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Comparison of eGFR using different equations and its relationship withmicroalbuminuria in patients with hypertension

V.Ramyasree, Aparna R. Bitla , Siva Kumar V, V Vanajakshamma
III MBBS, Professor and Head, Senior Professor, Professor
[1]SVIMS, SPMC(W), Tirupati
[2]Department of Biochemistry, [3]Department of Nephrology, [4]Department of Cardiology
Sri Venkateswara Institute of Medical Sciences, Tirupati, A.P, India

***Corresponding Author:**
Aparna R Bitla, MD
Professor and Head, Department of Biochemistry,Sri Venkateswara Institute of Medical Sciences,Tirupati, A.P, India

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Abstract

Patients with hypertension suffer from target organ damage. Hypertension is an important cause of chronic kidney disease (CKD). Early identification helps in initiating treatment early and slows progression. Albuminuria and elevated serum creatinine levels are widely used as indicators of renal dysfunction. Estimated glomerular filtration rate (eGFR) is another indicator of renal function and is used to classify patients with CKD. Since albuminuria measurement is not available in small centers, the present study aimed to assess the utility of eGFRs using different equations for assessing renal damage in patients with hypertension. In the present study, 20% of the patients with hypertension had albuminuria and impaired renal function assessed using the different eGFR equations. None of the patients in the present study had impaired renal function in the absence of albuminuria. Albuminuria correlated well with eGFR calculated using the various equations (CG, CKD-EPI and CKD-EPI modified for Asians) and could thus be useful as a screening test in rural areas where facility for microalbumin estimation is not available. This needs to be validated in a larger sample size before implementation.

Keywords: Albuminuria; Hypertension; Target organ damage; eGFR

INTRODUCTION

Hypertension is an important worldwide public-health problem causing 12.8% (7.5 million) of the total deaths worldwide.[1] The prevalence is higher in low, middle and upper middle-income countries (40%) and lower (35%) among high income countries.[1] In India, the prevalence has been reported to be around 25% to 30% in urban and 15% to 25% in rural population.[2]

Hypertension can cause target organ damage especially to the heart, kidney and blood vessels manifesting as left ventricular hypertrophy, renal impairment and vascular events like transient ischemic attacks or stroke.[1] Systemic hypertension causes intraglomerular hypertension that leads to glomerular hypertrophy and injury[3]further leading to chronic kidney disease (CKD). Renal replacement therapy in the form of dialysis or kidney transplantation is required in stage 5 CKD. This imposes significant economic burden on the family and the community as well. Thus, early identification of CKD is important.

The current guidelines recommend screening for signs of subclinical renal damage in all patients with hypertension.[4] This includes detection of eGFR between 30 mL/min/1.73 m^2 and 60 mL/min/1.73 m^2 or the presence of microalbuminuria (MAU).[4]

Microalbuminuria measurement is not easily available in rural areas and the use of formulas to estimate

kidney function is implemented more frequently in clinical practice. eGFR can be calculated using Cockcroft - Gault (CG),[5] Modification of Diet in Renal Disease (MDRD)[6] and chronic kidney disease-Epidemiology (CKD- EPI) formulae.[7] A modification of the CKD-EPI equation for Asians has been developed.[8] eGFRs have been shown to correlate with preclinical target organ damage (TOD).[9]

In India, the awareness among people living in the rural areas regarding target organ damage as a result of chronic conditions such as diabetes and hypertension is poor. These people also have limited access to health care services thereby delaying the diagnosis of CKD. Cost associated with treatment of CKD and the ensuing renal replacement therapy can pose a huge economic burden especially in developing countries like India. Thus, early identification of CKD in high risk individuals helps in designing strategies for prevention of progression of the disease.

With this background the present study was thus taken up to study the association of eGFR using different equations with hypertensive renal damage.

MATERIAL AND METHODS

The present case-control study was conducted in the Department of Biochemistry in a tertiary care teaching hospital in south India from August 2019 to September 2019. The study included thirty patients over the age of 18 and below 60 years attending the Nephrology OPD at our tertiary care teaching hospital and diagnosed with Hypertension as per the Joint National Committee (JNC) on Prevention, Detection, Evaluation and Treatment of High Blood Pressure criteria[10] after obtaining approval from the institutional ethics committee. Thirty age- and gender-matched apparently healthy subjects from among the patent relatives and hospital staff willing to participate in the study served as the control group. Patients with secondary hypertension, those with primary renal disease, acute kidney injury, end stage renal disease (ESRD) on haemodialysis/peritoneal dialysis and those not willing to participate in the study were excluded from the study. A written informed consent was obtained from all the study participants.

Blood pressure (BP) of each subject was measured in the morning using mercury sphygmomanometer by a physician 3 times after at least 10 minutes of rest in the sitting position. The average of the 3 BP readings was calculated and used in the subsequent statistical analysis. Pulse pressure was defined as the difference between systolic (SBP) and diastolic BP. Hypertension was defined as per JNC criteria[10] as SBP at least 140 mmHg and/or the use of blood pressure-lowering medication. Impaired renal function as per Kidney
Disease Improving Global Outcomes (KDIGO) guidelines[11] i.e<60mL/min/1.73m^2 Albuminuria was categorized as per the KDIGO guidelines[11] into A1 (<30 mg/g, mild to moderate), A2 (30-300 mg/g, moderately increased) and A3 (>300 mg/g, severely increased) groups.

Five mL of peripheral venous blood in fasting condition along with 4 mL of random urine sample was collected from all the study subjects. Blood and urine samples were centrifuged at 2000 rpm for 15 min. The separated serum and urine samples were stored at -80 $^{\circ}$C until analysis.

Body mass index (BMI) was calculated using the formula (weight in Kg) / (height in meters). [2] Plasma glucose, urea and creatinine, urinary creatinine and microalbumin were estimated by standard methods on AU 480 autoanalyser (Beckman Coulter, California, USA) using commercial kits. eGFR calculations were done using CG formula,[5] MDRD formula,[6] CKD-EPI[7] and CKD-EPI modified equation for Asians.[8]

Statistical analysis

Data distribution was checked using Kolmogorov-Smirnov test. The data is represented either as mean ± standard deviation for data which showed a normal distribution or as median (inter quartile range) for data which did not show normal data distribution. Difference in markers among study groups was tested using independent samples T test or Wilcoxon signed rank test as appropriate. Karl Pearson's correlation analysis and linear regression analysis was used to determine the relationships between eGFR and albuminuria. All statistical analysis were performed using Microsoft excel spread sheet for windows (Microsoft, Redmond, WA USA) and SPSS for windows version 16.0(SPSS Inc, Chicago, Illinois, USA). A two tailed 'p' value <0.05 was considered as statistically significant.

RESULTS

Distribution of data for all the markers included was studied using Kolmogorov-Smirnov test. The clinical

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and biochemical characteristics of the study subjects is shown in **Table 1.** The groups were matching in terms of age with a mean age of 47 years in controls and a mean age of 46.97 years in patients with hypertension. There were 20 males (66.66%) among the control subjects and 19 males (63.33%) among patients with hypertension. Patients with hypertension had a significantly higher BMI (mean 26.6 kg/m^2) compared to controls (mean 24.8 kg/m^2). Patients with hypertension had significantly higher serum urea, urinary microalbumin and urinary ACR compared to controls ($p<0.05$). There was no difference in serum creatinine levels between the two groups although patients with hypertension had slightly higher creatinine levels.

Table 2 shows the eGFR in the study subjects using the different equations. eGFR using the different equations was comparable between the groups. **Table 3** shows the presence of impaired renal function with the degree of albuminuria. As shown in **Table 3**, 6 subjects (20.0%) with hypertension having albuminuria had impaired renal function defined as an eGFR of ≤ 60 mL/min/1.73 m^2 using the CG equation, MDRD equation and CKD-EPI equation. On the other hand, 5 subjects (16.67%) with hypertension having albuminuria had impaired renal function defined as an eGFR of ≤ 60 mL/min/1.73 m^2 using CKD-EPI equation modified for Asians. None of the patients had impaired renal function in the absence of albuminuria.

Table 4 shows the correlation matrix between ACR with eGFR using different equations and other predictors of decline in renal function like age, duration of HT and the blood pressure. As shown in **Table 4**, a significant negative correlation was found between ACR and eGFR calculated using various formulae. No correlation was found between ACR and eGFR with age and duration of hypertension.

DISCUSSION

Hypertension is a public health problem and microalbuminuria represents a gold standard for early identification of renal damage. Patients with hypertension had a higher BMI compared to controls ($p=0.045$). Patients with hypertension had microalbuminuria ($p=0.016$) and higher UACR ($p=0.01$) compared to controls.

In the present study, 11 (36.7%) patients with hypertension had albuminuria while none of the control subjects had albuminuria. Among these 11 subjects, 8 (26.7%) had microalbuminuria defined as urinary albumin excretion of 30-300 mg/g creatinine while 3 had macroalbuminuria defined as urinary albumin excretion of more than 300 mg/g creatinine per day. This is in agreement with previous Indian studies which have reported a prevalence of 26.67% and 33.37% in Indian hypertensive patients.[12,13] Two other studies from India, reported a higher prevalence of microalbuminuria (44% and 47%) in patients with essential hypertension.[14,15] Studies have shown the prevalence of microalbuminuria to range from 6% to 58%.[16-19] In the i-SEARCH global study comprising of 21,050 hypertensive subjects from 26 countries, Bohm et al., reported the prevalence of microalbuminuria to be 58.4%.[18]

Microalbuminuria is an established marker of subclinical organ damage.[19-22] Increase in haemodynamic load seen in patients with hypertension has been implicated as a determinant of urinary albumin excretion in patients with mild hypertension[23-25] while increased glomerular vascular permeability secondary to generalized vascular dysfunction is the cause of albuminuria in patients with moderate to severe hypertension.[26] Albuminuria has been shown to be an independent predictor of CVD risk and all-cause mortality in patients with hypertension.[20,27,28] Severity of hypertension has been proposed as a predictor of microalbuminuria.[15] This is supported by the positive correlation observed between microalbuminuria with SBP ($p=0.026$) but not with DBP ($p=0.067$). This is in agreement with previous studies[14,29] ACR correlated positively with both SBP ($p<0.001$) and DBP ($p=0.002$). However, a BP independent relationship between LV hypertrophy and glomerular vascular damage was shown by Olsen et al[21] which supports the hypothesis that urinary albumin creatinine ratio reflects systemic vascular changes.

The current guidelines recommend screening for signs of subclinical renal damage in all patients with hypertension which includes detection of eGFR between 30 mL/min/1.73 m^2 or the presence of microalbuminuria (MAU).[4] eGFRs have been shown to correlate with preclinical TOD.[30,31] Impaired renal function was found in 6 subjects with hypertension in the present study. This is in agreement with a study from south India which reported a prevalence of 4.8%.[32]Vernooij*et al*[33]reported the presence of

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impaired renal function in 15% of their cohort of hypertensive subjects. The presence of two indicators of target organ damage was seen in 20% of the subjects in the present study. Vernooij *et al* [33] reported the prevalence of combined target organ damage in 8% of their study subjects. None of the patients in the present study had impaired renal function in the absence of albuminuria i.e nonalbuminuric target organ damage. This is contradictory to the observation made in an Indian study from north India.[34] The authors observed the presence of decreased eGFR as assessed by the MDRD equation in 7 (50%) of the subjects in the absence of increased albumin excretion. However, the cohort studied was patients with type 2 diabetes and hypertension.

Microalbuminuria measurement is not easily available in rural areas. Hence, eGFR was calculated in the present study using CG,[5] MDRD[6] and CKD- EPI formulae[7] and CKD-EPI equation modified for Asians[8] to assess its utility in detecting subclinical renal damage. Although, patients with hypertension had a lower eGFR compared to controls, the difference was statistically not significant (**Table 2**). This could be due to the small sample size taken in the present study.

UACR was found to correlate negatively with eGFR using all the four equations studied (**Table 4, Figure 1**). However, the correlation was stronger with the CG equation (r=-0.591) followed by the CKD-EPI equation (r=0.521), CKD-EPI modified for Asians (r=-0.476) and last with MDRD equation (r=-0.433). CKD-EPI equation has been shown to be superior to other equations and correlated better with the gold standard GFR estimation (c99m-diethylenetriaminepentaacetic acid) in an Indian study.[35] The accuracy of the CKD-EPI equation was shown to be better in patients with GFR> 60 mL/min.[36,37] Hence, caution is warranted while interpreting the eGFR results. The correlation was weak for eGFR using the MDRD equation and CG equations in their study. Mulay *et al*[35] also reported the highest bias (7.6 mL/min) using MDRD and a bias of 3.1 ml/min using the CG equation compared to the gold standard. Similarly, Singh *et al*[38] reported a positive bias of MDRD equation for calculating eGFR in a population-based study conducted in North India. The authors observed a significant difference in eGFR calculated using the CG and MDRD equation in subjects from north India. MDRD equation has been shown to underestimate GFR in Asian population.[36]However, the population studied was Japanese. CKD-EPI equation modified for Asians was validated in a cohort also comprising of majority of Chinese and one third of Japanese population. Hence, the validity of these equations needs to be further studied. The results of the present study also support a comparatively poor applicability of MDRD is Indian subjects.

Conclusion:

The findings of the present study suggest that eGFR calculated using CG, CKD-EPI and CKD-EPI modified for Asians correlate well with the degree of microalbuminuria in patients with hypertension and could thus be useful as a screening test in rural areas where facility for microalbumin estimation is not available. This needs to be validated in a larger sample size before implementation.

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Table 1: Clinical and biochemical characteristics of the study subjects

Parameter	Controls	Cases	p value
Age (years)	47.00 ± 6.18	46.97 ± 6.11	0.983
Gender			
Male	20(66.66) †	19 (63.33) †	0.787
Female	10(33.33) †	11(36.66) †	
BMI (Kg/m^2)	24.82 ± 2.71	26.57 ± 3.75	0.045§
SBP (mm Hg)	114.33 ± 6.26	126.00 ± 56.32	<0.001§
DBP (mm Hg)	72.67 ± 4.50	83.50 ± 5.11	<0.001§
Duration of hypertension (years)	-	3.5 (2.0-5.0)‡	-
Fasting plasma glucose (mg/dL)	86.93 ± 13.72	94.53 ± 33.09	0.319
Serum Urea (mg/dL)	19.37 ± 4.69	22.0 (18.75 –25.25)‡	0.045§
Serum creatinine (mg/dL)	0.76 ± 0.12	0.83 (0.63 – 1.05) ‡	0.239
Urine creatinine (mg/dL)	79.34 (19.92-114.74) ‡	77.64 (32.16 – 94.45) ‡	0.994
U.MA (mg/dL)	0.30 (0.15-0.50) ‡	0.50 (0.20 – 10.55) ‡	0.012§
UACR (mg/g creatinine)	5.11 (3.71-7.26) ‡	15.02 (5.74 – 53.37) ‡	0.001§

Data presented as Mean ± standard deviation/† Interquartile range/n (%)

§-Statistically significant

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BMI= Body mass index; SBP= Systolic blood pressure; DBP= Diastolic blood pressure; FBS = Fasting plasma glucose; U.MA = Urine Micro albumin; UACR= Urinary

albumin/creatinine ratio

Table 2: Comparison of eGFR using various formulae in the study subjects

Parameter	Controls	Cases	p value
eGFR (CG equation) (mL/min/1.73 m^2)	98.82 (88.82–110.16)	110.42 (77.45–123.92)	0.383
eGFR (MDRD) (mL/min/1.73 m^2)	104.82 (96.68–121.58)	101.63 (69.65 – 114.02)	0.196
eGFR (CKD-EPI) (mL/min/1.73 m^2)	104.23 (98.21–109.65)	103.45 (73.83 – 108.32)	0.156
eGFR (CKD-EPI Asians) (mL/min/1.73 m^2)	104.94 (96.83–110.59)	98.32 (66.05 – 112.45)	0.098

Data presented as median (Interquartile range)

eGFR-estimated Glomerular filtration rate; CG = Cockcroft - Gault; MDRD=Modification of Diet in Renal Disease; CKD-EPI=chronic kidney disease-Epidemiology Collaboration

Table 3: Impaired renal function (eGFR<60 mL/min/1.73 m^2) as per various formulae in hypertensive subjects based on albuminuria

Parameter	Normoalbuminuria + eGFR > 60 mL/min/1.73 m^2 n (%)	Normoalbuminuria + eGFR ≤60 mL/min/1.73 m^2 n (%)	Albuminuria + eGFR > 60 mL/min/1.73 m^2 n (%)	Albuminuria + eGFR ≤ 60 mL/min/1.73 m^2 n (%)
CG equation	19 (63.33)	0 (0)	5 (16.67)	6 (20.0)
MDRD equation	19 (63.33)	0 (0)	5 (16.67)	6 (20.0)
CKD-EPI equation	19 (63.33)	0 (0)	5 (16.67)	6 (20.0)
CKD-EPI equation for Asians	19 (63.33)	0 (0)	6 (20.0)	5 (16.67)

eGFR-estimated glomerular filtration rate; CG = Cockcroft - Gault; MDRD=Modification of Diet in Renal Disease; CKD-EPI=Chronic Kidney Disease-Epidemiology Collaboration

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Table 4: Correlation matrix of ACR with eGFR using different equations and predictors of impaired renal function

Parameters		ACR	eGFR_CG	eGFR_MDRD	eGFR_CKD_EPI	eGFR_CKD_EPI_Asians	Age	Duration of HT	SBP	DBP
ACR	Correlation coefficient P value	-	-0.591 0.001	-0.433 0.019	-0.521 0.004	-0.461 0.012	0.020 0.920	0.002 0.992	0.291 0.125	0.220 0.251
eGFR_CG	Correlation coefficient P value			0.826 <0.001	0.895 <0.001	0.850 <0.001	-0.138 0.467	-0.078 0.682	-0.175 0.356	-0.108 0.569
eGFR_MDRD	Correlation coefficient P value				0.943 <0.001	0.900 <0.001	0.005 0.980	0.062 0.667	-0.117 0.539	-0.186 0.326
eGFR_CKD_EPI	Correlation coefficient P value					0.907 <0.001	-0.188 0.319	-0.076 0.688	-0.203 0.282	-0.175 0.354
eGFR_CKD_EPI_Asians	Correlation coefficient P value						-0.137 0.470	-0.070 0.711	-0.167 0.379	-0.230 0.221
Age	Correlation coefficient P value							0.529 0.003	0.014 0.941	0.049 0.797
Duration of HT	Correlation coefficient P value								0.272 0.145	0.260 0.165
SBP	Correlation coefficient P value									0.624 <0.001

UACR= Urinary albumin/creatinine ratio; eGFR-estimated glomerular filtration rate; CG = Cockcroft - Gault; MDRD=Modification of Diet in Renal Disease; CKD-EPI=chronic kidney disease-Epidemiology Collaboration; HT= Hypertension; SBP= Systolic blood pressure; DBP= Diastolic blood pressure

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