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IMPACT OF UNTREATED HIGH BLOOD PRESSURE ON RENAL FUNCTION TESTS AT INITIAL DIAGNOSIS OF HYPERTENSION

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ABSTRACT

Background: Pakistani population is at higher risk of developing hypertensive complications at a younger age, resulting from undiagnosed and untreated hypertension (HTN). High cost of medical care is a barrier to early detection and assessment of end organ damage as well as physicians are disinclined to adopt more aggressive therapeutic management to improve blood pressure control. A cross sectional study was planned to determine the effect of high blood pressure on renal function tests in a random population aged 25-50 year, at initial diagnosis of hypertension. Methods: The study was conducted on total 276 subjects; 201selected from five general practitioners clinics in Karachi and were classified into pre hypertensive, and hypertensive stages I and II on the basis of 7th JNC report. Two BP readings were taken half an hour apart. A blood sample was drawn for measurement of serum urea, creatinine and a dipstick test was done to check protein in urine. The results were compared with 75 control, normotensive subjects. The percentage, mean and Standard deviation were computed. ANOVA was performed to compare four study groups and LSD test was applied to compare pair-wise group. Pearson's correlation was applied to find out association of renal function with stages of hypertension. Results: The mean urea and creatinine levels were on higher normal side in HTN stages-I and II (39.91±8.51 and 1.72±0.54 in stage-I and 44.51±9.93 and 1.91±0.88 in stage-II respectively). The frequency of proteinuria was also more in these groups, indicating declining renal function in these patients as compared to control and prehypertension groups. Conclusion: Subjects diagnosed with stage I and II HTN showed evidence of subclinical renal damage, along with the presence of proteinuria at the time of diagnosis.

KEYWORDS

Hypertension, blood pressure, Chronic Kidney disease, proteinuria, target organ damage

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 (Ulasi, 2011). As majority of hypertensive patients are symptomless, therefore their condition remains unrecognized and untreated, leading to a higher risk of developing complications. 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 (Cushman, 2003).

HTN related kidney disease affects every group and race; however certain groups are at higher risk; Among Pakistani ethnic subgroups, the prevalence of HTN was found to be highest among Baluchis, then Pashtuns and Muhajirs, and lowest among Punjabis and Sindhis (Jafar, 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, 2013).

Renal function is assessed by measuring serum urea, creatinine and passage of proteins in urine (proteinuria). Urea though a less satisfactory index of glomerular filtration is routinely measured as an important renal function test (Redón, 2006). The baseline creatinine level is a strong predictor of renal function thus every increase of 0.1 mg/dL in serum creatinine level increases the risk of CKD by six times (Segura, 2002). Moreover the predictive capacity of serum creatinine has been confirmed by the data presented by many studies including Intervention as a Goal in Hypertensive Treatment (INSIGHT), Systolic Hypertension in Europe (SYS-EUR), Systolic Hypertension in China (SYST-CHINA) and Systolic Hypertension in the Elderly Program (SHED) (Pahor, 1998).

Detection of albumin in urine represents an important diagnostic window for systemic micro or macro vascular damage and is an independent predictor of cardiovascular (CV) morbidity and mortality (Thoenes, 2007). The 7th JNC report recognized microalbuminuria (urinary excretion of albumin between 30-300 mg/day) as well as an estimated GFR below 60 ml/min as major CV risk factor, associated with unfavorable effects, such as left ventricular hypertrophy and peripheral atherosclerosis (Chobanian, 2009).

The proteinuria is a good predictor of CV risk and also seems to be a marker of systemic vascular damage (Russo, 2007). The data from the HOPE study confirmed its predictive value and its relevance as a CV risk factor in non-diabetic hypertensive patients has also been demonstrated (Schmieder, 2011). Significant data reflects impaired vascular and endothelial function and association with higher susceptibility to cardiovascular and renal events (Tangjatuporn, 2012). However several BP-lowering trials have demonstrated that reduction in BP might slow the progression of kidney disease among hypertensive subjects (Gerstein, 2001).

Our population is at higher risk of developing heart attack, stroke and renal failure etc resulting from failure in timely diagnosis of

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HTN. A survey conducted by National Health Survey of Pakistan revealed that HTN affects one every out of three Pakistanis over 45 years of age. However 70% of our population remains undetected, 25% are identified but inadequately treated, whereas only 3-5% is able to receive proper treatment and control over disease.

The major reason being that general practicing physicians in Pakistan lack structured process of patient care, proper follow up and early referral system thus either ignore or treat poorly the patients with high BP (Surour, 2004). This substantially increases the risk of cardiac and renal diseases especially when HTN is coupled with other risk factors such as obesity, smoking, high cholesterol or diabetes (Wong, 2006). In view of higher prevalence of HTN, early detection and treatment of HTN are critically important. This study reports the baseline renal function status at the time of initial diagnosis of HTN in general population aged between 25-50 years.

METHODS

The study design was cross sectional with purposive sampling, conducted on 276 subjects. Out of these, 201 subjects selected from five general practitioners clinics in Karachi from July 2009-2010, who were diagnosed to have high BP for the first time and categorized into three groups, prehypertension (pre-HTN), hypertension stage I and II, on the basis of cut off values determined by 7th JNC report.9 The three categories include:
Pre-HTN (n = 55): Systolic BP > 120 and < 140 mmHg and Diastolic BP> 80 and < 90 mmHg
HTN Stage-I (n = 70) with SBP> 140 and <160 mmHg; DBP>90 mmHg and < 100 mmHg
HTN Stage-II (n = 76) with SBP > 160 mmHg and Diastolic BP> 100 mmHg
The age-matched controls (n=75) had normal BP without any medication having systolic BP < 120 mmHg and diastolic BP< 80 mmHg. Patients suffering from any other disease (cardiac, renal, hepatic etc) were excluded from study (exclusion criteria). Majority of the subjects were educated and belonged to middle and lower middle socioeconomic class. Detail of subject profile was published previously.

Ethical considerations

Written consent of every participant of study was taken. The study was approved by Board of Advanced Studies and Research and Ethical Committee of Karachi University. The tests were done prior to referral to a physician or nephrologist for further investigations.

Determination of urea

Enzymatic in vitro assay for the quantitative determination of urea in human serum/plasma was done on Roche automated clinical chemistry analyzers (by using commercially available kit c‹o›bas®), based on Talke and Schubert's method using the coupled urease/glutamate dehydrogease (GLDH) enzyme system.
NORMAL VALUE: Serum urea: 10 – 50 mg /dL (1.7 – 8.3 mmol /L).

Determination of serum creatinine

Quantitative in vitro determination of creatinine in serum/plasma was done in 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 Female: 0.6 – 1.1 mg /dL
URINE ANALYSIS: An early morning sample of urine was collected in a sterile bottle and analyzed for the presence of albumin by soaking lower portion of dipstick reagents strips (URISTIX) in urine, an easy and cost effective method. The change in color was matched with the color chart given on the box, to check the presence of proteins in urine. Traces: < 30md/dl; +1 = 30mg/dl; +2 = 100mg/dl; +3 = 300 mg/dl; +4 = (1000 mg/dl)

Blood Pressure Measurement: Systolic and diastolic BP were measured by mercury sphygmomanometer and the first and fifth Korotkoff sounds were recorded by the height of mercury column. Two readings of both systolic and diastolic BP were taken and averaged.

Statistical analysis

Data was analyzed by using SPSS version-15. All qualitative variables were presented by Mean ± SD. Analysis of variance was performed to compare four study groups and LSD- test was applied to compare pair-wise groups.

Test of linear correlation (r) was applied to assess relationship of serum urea and creatinine with systolic and diastolic blood pressure in each group. Coefficient correlation of these variables was carried out with each other and within each of the four groups to identify the association between different variables with one another. Frequency and percentage was computed for presentation of urinary protein. Chi-square test was applied to compare these variables among four groups. Statistical significance was taken at $p < 0.05$

RESULTS

Most of the participants of this study were educated, belonging to middle and lower middle class, representing the most prevalent class of our population. The mean age in control group was significantly less than the mean age of HTN stage-I and stage-II groups ($p<0.001$) but insignificant with the mean age of pre-HTN group ($p=0.346$). Majority of subjects were overweight and obese (subject profile has been presented and published previously) (Syed, 2009).
The mean urea of HTN Stage-I and II were on higher normal side i.e. 39.61±8.51 (range; 26-64) and 44.53±9.93 (range; 30-84) respectively, as compared to control and pre-HTN groups. The comparison of mean urea among the study groups were significantly less $p<0.001$ (Table-1)

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Group	Control	Pre HTN	HTN stage-I	HTN stage-II
S #	(A) (n = 75)	(B) (n=55)	(C) (n = 70)	(D) (n = 76)
Mean± SD	31.77 ± 8.08	32.93 ± 9.51	39.61 ± 8.51	44.51 ± 9.93
Pair-wise comparison statistical significance	-	v/s A=0.47	v/s A<0.001*	v/s A<0.001*
	-	v/s C<0.002*	v/s D<0.001*	-
	-	v/s D<0.001*	-	-

Table 1: Comparison of mean Urea among study groups (n = 276)

The mean serum creatinine level was 0.91 ± 0.15 in control group, 1.04 ± 1.19 (range 0.7-1.5) in pre HTN group, 1.72 ± 0.54 (range; 0.9-4.0) in HTN stage-I, while it was 1.91 ± 0.88 (range; 0.8-6.6) in HTN stage-II. The comparison of mean serum Creatinine among the study groups were significantly less (p<0.001). The mean serum creatinine of control and pre-HTN groups were significantly less than HTN stage-I (p<0.005) and HTN stage-II (p<0.001) as shown in (Table 2).

Group	Control	Pre HTN	HTN stage-I	HTN stage-II
S #	(A) (n = 75)	(B) (n = 55)	(C) (n = 70)	(D) (n = 76)
Mean± SD	0.91 ± 0.15	1.04 ± 0.19	1.72 ± 0.54	1.91 ± 0.88
Pair-wise comparison statistical significance	-	v/s A=0.145	v/s A=0.002*	v/s A<0.001*
	-	v/s C<0.001*	v/s D=0.39	-
	-	v/s D=0.011*	-	-

Table 2: Comparison of mean serum Creatinine among study groups (n = 276)

Serum urea level was significantly and positively correlated (p<0.001) to both systolic and diastolic BP. Serum creatinine was also significantly correlated (p<0.001) to systolic and diastolic blood pressures showing their linear relationship (Table 3).

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Variable	Systolic BP	Diastolic BP
Urea	r=0.44, p<0.001	r=0.38, p<0.001
Creatinine	r=0.56 , p<0.001	r=0.53, p<0.001

Table 3: Coefficient correlation (r) of urea and creatinine with systolic & diastolic blood pressures

Traces of protein were higher in HTN stage-II (17.1 %) as compared to 7.1 % in stage-I, and 3.6% in pre-HTN groups respectively. In HTN stage-I, 4.3% subjects showed 3+ and same percentage showed 2+ proteinuria; while in stage-II, 3.9% showed 3+ and another 3.9% showed 2+ proteinuria. Table 4 presents a comparison of urinary protein excretion among study groups.

Group	Control	Pre HTN	HTN stage-I	HTN stage-II
Proteins mg/dL	(n = 75)	(n = 55)	(n = 70)	(n = 76)
Nil	73 (97.3)*	50 (90.9)	54 (77.1)	50 (65.7)
Traces(<30 mg)	2 (2.7)	2 (3.6)	5 (7.1)	13 (17.1)
1+ (30 mg)	0 (0)	2 (3.6)	5 (7.1)	7 (9.2)
2+ (100 mg)	0 (0)	1 (1.8)	3 (4.3)	3(3.9)
3+ (300mg)	0 (0)	0 (0)	3 (4.3)	3 (3.9)
4+ (1000 mg)	0 (0)	0 (0)	0 (0)	0 (0)

Table 4: Comparison of Urinary Albumin level among study groups (n = 276)

DISCUSSION

The study investigated the effects of increased BP on renal functions in symptomless subjects, who were diagnosed for the first time as hypertensive. Our data revealed insignificant difference of mean urea level among all four groups, but a progressive rise was observed from Pre-HTN group to HTN stage-II. The mean urea level was positively related to serum creatinine level in all the four groups and it was significantly correlated to both systolic and diastolic BP showing their linear relationship. The mean serum creatinine level of control group (0.91) was significantly less than that of HTN stage-I and II which were 1.72 and 1.91 respectively. Correlation analysis revealed that serum creatinine significantly correlated to both systolic and diastolic BP. Elevated serum urea and creatinine levels represent diminished renal function, predominantly due to uncontrolled HTN, whereas kidney disease itself may lead to HTN (secondary HTN). The Framingham Heart Study showed a prevalence of mild renal insufficiency in general population, based on serum creatinine level [8.7% males and 8.0% females] (Culleton, 1999). Previous studies indicated that presence of serum creatinine values (>1.7 mg/dL) at base line was a very potent predictor of 5 and 8 years all-cause mortality and independent risk factor for Cardiovascular (CV) events (De Zeeuw, 2006). The mechanism underlying the increase in CV risk is an accelerated progression of atherosclerosis

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and arterial stiffness in association with abnormalities of renal function in hypertensive patients (Benetos, 2002).

BP levels within the range of pre-HTN have also been reported to be significantly associated with proteinuria (Knight, 2003). An elevated urinary protein excretion below the limit of detection, also predicts not only a progressive deterioration of renal function but also a progressive rise in both renal and CV risk (Mann, 2003). A study revealed that a two fold increase in albumin from baseline value indicates higher mortality rates with renal outcomes including doubling of serum creatinine, dialysis and cardiovascular outcomes such as myocardial infarction, stroke and hospitalization for heart failure (Hillege, 2003). Another study reported that obese males with high salt intake are more prone to develop uncontrolled BP, dyslipidemia and microalbuminuria resulting in renal and CV functions impairment (Brenner, 2001) .This study revealed that proteinuria in terms of traces was significantly higher in HTN stage II group (17.1%) as compared to 7.1% in stage-I, 3.6% in pre-HTN, and 2.7% in control groups; whereas proteins in concentration of +1 (30 mg/dl) was present in 3.6% pre-HTN, 7% stage-1 and 9% stage-II groups respectively. The values of +2 (100 mg/dl) and +3 (300 mg/dl) were found in 4.3% patients of stage-1 and 3.9% of stage-II respectively, indicating the insidious effect of high BP on renal function.

A sustained elevation in BP can cause chronic kidney disease (CKD) and this study documents that presence of diminished renal function is more prevalent than previously assumed in essential HTN. A study documented six fold higher risk of LVH in patients with micralbuminuria (Guerra, 2011). Thus quantification of urinary albumin inhypertensive patients can optimize the early detection of renal and vascular damage (López, 2010).

Lifestyle modifications with intake of rich, fatty food, living stressful life and lack of exercise are major factors in the development of obesity, hyperlipidemia and HTN in our population. Unfortunately lack of public awareness and misconception about HTN and its complications are common on one hand and on the other hand it remained unrecognized and thus untreated resulting in greater risk of developing early kidney disease and end stage disease (Petrella, 2005). No evidence-based quality of care indicators have been established for treating HTN. There is dire need of effective implementation of Physician's knowledge concerning the need to control BP at "goal levels" as enhanced knowledge will contribute to improved BP control. The goal BP is defined as value <140/90 mmHg for the general hypertensive population and <130/80 for special population (diabetes, renal disease) (World Health Organization, 1999).

This study revealed that the patients with serum creatinine >2 and proteinuria > 300 mg/dl have higher incidence of decline in renal function as evidenced by correlation of renal function tests with HTN. Thus substantial focus should be on early identification and proactive management of HTN with dietary salt restriction, increasing physical activity and achieving a beneficial BP target to avoid complications.

CONCLUSION

Prevalence of cardiovascular as well as renal disease is increasing rapidly in our country. General practitioners are backbone of our health system but they underdiagnose and undertreat high BP, especially in elderly, leading to early development of complications. 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.

Suggestion: Strategies should be planned and implemented to improve the management of hypertensive patients by providing the general practitioners knowledge related to structured care management practice to improve quality of care and patient outcomes.

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