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An Evaluation of estimated GFR using serum cystatin C and creatinine in patients of essential hypertension.

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Abstract

Introduction: Hypertension is one of the most common worldwide disease affecting humans and is one of the leading cause of death and disability among adults all over the world. Essential hypertension accounts for 95% of all cases of hypertension. Hypertension is a leading cause of chronic kidney disease. Chronic kidney disease is a worldwide public health problem, and frequently leads to end-stage renal disease. Serum creatinine has been conventionally used as a marker of kidney disease. The measurement of glomerular filtration rate (GFR) is extensively used for the diagnosis and prognosis of chronic kidney disease and estimated GFR (eGFR) is calculated using different equations. Serum creatinine based equation has been traditionally used to calculate eGFR. Serum cystatin C and cystatin C based equation have been proposed as new endogenous markers of GFR. The objective of our study was to assess the above markers of renal function in patients of essential hypertension.

Materials & Methods:-The study population consisted of 100 hypertensive subjects of age group 30-60 years and 50 age and sex matched normotensive controls. Serum cystatin C was estimated by turbidimetric method, serum creatinine was estimated by Modified Jaffe's method. Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) serum cystatin C based equation (eGFR= 133 x min. $(S_{CYS}/0.8)^{-0.499}$ x max. $(S_{CYS}/0.8)^{-1.328}$ x $(0.996)^{Age}$ x (0.932) if female) and serum creatinine based equation (eGFR= 141 x min. $(S_{CR}/K)^{\alpha}$ x max. $(S_{CR}/K)^{-1.209}$ x $(0.993)^{Age}$ x (1.018) if female) was used to calculate eGFR.

Results:-The levels of serum cystatin C(p=0.020), serum creatinine(p=0.020) and $eGFR_{(SCYS)}$(p=0.001) were significantly higher in hypertensive subjects as compared to controls. The levels of serum cystatin C (mean=1.26mg/L) was elevated above the normal values (cystatin C 0.51-1.05mg/L) in hypertensive subjects. The mean value of serum cystatin C, $eGFR_{(SCYS)}$ and $eGFR_{(SCR)}$ was 1.09±0.31mg/L, 78.08±22.6ml/min/1.73m^2 and 100±19.1ml/min/1.73m^2 in stage 1 hypertension (130-139mm Hg and 80-89mm Hg) as compared to 1.44±0.74mg/L, 57.32±21.1ml/min/1.73m^2 and 84.98±21.2ml/min/1.73m^2 in stage 2 hypertension (≥140 and ≥90mm Hg).

Conclusion:-Our study shows that levels of serum cystatin C, the use of simple serum cystatin C based equations for calculating eGFR can be used for assessment of early renal damage in patients of EH. Our study also shows that serum cystatin C and cystatin C based equation are more sensitive markers of renal function as compared to serum creatinine.

Keywords:-Essential hypertension, creatinine, cystatin C, estimated GFR (e-GFR), early renal damage and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Introduction

Hypertension is one of the most common worldwide disease affecting humans and is one of the leading cause of death and disability among adults all over the world. It remains the major risk factor for coronary, cerebral and peripheral vascular disease[1]. A classification proposed by the American Heart Association (AHA) and American College of Cardiology (ACC) Guidelines in the year 2017 has defined a blood pressure of less than 120/80mmHg as acceptable, beyond which is considered as hypertension[2]. It is an extremely prevalent condition and it is responsible for significant mortality and morbidity[1].

As per World Health Organization report 2013, worldwide, approximately 40% of adults aged 25 and above had been diagnosed with hypertension. The prevalence of hypertension in India is 23.1% in men and 26.6% in women[3].

Hypertension is divided to either essential (primary) and secondary hypertension. Essential or primary hypertension is defined as high blood pressure in which secondary causes such as renovascular disease, renal failure, pheochromocytoma, aldosteronism or other causes of secondary hypertension are not present. Essential hypertension account for 95% of all cases of hypertension. Essential hypertension is a heterogenous disorder with different patients having different causal factor that lead to high blood pressure[4].

Majority of hypertensive patients are asymptomatic and if left untreated, many complications develop and become fatal[5]. More than 20% of patients with systemic hypertension have hypertensive nephropathy[6]. Hypertensive renal disease is the second most common cause of chronic renal failure requiring dialysis or renal transplantation in India[7]. Various mechanisms have been proposed as causing elevated renal function tests in hypertension[5].

Mild to moderate reduction in kidney function are relatively common in hypertensive patients[8]. It is well known that hypertensive patients usually have high blood volume and enhanced vasoconstriction, both of which lead to increased glomerular pressure[9]. Increase glomerular pressure may predict an early manifestation of hypertension and directly contribute to the progression of chronic kidney disease[10]. Hypertensive nephropathy is a common finding in patients with hypertension and is a common cause of chronic kidney disease[11]. Many patients with chronic kidney disease are unaware until their kidney function is decreased to more than 25% of normal[8].

Serum urea and creatinine are the most common conventional markers used for the assessment of renal function, monitor disease progress and response to treatment[12]. Urea is formed in the liver from ammonia released by deamination of amino acids. Creatinine is a breakdown product of creatine phosphate in muscle. About 1-2% of muscle creatine is converted daily to creatinine[13]. Creatinine is removed from the blood chiefly by the kidneys, primarily by glomerular filtration, but also by proximal tubular secretion[14]. The widely accepted endogenous renal marker is serum creatinine and its estimated GFR[15]. However, its use is limited because it is insensitive to early renal impairment and it is affected by

spectral interferences. Serum creatinine is also affected by age and gender[16]. The limited use of serum creatinine necessitated evaluation of other renal markers like cystatin C[17].

Cystatin C is a 13kDa, non-glycosylated basic protein belonging to the cystatin superfamily of cysteine protease inhibitor[18]. It seems to be produced by all nucleated cells. It is produced at a stable rate, which is unaffected by infections, inflammatory processes, sex, age, diet and nutritional status. In the normal kidney, cystatin C is freely filtered through the glomerular membrane and then almost completely reabsorbed and degraded by the proximal tubular cells. Therefore a plasma concentration of cystatin C is almost exclusively determined by the GFR, making cystatin C an excellent indicator of GFR[18].

In most forms of chronic kidney disease, glomerular filtration rate (GFR) tends to decrease progressively once a certain threshold of nephron destruction has occurred. The GFR is one of the best measures of kidney function. The measurement of GFR is extensively used for the diagnosis and prognosis of chronic kidney disease[19]. Several methods are available to measure the GFR. Most involve the ability of the kidneys to clear an exogenous or endogenous marker[20]. The three most commonly used equations to estimate GFR are serum creatinine based Cockcroft-Gault, Modification of Diet in Renal Disease(MDRD) 2006 and Chronic Kidney Disease Epidemiology Collaboration(CKD-EPI) 2009 creatinine equations[21].

The CKD-EPI 2009 creatinine formulae was developed to overcome the limitations of 2006 MDRD formulae[22]. Creatinine and urea are the conventional markers used for the measurement of GFR[19]. Cystatin C has been emerging as a marker of GFR. Similar to serum creatinine several equations have been elaborated to estimate GFR based on serum cystatin C[23].

Considering the fact that the presence of hypertension is strongly associated with functional and structural abnormalities that damage kidneys and lead to premature morbidity and mortality and that chronic hypertension is an independent risk factor for hypertensive nephropathy, the objective of the present study were to evaluate estimated GFR (eGFR) using serum creatinine and serum cystatin C based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for the assessment of renal function in essential hypertension.

Materials and Methods

The present study was carried out in the Department of Biochemistry, in association with the Department of Medicine, Government Medical College, Haldwani. 100 hypertensive subjects of age group 30-60 years attending the Medicine OPD of GMC, Haldwani and 50 age and sex matched normotensive controls were included in the study.

Patients with diabetes mellitus, secondary hypertension, thyroid dysfunction, overt cardiovascular disease and pregnant women were excluded from the study.

All patients were subjected to detailed history and thorough physical examination.

Taking all aseptic precautions, about 5 ml of blood was drawn by veinpuncture from a peripheral vein, with a disposable syringe. All samples were collected in the morning after an overnight fast. The blood was collected in clean dry tubes and was allowed to stand for 30 minutes at room temperature for the retraction of clot. This was then centrifuge at 3000 r.p.m. for 10 minutes to separate the serum. The serum was stored at 4^{o}C in the refrigerator for analysis.

Estimation of serum creatinine was done by using fully automated Roche Cobas c 501 analyzer.

Estimation of serum cystatin C was done by turbidimetric method using semiautomatic analyzer (MERCK Microlab 300).

Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) serum cystatin C based equation (eGFR= 133 x min. $(S_{CYS}/0.8)^{-0.499}$ x max. $(S_{CYS}/0.8)^{-1.328}$ x $(0.996)^{Age}$ x (0.932) if female) and serum creatinine based equation(eGFR= 141 x min. $(S_{CR}/K)^{\alpha}$ x max. $(S_{CR}/K)^{-1.209}$ x $(0.993)^{Age}$ x (1.018) if female) was used to calculate eGFR.

Statistical Analysis

The data were compiled and entered in MS Excel sheet and the analysis was carried out using the Statistical Package for the Social Sciences (SPSS 19.0.2) program for windows. Unpaired "t" test was used to analyze all the data for statistical significance.

Results

Of the 100 cases studied, 39 had stage I hypertension and 61 had stage II hypertension according to 2017 AHA/ACC Guidelines.

Table 1: Distribution of age-group among cases (n=100).

Age group (yrs)	Male		Female		Total	
	No	%	No	%	No	%
30-40	15	15	08	08	23	23
41-50	19	19	11	11	30	30
51-60	28	28	19	19	47	47
Total	**62**	**62**	**38**	**38**	**100**	**100**

Table 1 shows the age and sex distribution among cases. All the cases were of the age group 30-60 years. 23% of the cases were in the age group 30-40 years followed by 30% within 41-50 years, 47% within 51-60 years.

Table 2: Serum Creatinine and serum cystatin C levels in stage I and stage II hypertensive subjects.

Parameter	Stage I Hypertension (n = 39) Mean±SD	Stage II Hypertension (n = 61) Mean±SD
Serum Creatinine (mg/dl)	0.87±0.28	0.94±0.41*
Serum cystatin C (mg/L)	1.15±0.41	1.37±0.71**

*significance level as compared to stage I hypertension: *p* = NS

**significance level as compared to stage I hypertension: $p < 0.003$

Estimation of serum creatinine and serum cystatin C was done in all hypertensive subjects and the final result was expressed as mg/dl and mg/L respectively. **Table 2** shows the mean serum creatinine and serum cystatin C level in stage I (0.87±0.28 and 1.15±0.41) and stage II (0.94±0.41 and 1.37±0.71) hypertensive subjects. The mean serum creatinine level was raised in stage II hypertensive subjects as compared to stage I hypertensive subjects. This difference was not found to be statistically significant (*p* = NS). The mean serum cystatin C level was significantly raised in stage II hypertensive subjects as compared to stage I hypertensive subjects. This difference was found to be statistically significant ($p < 0.003$).

Table 3: e-GFR by CKD-EPI formula using serum creatinine in stage I and stage II hypertensive subjects.

Parameter	Stage I Hypertension (n = 39) Mean±SD	Stage II Hypertension (n = 61) Mean±SD
eGFR(Scr) (ml/min/1.73 m^2)	96.36±22.80	88.79±20.35

*significance level as compared to stage I hypertension: *p* = NS

Estimation of e-GFR by CKD-EPI formula using serum creatinine was done in all hypertensive subjects. The final

result was expressed as ml/min/1.73m^2. **Table 3** shows the mean e-GFR(Scr) level in Stage I (96.36±22.80) and Stage II (88.79±20.35) hypertensive subjects. The mean eGFR(Scr) level was decreased in stage II hypertensive subjects as compared to stage I hypertensive subjects. This difference was not found to be statistically significant (p = NS).

Table 4: e-GFR by CKD-EPI formula using serum cystatin C in stage I and stage II hypertensive subjects.

Parameter	Stage I Hypertension (n = 39) Mean±SD	Stage II Hypertension (n = 61) Mean±SD
eGFR(Scys) (ml/min/1.73 m^2)	75.87±26.14	60.79±20.76*

*significance level as compared to stage I hypertension: $p < 0.003$

Estimation of e-GFR by CKD-EPI formula using serum cystatin C was done in all hypertensive subjects. The final result was expressed as ml/min/1.73m^2. **Table 4** shows the mean eGFR(Scys) level in stage I (75.87±26.14) and stage II (60.79±20.76) hypertensive subjects. The mean eGFR(Scys) level was significantly decreased in stage II hypertensive subjects as compared to stage I hypertensive subjects.. This difference was found to be statistically significant (p <0.003).

Table 5: Comparision of CKD-EPI based e-GFR using serum creatinine and cystatin C in stage I and stage II hypertensive subjects.

Parameter	Stage I hypertension (Mean±SD)	Stage II hypertension (Mean±SD)
eGFR$_{Scr}$ (CKD-EPI)	96.36±22.80	88.79±20.35
eGFR$_{Scys}$ (CKD-EPI)	75.87±26.14	60.79±20.76*

*Significance level as compared to stage I hypertension: $p < 0.003$

Table 5 shows the mean eGFR calculated by CKD-EPI formula based on serum creatinine and cystatin C in stage I (96.36±22.80 and 75.87±26.14) and stage II (88.79±20.35 and 60.79±20.76) hypertensive subjects respectively. eGFR by CKD-EPI formula using serum creatinine was found to be decreased in stage II hypertensive subjects as compared to stage I hypertensive subjects. This difference was not found to be statistically significant. eGFR by CKD-EPI formula using serum cystatin C was significantly reduced in stage II hypertensive subjects as compared to stage I hypertensive subjects. This difference was found to be statistically significant ($p < 0.003$).

Discussion

Hypertension is one of the major public health problem because of its high morbidity and mortality arising from the concomitant risks of cardiovascular and renal disease[24]. The association between hypertension and chronic kidney is well known. Hypertension can also determine the emergence of chronic kidney disease and contribute to its progression to the terminal stage[25]. Associations between blood pressure levels and kidney function deterioration have been shown by many research studies.

Hypertension represents a pertinent and persistent risk factor for the development and progression of kidney disease particularly in the absence of appropriate blood pressure control measures[26]. Chronic kidney disease is a known complication of hypertension especially when the blood pressure is uncontrolled[27].

In the present study, according to 2017 AHA/ACC guidelines, out of 100 subjects studied, 39 subjects met the stage I and 61 met the stage II hypertension criteria**.** In our study, 47% of hypertensive subjects were within the age group of 51-60 years **(Table 1).** Pramiladevi R *et al*.,

(2011) in their study showed that 52% of the hypertensive subjects were within the age group of 51-60 years[28]. In the study of Basant *et al*., (2016) 55% of the hypertensive subjects were in the age group of 50-60 years[29]. In the study of Anil kumar H *et al*., (2016) 42% of the hypertensive subjects were in the age group of 51-60 yearrs[30].

Serum creatinine is the most commonly measured parameter for the monitoring of renal function in patients of hypertension. Increased level of creatinine has been widely accepted as an indicator of renal insufficiency[29]. In our study, serum creatinine levels were raised in stage II hypertensive subjects as compared to stage I hypertensive subjects **(Table 2)** but this difference was not found to be statistically significant difference **(*p* = NS)**. Study by Rakhee Yadav *et al*., (2014) found serum creatinine levels to be higher only in stage II hypertensive and also found them to be statistically significant[31]. Sadiqa *et al*., (2014) also found serum creatinine levels to be significantly elevated in both stage I and stage II hypertension[32]. Arindam Sur *et al*., (2015) observed that stage II hypertensive group showed significantly higher levels of serum creatinine as compared to stage I hypertensive subjects.[33]. A study done in Japan by Ishida *et al*., (2001) to know the effect of high BP on renal function by estimating serum creatinine as a marker of kidney function showed a significantly high serum creatinine level in hypertensive subjects[34].

Serum cystatin C is a useful biochemical marker in assessing subclinical hypertensive renal disease, since it could accurately reflect glomerular filtration rate[35]. Many studies have validated the use of serum cystatin C as an early marker of renal dysfunction in hypertensive patients. In our study serum cystatin C levels were significantly elevated **(*p* < 0.003)** in stage II hypertensive subjects when compared to stage I hypertensive subjects **(Table 2).** This result is in confirmation with the findings of Newman *et al*., (1994) who observed that the levels of serum cystatin C were significantly elevated in the studied subjects as compared to controls[36]. Arindam sur *et al*., (2015) demonstrated that serum cystatin C levels were significantly elevated in hypertensive cases when compared with controls[33]. Dharnidharka VR *et al*., (2002) in their study showed that levels of serum cystatin C were significantly raised in stage II hypertensive patients as compared to stage I hypertensive subjects[37].

Multiple studies identified serum cystatin C as a more accurate marker for mild reductions in kidney function than serum creatinine alone. Karina Soto *et al*., (2010) observed serum cystatin C to be an excellent marker of renal function[38]. A study done by Jithesh TK *et al* ., (2013) demonstrated that serum cystatin C is more sensitive and reliable marker for assessing renal function than serum creatinine[39]. The finding of meta-analysis done by Wang Y *et al*., (2008) suggested the superiority of serum cystatin C concentration comparing with serum creatinine in patients of essential hypertension[40].

Accurate assessment of GFR is essential for interpreting the symptoms, signs and laboratory abnormalities that may indicate kidney disease and for detecting and managing chronic kidney disease[39]. In this study we have used CKD-EPI formula based upon serum creatinine and serum cystatin C for estimating GFR. In our study eGFR by CKD-EPI formula using serum creatinine was decreased in stage II hypertensive subjects as compared to stage I hypertensive subjects but this difference was not statistically significant **(Table 3)**. In the present study eGFR by CKD-EPI formula using serum cystatin C was significantly decreased **(*p* < 0.003)** in stage II hypertensive subjects when compared with stage I hypertensive subjects **(Table 4).**

Comparision of eGFR by different formula using serum creatinine and serum cystatin C was done in many studies. In the present study we compared e-GFR by CKD-EPI formula using serum creatinine and serum cystatin C levels. Comparison of eGFR by CKD-EPI formula using serum creatinine and serum cystatin C in stage I and stage II hypertensive subjects showed that eGFR using serum cystatin C was significantly decreased **($p < 0.003$)** in stage II hypertensive subjects as compared to stage I hypertensive subjects whereas eGFR using serum creatinine was not significantly decreased **($p > 0.05$)** in stage II hypertensive subjects as compared to stage I hypertensive subjects **(Table 5)**. This supports the fact that CKD-EPI cystatin C formula is better than CKD-EPI creatinine formula for calculating eGFR. A study by Lesley A *et al*., (2012) observed that eGFR by CKD-EPI formula using serum cystatin C is better than eGFR by CKD-EPI formula using serum creatinine for early decline in renal function[41]. Study by Inker LA *et al*., (2011) showed that eGFR by CKD-EPI formula using serum cystatin C is more sensitive and reliable for assessing renal function when compared with CKD-EPI formula using serum creatinine[42]. A study by Mac Isaac RJ *et al*., (2006) also demonstrated the sensitivity of eGFR by CKD-EPI cystatin C formula over CKD-EPI creatinine formula in assessing early decline in renal function[43]. These results are in confirmation with the finding of our study.

Conclusion

The present study showed that levels of serum cystatin C can be used to assess early renal damage in patients of essential hypertension. eGFR calculated using serum cystatin C based equations can also be used as a good marker of early renal damage. Our study also shows that serum cystatin C and cystatin C based equation are more sensitive markers of renal function as compared to serum creatinine.

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