

Original article:

Evaluation of blood urea, creatinine and uric acid as markers of kidney functions in hypertensive patients: a prospective study

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ABSTRACT

Introduction: Hypertension is one of the leading contributors towards the adverse effects on kidneys. Renal dysfunction can be studied by the measurement of biochemical parameters in blood; hence we carried out this study to examine the status of blood urea, creatinine and uric acid as the possible markers for the renal functions in hypertensive patients.

Materials and methods : 90 patients, clinically diagnosed to be hypertensive and who were under regular visit to OPD, were included in this study. 30 age and sex matched healthy individuals were recruited as the control group in our study. Fasting venous blood samples were collected from the patients as well as the controls and they were analysed by using an automated analyser for blood urea, creatinine and uric acid. The results were analysed statistically by using the Student's "t" test and correlation coefficients.

Results : The levels of blood urea, creatinine and uric acid were significantly higher in hypertensive patients as compared to healthy controls (p value <0.001). We further evaluated the status of our study parameters in our hypertensive patients group by dividing them according to their stages based on the classification given by Joint National Committee (JNC) VII report. We found a positive correlation in the levels of blood urea, creatinine and uric acid with the severity of the disease.

Conclusion : The clinical investigations of renal functions such as blood urea, creatinine and uric acid are important to identify the renal dysfunctions in hypertensive patients especially in a setting where facilities for the definitive elaborate renal assessments are not feasible.

Key words : Kidney functions, hypertension

INTRODUCTION

Hypertension is one of the leading causes of the global burden of disease. Hypertension doubles the risk of cardiovascular diseases, including coronary heart disease (CHD), congestive heart failure (CHF), ischemic and hemorrhagic stroke, renal failure, and peripheral arterial disease.

No single or specific cause is known for most cases of hypertension, and the condition is referred to as primary in preference to essential. Persistent hypertension can develop in response to an increase in cardiac output or a rise in peripheral resistance and the interplay of various derangements in

factors affecting cardiac output and peripheral resistance may precipitate the disease, and these abnormalities may differ in both type and degree in different patients (1). From an epidemiologic perspective, there is no obvious level of blood pressure that defines hypertension. The Multiple Risk Factor Intervention Trial (MRFIT), which included >350,000 male participants, demonstrated a continuous and graded influence of both systolic and diastolic blood pressure on CHD mortality, extending down to systolic blood pressures of 120 mmHg (2).

Clinically, hypertension may be defined as that level of blood pressure at which the institution of therapy reduces blood pressure-related morbidity and mortality. Current clinical criteria for defining hypertension generally are based on the average of

two or more seated blood pressure readings during each of two or more outpatient visits (2).

Based on the seventh report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure (JNC VII report) BP is classified into the following stages (**table 1**):

Table 1: classification of blood pressure according to JNC VII report (3):

Category	Systolic blood pressure (SBP) mm of Hg	Diastolic blood pressure (DBP) mm of Hg
Normal	<120	and <80
Prehypertension	120-139	or 80-89
Hypertension, stage I	140-159	or 90-99
Hypertension, stage II	≥160	or ≥100

It is a well-known fact that many conditions affect the ability of the kidneys to carry out their vital functions. Initially this study was conducted to assess the renal functions in patients with hypertension by measuring the serum urea and creatinine but we further included the measurement of uric acid in our study owing to the frequent presence of hyperuricemia in hypertensive patients thereby reflecting underlying renal dysfunction or reduced renal perfusion (4,5).

The aim of the present study was to determine the status of blood urea, creatinine and uric acid in the hypertensive patients and to compare and correlate these parameters with those of age and sex matched healthy controls. We further aimed to evaluate the effect of severity and duration of hypertension on our study parameters.

MATERIALS AND METHODS

90 patients (59 males and 31 females) clinically diagnosed to be hypertensive, under regular visit to OPD were recruited to participate in this study as cases. These patients were visiting the hospital for

follow up check-ups from time to time. An inclusion criterion for them was adult males and females diagnosed as hypertensive according to JNC VII classification, with or without complications or any co-morbid conditions like diabetes mellitus type 2, coronary artery disease etc. However, patients with secondary hypertension, gout, significant history of alcohol abuse were excluded from our study. 30 age and sex matched normotensive healthy individuals who visited the hospital for medical check-ups in the general outpatients department were considered as the controls. All the subjects, including the controls, were fully informed about the study and their voluntary informed consents were taken.

Fasting venous blood was collected from the cases (hypertensive patients) as well as the controls (healthy subjects), it was centrifuged and the serum was separated for the analysis on the same day for serum urea, creatinine and uric acid as per the routine procedure which was followed in the department.

The sample analysis was carried out on a fully automated analyser by using different reagent kits as per the procedure defined by the manufacturer. Measurement of serum urea was done using enzymatic (urease) kinetic method and creatinine was done by Jaffe kinetic method. For the estimation of serum uric acid, enzymatic (uricase) method was used.

The results were analysed statistically using student's "t" test on the suitable software. P values of <0.05 were considered as statistically significant.

OBSERVATION AND RESULTS

There is a strong relationship between hypertension and chronic kidney diseases. Hypertension is known to be an important cause of end stage renal

disease (ESRD); most importantly contributing to its progression. To evaluate this relationship between abnormal blood pressure and kidney dysfunction; the present study was conducted where we had chosen blood urea, creatinine and uric acid as representative markers for kidney functions. We evaluated these parameters in 90 hypertensive patients (cases) and 30 healthy control subjects. The clinical characteristics of all the study subjects have been shown in **table 2**. The mean ages between cases and controls were comparable and the difference was not significant. The systolic as well as diastolic blood pressure was significantly higher in all the cases as compared to healthy controls (p value <0.001).

Table 2: Comparison of clinical characteristics between all hypertensive cases and controls

Characteristics of the subjects	Hypertensive cases (Group I) (n=90)	Controls (Group II) (n=30)	p value
Age (years)	52.13±10.04	50.15±5.58	Not significant
Sex (males:females)	59:31	18:12	-
Systolic blood pressure (SBP) (mm of Hg)	149.05±16.45	121.8±7.29	<0.001
Diastolic blood pressure (DBP) (mm of Hg)	90.2±11.5	82.1±4.87	<0.001
Blood urea (mg/dl)	32.86±11.3	20.75±3.35	<0.001
Serum creatinine (mg/dl)	0.92±0.29	0.49±0.23	<0.001
Serum uric acid (mg/dl)	5.8±1.1	4.28±0.92	<0.001

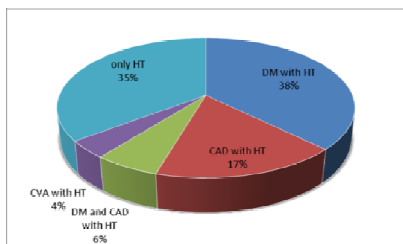
We included all cases of hypertension irrespective of their co-morbid conditions and we found that 65% of our cases presented with either one or the other co-morbidities like Diabetes mellitus type 2

(DM-2), coronary artery disease (CAD) or both CAD and DM-2 along with hypertension. A small percentage (4%) of patients presented with cerebrovascular accident. 35% of the cases in our

study presented only with hypertension and was free from any other ailment. The distribution of

different co-morbid conditions in all hypertensive patients of our study is depicted in **figure 1**.

Figure 1: The distribution of different co-morbid conditions in all hypertensive patients.



The biochemical parameters which we considered in our study were blood urea, creatinine and uric acid as representatives of assessing kidney functions. The difference between these parameters between different groups is depicted in **table 2**. We found that these parameters were significantly high in cases as compared to controls (p value <0.001) thereby indicating that the functions of the kidneys are affected in hypertensive patients.

We further evaluated the status of our study parameters in different stages of hypertension after dividing our 90 hypertensive cases according to JNC VII classification into three sub groups I_A, I_B and I_C as pre-hypertension, hypertension stage I and hypertension stage II respectively. Their comparison with control group (group II) is being depicted in **table 3**.

Table 3: Comparison of study parameters between different sub-groups of hypertensive patients (based on JNC criteria) and control group

Study parameters	Sub-group I _A Pre-hypertension stage (n=27)	Sub group I _B Stage I hypertension (n=41)	Sub-group I _C Stage II hypertension (n=22)	Group II Healthy controls (n=30)
SBP (mm Hg)	134.03±4.16	146.66±6.7	171.8±13.89	121.8±7.29
DBP (mm Hg)	88.03±8.5	87.66±12.9	98±7.72	82.1±4.87
Blood urea (mg/dl)	28.1±7.6	32.2±10.24	33.95±14.8	20.75±3.35
Serum creatinine (mg/dl)	0.86±0.3	0.87±0.22	0.98±0.3	0.49±0.23
Serum uric acid (mg/dl)	5.6±1.2	5.8±0.99	6±1.24	4.28±0.92

We found that patients in hypertension stage II (sub group I_C) had higher values of blood urea, creatinine and uric acid as compared to patients in sub groups I_A and I_B, thereby indicating some compromise towards kidney functions in the group with higher blood pressure. On comparing the two subgroups I_A and I_B, the systolic blood pressure was significantly higher in stage I hypertension as compared to pre-hypertension group (p<0.05) whereas the difference was not significant when diastolic blood pressure was compared between these two sub-groups. Regarding the study parameters, there was no significant difference between the two sub-groups but blood urea was found to be higher in the patients of stage I hypertension as compared to the patients of pre-hypertension.

Patients of stage II hypertension (sub-group I_C) had significantly higher systolic as well as diastolic blood pressures when compared with sub-groups I_A and I_B respectively (p value <0.05). As far as the status of study parameters is concerned, the levels of serum creatinine and uric acid was significantly

higher in patients with stage II hypertension as compared to patients with pre-hypertension or stage I hypertension (p value<0.05).

Thus, as the systolic and diastolic blood pressure of the hypertensive patients rises in its different sub-groups, there had been changes in our study parameters, especially higher levels of blood urea, creatinine and uric acid in patients of stage II hypertension.

In our study, we further evaluated the effect of duration of hypertension on the study parameters as chronicity of hypertension affects kidney functions in the long run. So we divided group I subjects (hypertensive patients) based on their duration of illnesses as shown in **table 4**. We found that as the duration of illness increases, there is increase in the value of serum creatinine and uric acid, more so in the patients with long standing duration of illness >10 years when compared with recent onset hypertension. However, the sample size of the former group i.e. the patients with hypertension >10 years is very small to draw any valid conclusion (n=4).

Table 4: comparison of different study parameters in hypertensive patients based on their duration of illness

Study parameters	Duration of hypertension <5 years (n=71)	Duration of hypertension 5-10 years (n=15)	Duration of hypertension >10 years (n=4)
Blood urea (mg/dl)	32.12±10.6	34.5±15.52	34±5.19
Serum creatinine (mg/dl)	0.8±.25	1.13±0.4	1.14±0.1
Serum uric acid (mg/dl)	5.72±1.09	6.2±1.4	6.4±0.4

DISCUSSION

Hypertension is strongly associated with functional and structural abnormalities that damage kidneys and other organs and lead to premature morbidity and mortality (6). Data from several renal databases identifies systemic hypertension as the second most common cause of end stage renal disease (ESRD) with diabetes mellitus being the first (7).

Glomerular filtration rate (GFR) is the best estimate of number of functioning nephrons and functional renal mass. Accurate measurement of GFR is a time consuming and expensive, thus measurement of the blood levels of the elements regulated by the kidneys can become useful in evaluating kidney functions especially where there are limited resources (8). In this respect, we took serum urea, creatinine and uric acid as markers of renal function in our case control study.

We found that the levels of blood urea, creatinine and uric acid were significantly higher in hypertensive patients as compared to the normotensive control subjects. When we further divided our cases depending upon the different stages of hypertension and analysed the study parameters, we found that the increment in the values of serum urea, creatinine and uric acid was most pronounced in the patients with stage II hypertension as compared to those with pre-hypertension and stage I hypertension. There was a positive correlation between our study parameters with severity of the disease as well as chronicity of the disease (9).

The kidney is both a target and a cause of hypertension. Primary renal disease is the most common etiology of secondary hypertension. Mechanisms of kidney-related hypertension include a diminished capacity to excrete sodium, excessive renin secretion in relation to volume status, and sympathetic nervous system overactivity.

Conversely, hypertension is a risk factor for renal injury and end-stage renal disease. The increased risk associated with high blood pressure is graded, continuous, and present throughout the distribution of blood pressure above optimal pressure. Renal risk appears to be more closely related to systolic than to diastolic blood pressure. (10)

Atherosclerotic, hypertension-related vascular lesions in the kidney primarily affect preglomerular arterioles, resulting in ischemic changes in the glomeruli and postglomerular structures. Studies of hypertension-related renal damage, primarily in experimental animals, suggest that loss of autoregulation of renal blood flow at the afferent arteriole results in transmission of elevated pressures to an unprotected glomerulus with ensuing hyperfiltration, hypertrophy, and eventual focal segmental glomerular sclerosis. With progressive renal injury there is a loss of autoregulation of renal blood flow and glomerular filtration rate, resulting in a lower blood pressure threshold for renal damage and a steeper slope between blood pressure and renal damage. The result may be a vicious cycle of renal damage and nephron loss leading to more severe hypertension, glomerular hyperfiltration, and further renal damage. Glomerular pathology progresses to glomerulosclerosis, and eventually the renal tubules may also become ischemic and gradually atrophic (11).

As hypertension induced nephrosclerosis proceeds, the plasma creatinine levels begin to rise, and eventually renal insufficiency may develop. (12)

Several investigators favour the opinion that a higher serum creatinine reflects generalised endothelial dysfunction or a prothrombotic state (13,14).

The complex association of serum uric acid and hypertension has recently been addressed in a

number of studies, where the possible role of uric acid in the pathogenesis of vascular diseases and renal disease progression has been interestingly elucidated.

Hyperuricemia is present in 25% of untreated hypertensive subjects, in 50% of subjects taking diuretics, and in >75% of subjects with malignant hypertension (15). The increase in serum uric acid in hypertension may be due to the decrease in renal blood flow that accompanies the hypertensive state, since a low renal blood flow will stimulate urate reabsorption. Hypertension also results in microvascular disease, and this can lead to local tissue ischemia (16). In addition to the release of lactate that blocks urate secretion in the proximal tubule, ischemia also results in increased uric acid synthesis (17). With ischemia, ATP is degraded to adenine and xanthine, and there is also increased generation of xanthine oxidase. The increased

availability of substrate (xanthine) and enzyme (xanthine oxidase) results in increased uric acid generation as well as oxidant (O_2^-) formation. The finding that ischemia results in an increase in uric acid levels may also account for why uric acid is increased in preeclampsia (18) and congestive heart failure (19).

CONCLUSION

The three measurements (serum urea, creatinine and uric acid) that we have used in this study are neither very sensitive nor very specific markers of renal function, still they provide a valuable insight towards the renal status in the setting of hypertensive disease and thereby become useful tools in the monitoring of the renal status of these patients especially at the centres where the facilities to carry out expensive and time consuming definitive studies are not available.

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