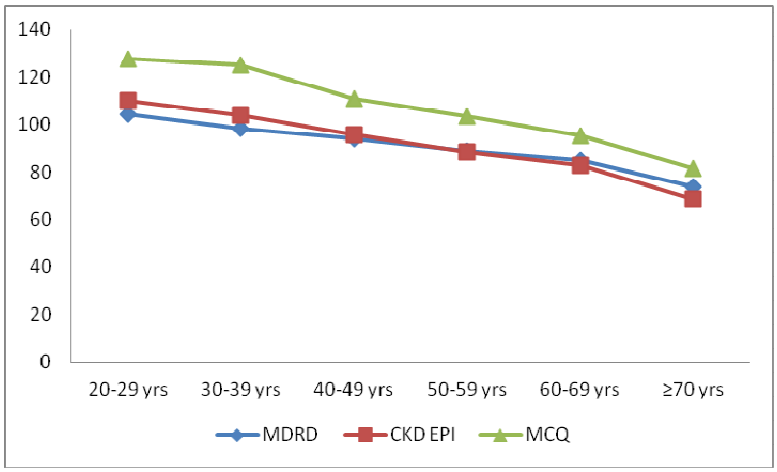
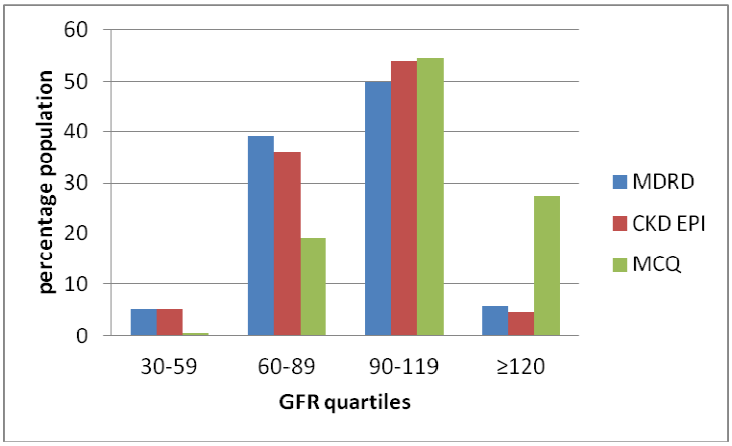


Table 3
mean eGFR and percentage population(% n) categorised in the different quartiles based on various formulae.

	30-59	60-89	90-119	≥120
MDRD	54.1(%n=5.2)	77.2(%n=39.3)	100.8(%n=49.8)	132.7(%n=5.7)
CKD EPI	51.8(%n=5.2)	77.8(%n=36)	102.2(%n=54)	122.9(%n=4.7)
MCQ	55(%n=0.4)	82.2(%n=19)	104.3(%n=54.5)	129.8(%n=27.5)

Graph 3
percentage population categorised in the different quartiles based on various formulae



DISCUSSION

The present study made an attempt to assess renal function in normal healthy individuals by using eGFR values. We observed a reduction in eGFR in 44.5 % of the subjects according to MDRD formula. There are many studies done in diagnosed CKD but very few to determine the prevalence in apparently healthy population. Apparently healthy people might be having mild impairment of renal function and diagnosis of renal dysfunction in them might be missed if serum creatinine alone is taken as biochemical criteria for kidney

disease. Measurement of GFR thus, could help in screening, diagnosis and prognosis of chronic kidney disease in the population. Studies have shown that there is a reduction in GFR well before a rise in serum creatinine levels. [7,8] A cross sectional study by Varma et al. [4] on the prevalence of early stages of CKD in healthy central government employees of India showed 15.04% and 13.12% were in early stages of CKD using the MDRD and CKD-EPI criteria for GFR, respectively. An estimated GFR within 30% of a measured GFR was considered acceptable by the National Kidney Foundation Kidney Disease Outcome Quality Initiative (NKF KDOQI) for clinical interpretation to identify individuals with CKD[9]. According to Rule et al[5] the MDRD equation underestimated GFR by 29% in healthy persons. However, persistent reduction in GFR less than 60 mL/min/1.73 m^2 and individuals with a GFR greater than 60 and with markers of kidney damage, such as proteinuria, are said to have chronic kidney disease [9, 10].

In the present study we observed that MCQ equation gave the highest mean value of GFR followed by CKD EPI and MDRD equations. However, this difference was statistically not significant. MDRD GFR values showed significant negative correlation with age. There was significant correlation among the various equations with respect to the GFR values calculated. But there are lot of discrepancies in the values given by the formulas and hence using one of the formulas could lead to misclassification of an individual as CKD. There are lot of discrepancies when the formulas are used in various diseased population and variation in parameters like age and ethnicity [2,11,12,13]. Modified estimations of the MDRD and Isotope Dilution Mass Spectrometry(IDMS) traceable MDRD study equations is said to improve the performance of GFR estimation [12,14]. Serum Cystatin C has shown more diagnostic accuracy than serum creatinine, hence this new endogenous marker can be used for GFR assessments [15, 16]. Correlation among the various equations was statistically significant. This could be due the fact that the equations are derived with the similar variables of serum creatine, age, ethnicity and sex of the individual. The correlation with the first two equations was highly significant as they are derived and standardised in CKD population. Whereas the correlation analysis showed a weak association between other two equations and MCQ as the later was standardised to normal population[11].

Quartile wise eGFR distribution in the study showed that the majority of the percentage population were in the third quartile, determined by all the three formula. The next highest was in the second quartile (except MCQ equation which depicted the last quartile). The first quartile based on first two formulae showed a small population, with the MCQ being negligible. The MDRD study equation developed in CKD population is said to have imprecision and systematic underestimation of measured GFR at higher values [17]. The CKD-EPI equation is said to have better performance over the MDRD equation at higher GFR, with less bias, improved precision and greater accuracy [1, 18]. However in CKD stages 3–4 group it is said that all the three equations perform equally which is contrary to the present study [11].

Previous studies have raised the concern that MDRD equations may underestimate GFR in healthier populations [16, 19, 20, 21, 22, 23.] Study by Rule et al[3] pointed out that MCQ equation may be more accurate than the MDRD equation in estimating GFR when kidney disease status is unknown. The MDRD underestimated GFR in 20% of the population, CKD in 23%, as compared to measured GFR [5]. Limitations of the study are that the GFR should have been compared with the measured GFR by the gold standard methods. The anthropometric measurements like BMI and other factors which could influence the predicted GFR values should be assessed and considered. Assessment of GFR by cystatin C based equations would have also given a better comparison and idea about the GFR

CONCLUSION

From the present study, eGFR appears to be a predictive marker of early stages of renal dysfunction in otherwise normal apparently healthy individuals with normal serum

creatinine. Thus screening of a general population for CKD is useful in early diagnosis and prevention which would prove beneficial and cost-effective. GFR estimating equations standardised with more accurate markers like cystatin C would prove beneficial. Cystatin c is an independent marker of CKD but eGFR can be used as a general test which also appears to be a predictive marker of early stages of renal dysfunction.However there is a need to evaluate further and re-establish the normal reference ranges according to each of the formulae.

CONFLICT OF INTEREST

Conflict of interest declared none

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