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RESEARCH ARTICLE

A STUDY OF SERUM UREA, CREATININE AND PROTEINURIA IN HYPERTENSIVE PATIENTS

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ABSTRACT

Introduction: Hypertension is defined as sustained increase at or above 140 mmHg of Systolic blood pressure (SBP) and 90 mmHg of diastolic blood pressure (DBP).Hypertensive nephropathy or renal disease occurs as a result of high blood pressure in hypertensive patient. This disease is characterized by damage to the vasculature of the kidneys as blood pressure increases. Proteinuria is closely associated with hypertension, presumably reflecting the severity of hypertension induced renal damage.

Objectives: The objectives of the present study were A study of serum urea, creatinine and proteinuria in hypertensive patients.

Material & Methods: Total 118 Hypertensive patients, of age group 25-55 years were included in this study. Detailed history was taken and renal function tests were done in all the patients.

Results:-In the present study, Serum urea ($p<0.01$) and creatinine ($p<0.01$) levels were found to be significantly higher in cases as compared to those normal subjects. In hypertensive patients with renal failure, significant correlation was found between SBP and level of serum urea (correlation coefficient -0.4).

Conclusion: Proteinuria with high BP is an indicator of declining kidney function. It is simple,accurate, and convenient measurement which is not only quatitative, but also semiquantitative as it can predict the total amount of protein loss through kidneys.It is a good replacement for tedious, time consuming 24 h urine protein estimation, especially in countries like India where hospitals cannot cope up with a large number of in-patients. We can also use other parameters as random urine albumin-creatinine ratio for the prediction of significant proteinuria in HTN patients.

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INTRODUCTION

Hypertension (HTN) is regarded as a silent killer and unless diagnosed earlier and treated properly, it can cause many complications such as coronary artery disease, heart attack, stroke, impaired renal function and ultimately renal failure. Among all cardiovascular diseases hypertension is the commonest in all over the world. (Sarkar *et al*., 2006) Hypertension defined as a systolic blood pressure of ≥140 and a diastolic blood pressure ≥90 is an extremely prevalent condition; and it is responsible for significant mortality and morbidity. The prevalence of hypertension in India is 23.10% in men and 26.60% in women. (World Health Organisation, 2012) Hypertension and renal dysfunctions are closely related. Majorities of hypertensive patients are asymptomatic and left untreated. So complication develops and become fatal. It has been reported that even small elevations above optimal blood pressure (BP) values (>120/80 mmHg) increases the likelihood of developing HTN and increasing target organ damage.

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(Cushman, 2003) HTN is a major determinant of progression of chronic kidney disease (CKD), irrespective of cause and the relative risk of developing end-stage renal disease increases with a steady increase in diastolic BP. (Tailakh *et al*., 2013) Chronic kidney failure usually develops and becomes slowly with few signs or symptoms in early stages. (Sarkar *et al*., 2006) Glomerular filtration Rate is the best estimate of number of functioning functional renal mass. Accurate measure of GFR is time consuming and expensive; but a number of filtered substances may be measured to estimate GFR including blood urea, serum creatinine. (Amin *et al*., 2010) The elevation of serum urea and creatinine may be relevant to the decreased GFR as a result of hypertension effect on renal function. Decrease in renal blood flow results in decrease in GFR this leads to decrease in distal tubular flow rate which leads to increase in urea reabsorption and decreased secretion which may be the reason for elevated serum urea concentration. (Isra'a 2010) The elevation of serum creatinine concentration in hypertension may be attributed to the decrease in creatinine clearance due to decrease in GFR. Creatinine Clearance rate determines how efficiently kidneys are clearing creatinine from the blood. Hence it serves as an estimate of kidney function. (Sarkar *et al*., 2006) The proteinuria is a good predictor of CV risk and also seems to be a marker of systemic vascular damage the data from the HOPE (Heart Outcomes

Prevention Evaluation) study confirmed its predictive value and its relevance as a CV risk factor in non-diabetic hypertensive patients has also been demonstrated. (Schmieder *et al*., 2011) Significant data reflects impaired vascular and endothelial function and association with higher susceptibility to cardiovascular and renal events. (Tangjatuporn *et al*., 2012) However several BP-lowering trials have demonstrated that reduction in BP might slow the progression of kidney disease among hypertensive subjects. (Gerstein *et al*., 2001) A number of studies were conducted on effect of hypertension on kidney functions, but little is known about rural population in India. This study was conducted to compare the renal function tests and creatinine clearance in hypertensive patients.

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. After a written informed consent, all patients were subjected to detailed history and thorough clinical examination. Total 118 patients, of age group 25-55 years were included in this study. Detailed history was taken and renal function tests were done in all the patients. Of the studied sample 60 patients were being treated for renal failure (group I cases), 30 patients with hypertension did not have renal failure (group II) and 28 were healthy age and sex matched controls. H/o cardiovascular disease, respiratory disease, drug Medications (steroids, α methyl dopa) for past three months, renal disease and endocrine disease subjects excluded from the study.

Taking all aseptic precautions, about 5 ml of blood was drawn by vein puncture from a peripheral vein, with a disposable syringe. All samples were collected in the morning after an overnight fast. Sample for urea, creatinine were collected in a plain vial. The blood thus collected in clean dry glass tubes was allowed to stand for 30 minutes at room temperature for the retraction of clot. This was then centrifuge at 2500 r.p.m. for 30 minutes to separate the serum. The serum was stored at 4°C in the refrigerator for analysis. 24hr urine sample for microalbuminuria was collected in a clean plastic container. The preservative used was 10% HCL. After giving half an hour rest to the person in the departmental laboratory, blood pressure was measured in supine position by mercury sphygmomanometer. The pressure at which Korotkoff's sound first heard (Phase I) was taken as systolic blood pressure and the pressure at which these sounds disappeared (Phase V) was taken as diastolic blood pressure. Blood pressure was measured three times. The average of second and third readings will be taken as correct systolic and diastolic blood pressure.

Determination of urea

Quantitative in vitro determination of urea in serum was done in semi-automatic analyzer using commercially available UREA kit. Assay is based on that urease hydrolyses urea to ammonia and Co_2. The ammonia formed further reacts with a phenolic chromogen and HCL to form a green color complex. Intensity to the color formed is directly proportional of urea present in the sample.

Normal value: Serum urea: 20-45 mg /dl.

Determination of serum creatinine

Quantitative in vitro determination of creatinine in serum was done in semi-automatic analyzer using commercially available CREATININE (CREA) kit. The assay is based on reaction of creatinine in alkaline solution with sodium picrate as described by Jaffe, forming a red complex. The intensity of color formed is proportional to creatinine concentration in the sample.

Normal value:
Male: 0.7 – 1.4 mg /dl
Females: 0.6 – 1.1 mg /dl

Creatinine clearance by Cockcroft-Gault Formula

$$\text{Estimated Creatinine Clearance (females)} = \frac{[140 - \text{Age in years}] \times \text{Body weight in kg}}{\text{Serum creatinine mg/dl} \times 72}$$

$$\text{Estimated Creatinine Clearance (males)} = \frac{[140 - \text{Age in years}] \times \text{Body weight in kg}}{\text{Serum creatinine mg/dl} \times 85}$$

Normal Creatinine Clearance:

Males:-95-140ml/min.**Females:** - 85-130 ml/min

Microalbuminuria done by Pyrogallol Red method (end point assay)

Protein in acidic medium combines with pyrogallol red and molybdate to form ablue purple color complex. Intensity of the color formed is directly proportional to the amount of proteins present in the sample

Normal value: - 28-140 mg/24hrs

Statistical analysis

Results were expressed as mean ± SD. The data were analyzed with the help of SPSS software program using the relevant tests of significance such as Unpaired't' test. Using Pearson's correlation coefficient formula, statistically significant correlation was found between SBP &creatinine clearance. A level of $p < 0.05$ was accepted as statistically significant.

OBSERVATIONS AND RESULTS

A total of 118 hypertensive men and women enrolled in our study, out of which 60 hypertensive patients with renal failure were taken as cases (group I). 30 patients were hypertensive without renal failure (group II), 28 were healthy non hypertensive taken as controls. The age and sex distribution of present study were, in the cases (group I) 25% of the patients were in the age group 18-33 years followed by 20% within 34-49 years, & 55% of 50-60 years. And in group II, 24% are in 18-33 years, 6.8% of 34-39 and 20.6% of 50-60 years. In the present study, Serum urea ($p<0.01$) (171.68±115.410) and creatinine ($p<0.001$) (6.78±4.61) levels were found to be significantly higher in cases (group I) as compared to those normal subjects. (Table 1)

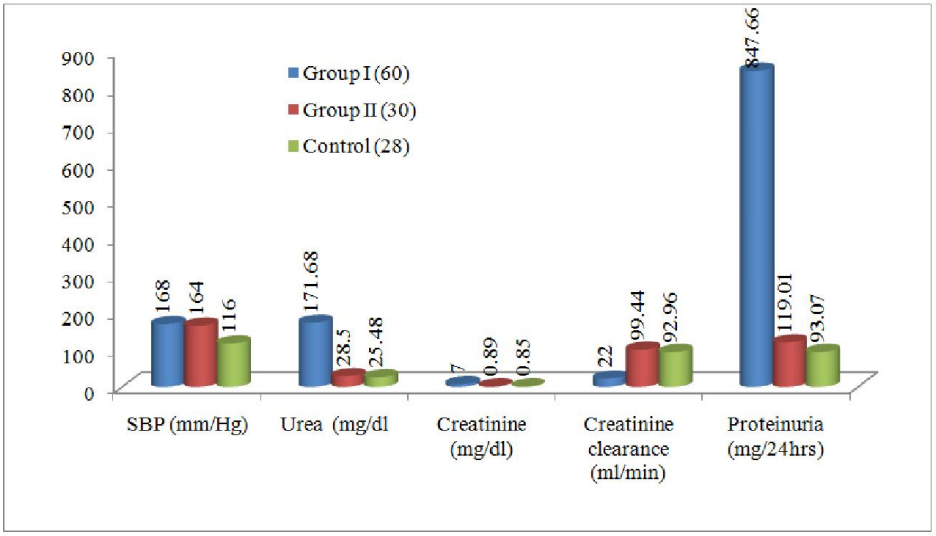

Fig 1. Distribution of SBP, Serum Urea, Creatinine, Creatinine Clearance and Proteinuria in studied subjects as compared to controls

Table 1. Distribution of SBP, Serum Urea, Creatinine, Creatinine Clearance and Proteinuria in studied subjects as compared to controls

	Cases (Group I) (n=60)	Group II (n=30)	Controls (n=28)	*p* value	Range
SBP (mm/Hg)	168	164	116	0.036	<130
Urea (mg/dl	171.68	28.5	25.48	<0.001	12.8-42.0
Creatinine (mg/dl)	6.78	0.89	0.85	<0.001	0.9-1.3
Creatinine clearance (ml/min)	22	99.44	92.96	0.036	95-140
Proteinuria (mg/24hrs)	847.66	119.01	93.07	<0.001	28-140

Table 2. Severity of hypertension in cases (group I) and group II among to SBP

SBP(mmHg)	Cases % (group I)	Group II
Mild hypertension (140-149)	25	20
Moderate hypertension (150-179)	43	53
Severe hypertension (≥180)	32	27

Table 3. Severity of proteinuria in cases and controls

	Cases (Group I) (n=60)	Group II n=30	Controls n=28
Mild proteinuria (150-500mg/24hr)	36	8.6	0
Moderate proteinuria (501-1000mg/24hr)	38	0	0
Severe proteinuria (1001-3500mg/24hr)	22	0	0
Nephrotic proteinuria (above 3500mg/24hr	4	0	0

Table 4. Correlation coefficient (r) between SBP and creatinine clearance in cases

	N	Correlation coefficient(r)	*p* value
SBP	60	-0.27	0.036
Creatinine clearance	60	-0.27	0.036

Table 5. Correlation coefficient (r) between SBP and creatinine clearance in cases

	N	Correlation coefficient(r)	*p* value
SBP	60	-0.27	0.036
Urea	60	-0.4	<0.001

Present study shows that 43% of cases (group I) had moderate hypertension & 32% had severe hypertension while 53% of group II had moderate and 27% of group II had severe hypertension. (Table 2) Data of present study also shows 85% of cases (group I)& 3.4% of hypertensive controls (group II) had the serum creatinine levels>1.1 mg/dl and 88.33% of cases (group I) and 12.06% hypertensive controls (group II) had serum urea levels >40mg/dl. Elevated serum creatinine & urea levels are an early indicator of renal disease. In hypertensive patients with renal failure, significant correlation was found between SBP and creatinine clearance as compared to normal subjects (correlation coefficient -0.27) and

significant correlation was also found between SBP and level of serum urea (correlation coefficient -0.4). (Table 4&5)

DISCUSSION

Hypertension is one of the commonest diseases and is a leading risk factor for kidney failure and heart disease. (Sarkar *et al*., 2006) Hypertension is more prevalent, of earlier onset and more severe in African Americans (AA) and AAs have an increased risk of ESRD from hypertensive nephropathy. (Rahman *et al*., 1997) Primary hypertension participates actively in the development of cardiac (coronary artery disease, heart failure, and atrial fibrillation), cerebral (stroke and transient ischemic attack), and peripheral arterial disease. The presence of CKD, usually considered as a form of target organ damage, can be detected throughout the CV continuum. The higher the level of global CV risk, the higher the level of accompanying CKD with up to 35% of people with hypertension and high or very high added risk having an eGFR values below 60 mL/min/1.73 m^2. (Ruilope, 2002) Data of the present study indicates, that higher levels of systolic blood pressure were positively and significantly related to declining in kidney function among hypertensive patients. Increased level of serum urea and creatinine were found among hypertensive patients with renal failure, therefore these parameters can be used as a diagnostic marker to predict the severity of the renal impairment. Significant correlation was also found between creatinine clearance and serum urea level in hypertensive patients with renal failure. According to Michael J.Klag *et al.* (2003), higher levels of BP were positively and significantly related to early decline in kidney function among hypertensive patients. (Michael *et al*., 2003) Marcello Tonelli *et al.* (2006), demonstrated convincingly thehigh risk of progression of chronic renal failure associated with high BP. Elevated BP and moderate proteinuria have shown to be significant risk factors for progression of CRF. Josef coresh *et al* in 1994 investigated the severity of renal disease according to serum creatinine levels and the prevalence of end stage renal disease and CRF. They studied 16589 subjects, aged 17 and older. As a result they found higher systolic blood pressure (SBP), diastolic blood pressure (DBP), older age and diabetes mellitus were all associated with higher serum creatinine levels. They concluded that elevated serum creatinine level, an indicator of chronic renal disease, is common and strongly related to inadequate treatment of high blood pressure. (Josef Coresh *et al*., 2004) Andreus D. Rule *et al* 2006 studied 2653 subjects; they used modifications of Diet in Renal Disease equations to determine GFR from serum creatinine. The purpose of their study to defined kidney disease by reduced GFR and elevated serum creatinine. They concluded that kidney disease identified by elevated serum creatinine with reduced GFR. William F. Owen *et al* 1993 determined the effects of blood urea in ESRD patients. The study population consisted of 13,473 patients. As a result they found 60% patients with high levels of urea had higher risk of death. The degree of proteinuria correlates with the rate of progression of the underlining nephropathy and is the most reliable prognostic factor in chronic renal failure. Proteinurias, previously considered a marker of renal disease, is itself pathogenic and is the single best predictor of disease progression. Reducing urinary protein excretion slow the progressive decline in renal function in kidney disease (Malvinder S Parmar, 2002). Marcello Tonelli *et al* in 2006 studied 4098 men and women; the purpose of their study was to detect the impairment of kidney function on the basis of glomerular filtration rate (GFR) and proteinuria. They concluded that both proteinuria and low GFR were higher risk of renal failure. (Michael J. Klag *et al*., 2003) Proteinuria, microalbuminuria and nephrotic syndrome may each occur in patients with hypertensive nephropathy. Proteinuria is a non-specific finding in patients with vascular disease and is associated with increased risk of cardiovascular events. The majority of patients with benign nephrosclerosis have proteinuria in the range of 0.5 to 1 g/24hours. (Michael J. Klag *et al*., 2003) Proteinuria also occurs in hypertensive renal disease. In one study of 145 patients with hypertensive nephrosclerosis who underwent renal biopsy between 1960 and 1982, only 18 (12%) had nephroticsyndrome. Six of these patients had malignant HTN, while the remaining 12 had nephrotic range proteinuria but only benign nephrosclerosis. Authors suggested that hypertensive nephropathy should be included in the differential diagnosis of nephrotic range proteinuria in patients with azotemia and poorly controlled HTN and pointed out that benign HTN may lead to nephrotic syndrome. (Mujais *et al*., 1985) In a 2002 a study was conducted to determine the frequency of nephrotic range proteinuria in patients with hypertensive nephrosclerosis.

Conclusion

Control of hypertension can decrease the chances of developing renal failure. Regular monitoring of serum urea, creatinine and proteinuria is recommended in these patients. Proteinuria with high SBP is an indicator of declining kidney function. It is simple, accurate, and convenient measurement which is not only quatitative, but also semiquantitative as it can predict the total amount of protein loss through kidneys.It is a good replacement for tedious, time consuming 24 h urine protein estimation, especially in countries like India where hospitals cannot cope up with a large number of in-patients. We can also use other parameters as random albumin-creatinine ratio for the prediction of significant proteinuria in hypertensive patients. Timely detection of HTN in a general practitioner's clinic is an effective method of prevention of renal damage from a raised BP. use of simple tests like estimation of serum creatinine and proteinuria by dipsticks, will not only provide a basis for timely detection of HTN and related diseases, but also lead to early referral to a physician or nephrologist to reduce the progression to impaired renal function.

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