Assessment of chronic kidney disease in Nepalese people with hypertension

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ABSTRACT

Hypertension is one of the leading causes to develop chronic kidney disease (CKD) and could be a risk factor for progression of CKD to end stage renal disease (ESRD).Uncontrolled hypertension worsens CKD. Hypertension control may contribute to prevent CKD in early stages and retards the progression of CKD stages to ESRD. Prevalence of CKD in people with diagnosed and chronic hypertension is known to be high, but little is known about the prevalence of CKD in those with newly diagnosed Hypertension. Present work was undertaken to see the prevalence of CKD among people with newly diagnosed hypertension. In this cross-sectional study, we accessed the CKD in newly diagnosed hypertensive patients and determined the association between hypertension and CKD. CKD was defined as either kidney dysfunction or kidney damage or both as per National Kidney Foundation Guidelines. 106 of newly diagnosed patients and 106 of normotensive controls were recruited in the study. 51.9% of newly diagnosed hypertensive patients and 23.6% of normotensive controls had CKD which was statistically significant (p-value <0.001). Difference in the mean value in eGFR and spot urine ACR (mg/mmol) between hypertensive patients and normotensive controls was statistically significant (p-Value <0.001). Both systolic BP and diastolic BP negative significantly correlated with eGFR (p-Value < 0.001 and 0.024 respectively) and positive significantly correlated with ACR (p-Value 0.003 and 0.003 respectively). The prevalence of CKD is high among people with newly diagnosed hypertension. Those people might benefit from interventions aimed at preventing development and/or progression of both CKD and hypertension.

Keywords: Hypertension, Chronic Kidney Disease (CKD), End Stage Renal Disease (ESRD) Albumin Cratinine Ratio (ACR), estimated GFR (eGFR)

INTRODUCTION

Hypertension is the growing issues of public health problem of adult population in both developed as well as developing world, affecting single person in every four people.[1] The prevalence of hypertension in Asian world was varied from as low as 2% in rural area to 24% in urban areas.[2] The exact cause for hypertension is difficult to predict because Hypertension results from a complex interaction of genes and environmental factors[1]. The prevalence of hypertension, mean systolic and diastolic blood pressure is varied from one part of world to another part of world and from one community to another community with in the same country.[2-4] Some studies showed the higher prevalence rate among the male population compared with female population at least until old age.[5] In the Asian countries the prevalence of hypertension varies among them but generally they are similar to prevalence rates in western countries.[6] Though the exact data regarding hypertension in Nepalese adult population is not available, the Nepal Hypertension Society (Estd. 2004) reported on their website that near about 33% (i.e. one in every three) adult population suffer from hypertension.[7]

Hypertension is the second leading cause (first diabetes mellitus) of Chronic Kidney Disease (CKD)[8] and is both a cause and consequence of chronic kidney disease (CKD).[9] High BP may develop early in the course of CKD and can be associated with adverse outcomes such as worsening renal function and development of cardiovascular disease. Hypertension is a major promoter of the decline in GFR in both diabetic and non diabetic kidney disease.[10] Prevalence of CKD in people with diagnosed and chronic hypertension is known to be high, but less information is available about the prevalence of CKD in those with newly diagnosed Hypertension. Thus it urges us to diagnose the CKD in newly diagnosed hypertension. In this study we aimed to show the association of newly diagnosed hypertension with CKD.

Table-1: Association between Chronic Kidney Disease and Blood Pressure

Chronic Kidney Disease	Blood Pressure			X^2 P-value
	Normal	Hypertension	Total	
	n. (%)	n. (%)	n. (%)	
CKD Present	25(23.6)	55(51.9)	80(37.7)	<0.001*
CKD Absent	81(76.4)	51(48.1)	132(62.3)	
Total	106(100)	106(100)	212(100)	

Applied Chi square test, *statistically significant at P-value <0.05

MATERIALS AND METHODS

Study design and the participants: This hospital based cross-sectional study was conducted in the Department of Clinical Biochemistry in collaboration with Department of Internal Medicine (nephrology unit), Tribhuvan University Teaching Hospital (TUTH), Institute of Medicine (IOM). TUTH is a tertiary care hospital in capital city of Nepal and it provides the health services to patients visiting TUTH from different part of Nepal. Hence this site was chosen for the study.

Data collection: This study was carried out from 2008 February to 2010 August. The study population included patients visiting medical out patients door (OPD) and nephrology unit of TUTH from different parts of Nepal. A medical history was taken and a physical examination was performed by a physician. Known cases of confirmed hypertensive with antihypertensive medication were not include in the study and only newly diagnosed hypertensive participants were included in the study. Hypertension was defined by blood pressure e" 140/90 mmHg.[11] Subjects were resting for at least 20 minutes before taking the blood pressure. Blood pressure measurement was done using aneroid sphygmomanometer with an adequate cuff size. Systolic blood pressure (SBP) was taken by the first heard sound (Korotkoff Phase I). Diastolic blood pressure (DBP) was recorded at the level when the sound just disappeared (Korotkoff Phase V) or sometimes the K4 point, where the sound is abruptly muffled.[12] Weight was taken using a platform weighing machine. Standing height measurement was done with the participants in bare foot, eyes looking ahead. After having the written consent from the participants, 106 newly diagnosed hypertensive participants over the age of 16 years and below 65 years were eligible for the assessment of CKD. We also measured biochemical profile including urea, creatinine, uric acid, sodium, potassium, calcium, phosphorous and so on. Furthermore, age and sex matched healthy control i.e. non-hypertensive were also enrolled. Age, sex, weight were collected from the participants. Participants with haemophilia and recent cancer chemotherapy were excluded from the venipuncture. Five mL of blood was drawn after an overnight fast (12-16 hours) by venous puncture and a routine urine sample were also collected. After clotting of blood, serum was separated, within an hour; by centrifugation at 3000 - 5000 g for 5 min. Serum is used for biochemical profile. The Urine sample was also processed on the same day and estimated for urine albumin and urine creatinine. Laboratory standard operation procedures were maintained for all laboratory analysis. Internal quality control sera, both normal and pathological, were also run for each lot of the test, for the validation of the results.

Inclusion criteria: Age of more than sixteen years and less than sixty years with newly diagnosed hypertension were enrolled as a study population. Similarly the age of more than sixteen years and less than sixty years without hypertension were enrolled as a healthy control group.

Exclusion criteria; For study cases: age less than sixteen years and more than sixty five years, Pregnancy, HIV infection, Diabetes Mellitus, Chronic Disease like Tuberculosis, Chronic Obstructive Pulmonary Disease (COPD), liver disease, known case of CKD, endocrine disorder, patients under medication for Diabetes Mellitus, Hypertension.

For healthy controls: age less than sixteen years and more than sixty five years, Pregnancy, HIV infection, Chronic Disease like Malignancy, Chain Smokers, Tuberculosis, Chronic Obstructive Pulmonary Disease (COPD), liver disease, endocrine disorder, patients under medication for Diabetes Mellitus, Hypertension, any medical history of CKD, known family history of CKD.

Measured variables: Hemoglobin (Hb), serum level of urea, creatinine, uric acid, sodium (Na^+), potassium (K^+), calcium (Ca^{++}) and phosphorous (PO_4^{---}). Urinary level of albumin, urinary total protein (UTP) and urinary creatinine were also measured.

Defining variables: Hypertension was categorized according to blood pressure readings by JNC-VII definitions: normal (systolic <120 mm Hg and diastolic <80 mm Hg), prehypertension

Table-2: Association of Chronic Kidney Disease with Stages of Blood Pressure

Chronic Kidney Disease	Stages of Blood Pressure				X^2 P-value
	Normal	Hypertension		Total	
	n. (%)	Stage I n. (%)	Stage II n. (%)	n. (%)	
CKD Present	25(23.6)	23(21.7)	32(30.2)	80(37.7)	
CKD Absent	81(76.4)	31(29.2)	20(18.9)	132(62.3)	<0.001*
Total	106(100)	54(51)	52(49)	212(100)	

Applied Chi square test, *statistically significant at P-value <0.05

Table-3: Association of Stages of CKD with Hypertensive Patients and Normotensive Individuals

Stages of Chronic Kidney Disease (CKD)	Stages of Blood Pressure			Total	X^2 P-value
	Normal BP	Stage I BP	Stage II BP	n. (%)	
	n. (%)	n. (%)	n. (%)		
Non-CKD	82(61.2)	32(23.9)	20(14.9)	134(100)	<0.001*
Stage I CKD	8(80)	1(10)	1(10)	10(100)	
Stage II CKD	16(45.7)	11(31.4)	8(22.9)	35(100)	
Stage III CKD	0(0)	10(32.3)	21(67.7)	31(100)	
Stage IV CKD	0(0)	0(0)	2(100)	2(100)	
Stage V CKD	0(0)	0(0)	0(0)	0(0)	
Total	106(50)	54(25.5)	52(24.5)	212(100)	

Applied Chi square test, *statistically significant at P-value <0.05

(systolic 120 to 139 mm Hg or diastolic 80 to 89 mm Hg), hypertension stage I (systolic 140 to 159 mm Hg or diastolic 90 to 99 mm Hg), and hypertension stage II (systolic e"160 or diastolic e"100 mm Hg). Since in this study only hypertensive patient were taken so, patients were categorized into stage I hypertension and stage II hypertension.[11,13]

CKD was defined as either (a) the presence of microalbuminuria (> 3.4 mg albumin/mmol creatinine) as a marker of kidney damage or (b) reduced excretory function with an eGFR <60 mL/min/1.73 m^2 as a marker of kidney dysfunction or both for more than two months.[14-16]

In spot urine sample albumin was measured quantitatively and adjusted to creatininuria then interpreted as albumin cratinine ratio (ACR) e"3.4–33.9 mg albumin/mmol creatinine as microalbuminuria.[16]

The formula of Cockcroft and Gault[17] for creatinine clearance (Ccr) in males:

Ccr, = [140 - age (in years)] x weight (in kg) × 88.4 / [72 x serum creatinine (imol/L)]

A companion equation for women was proposed, based on their 15% lower muscle mass (on average):

Ccr = [140 - age (in years)] x weight (in kg) × 88.4 x .85 / [72 x serum creatinine (imol/L)]

After establishing the chronic kidney disease, it was further classified into five different stages of CKD as[15]: Stage I CKD (if eGFR is >90 mL/min/1.73 m^2), Stage II CKD (if eGFR is between 60 and <90 mL/min/1.73 m^2), Stage III CKD (if eGFR is between 30 and <60 mL/min/1.73 m^2), Stage IV CKD (if eGFR is between 15 and <30 mL/min/1.73 m^2) and Stage V CKD (if eGFR is <15 mL/min/1.73 m^2).

Other variables including age, sex, blood pressure and weight.

Ethical committee approval: Ethical committee approval was taken from the ethical board of Institute of Medicine, Kathmandu.

Data management and statistical analysis: The data was analyzed using Excel 2003, R 2.8.0 Statistical Package for the Social Sciences (SPSS) for Windows Version 16.0 (SPSS Inc; Chicago, IL, USA). Association between hypertension and chronic kidney disease was tested by Chi-square test. Comparison of mean of continuous data between hypertensive cases and normal healthy control group was tested by student t-test. A p-value of <0.05 (two-tailed) was used to establish statistical significance.

RESULTS

Among the patients visiting medical outpatient department (OPD) and nephrology unit of TUTH from May 2008 to August 2010, only 106 patients with newly diagnosed hypertension and 106 with normal blood pressure for control group were included for this study. In this hypertensive group 60 patients were male and 46 patients were female. In normal BP healthy control 58 were male and 48 were female. For both hypertensive and normal BP group, the age of participants from 16 years to 65 years was included. The Mean±SD of hypertension and control were 44.57±10.68 and 42.99±10.48 respectively.

Table-1 shows among hypertensive

Table-4: Spearman correlation between different characteristics

Spearman's correlation of eGFR with other characteristics			Spearman's correlation of ACR with other characteristics		
Characteristics	Spearman's rho	P-value	Characteristics	Spearman's rho	P-value
Age (years)	-0.556	<0.001**	Age (years)	0.362	<0.001**
SBP (mmHg)	-0.335	<0.001**	SBP (mmHg)	0.286	0.003*
DBP (mmHg)	-0.219	0.024*	DBP (mmHg)	0.286	0.003*
Creatinine (µmol/L)	-0.585	<0.001**	Creatinine (µmol/L)	0.582	<0.001**
eGFR (ml/min/1.73m^2)	1		eGFR (ml/min/1.73m^2)	-0.758	<0.001**
ACR (mg/mol)	-0.758	<0.001**	ACR (mg/mol)	1	

Applied spearman's correlation, **statistically significant at the level of P-value 0.001 and *statistically significant at the level of P-value 0.05

Table-5: Comparison of mean of different parameter between hypertensive patients and normal healthy control

Different parameters	Hypertension Mean±SD	Control Mean±SD	P-value
SBP in mmHg	144.04±14.17	113.58±6.75	<0.001**
DBP in mmHg	96.6±7.18	74.52±5.14	<0.001**
Urea in mmol/L	4.87±1.18	3.76±0.43	<0.001**
Creatinine in µmol/L	101.06±26.98	70.51±10.85	<0.001**
eGFR in ml/min/1.73m^2	70.35±24.97	94.19±27.32	<0.001**
Hb in gm/dl	13.41±1.49	14.09±0.99	<0.001**
UTP in mg/L	268.89±66.01	175.92±15.69	0.013*
Urinary PCR in mg/mmol	48.55±11.89	25.17±8.55	0.011*
Urinary MAU in mg/L	60.64±4.97	19.62±5.67	<0.001**
Urinary ACR in mg/mmol	11.02±4.45	3.14±1.89	<0.001**
Na^+	139.09±4.2	140.08±3.26	0.057
K^+	4.18±0.042	3.89±0.23	<0.001**
Ca^{++}	2.16±0.23	2.19±0.21	0.377
PO_4^{---}	4.28±0.54	4.45±2.9	0.553
Uric Acid	411.65±106.75	330.41±61.38	<0.001**

Applied student t test, **statistically significant at the level of P-value 0.001 & *statistically significant at the level of P-value 0.05

patient and control group, the percentage of CKD and non CKD were 51.9% Vs 48.1.6% and 23.6% Vs 76.4% respectively which is statistically significant (P-value <0.001).

Table-2 shows association of CKD with Hypertension and Normal healthy control, in which BP was classified as normal i.e. control group and hypertension as stage 1 and stage 2. Similarly, CKD is shown as either present or absent. The prevalence of chronic kidney disease is higher in hypertensive patients than healthy control group with normal Blood Pressure which is statistically significant (P-value <0.001). In this study 23.6% of normal blood pressure had CKD and 76.4% of normal blood pressure did not have hypertensive. Similarly, 21.7% of stage I and 30.2% of stage II hypertensive patients had CKD and 29.2% of stage I and 18.9% of stage II hypertensive patients did not have CKD.

Table-3 shows that with increases of BP, stages of chronic kidney disease are also increases which are statistically significant (P-value 0.001).

Table-4 shows that the spearman's correlation of eGFR (as a marker of kidney dysfunction) and ACR (as a marker of kidney damage) with different characteristics. Table also shows the statistically significant the level of both P-value 0.001 and 0.05.

Table-5 shows that the comparison of mean±SD of biochemistry profile between hypertensive patients and normal healthy control group. Table also shows the statistically significant at the level of P-value 0.001 and 0.05.

DISCUSSION

We found that the prevalence of CKD to be high among individuals with newly diagnosed hypertensive patients in the Nepalese population compared with normotensive healthy control group. Although CKD was most prevalent among those with newly hypertensive patients, normotensive control groups accounted for nearly one-third of all CKD cases in the study. In addition, we found that most of the CKD individuals as well as non-CKD individuals were unaware about CKD.

Although the CKD was most prevalent among those with establish hypertension,[9,18-20] person with newly diagnosed hypertension also showed high prevalence of CKD, accounting for 51.9% of CKD in hypertensive population in our study. However, we did not consider the established hypertensive patients in our study. Most of the participant of our study did not have the awareness towards hypertension. In addition CKD is more complex that such individuals are largely unaware of their kidney disease.

We found that the prevalence of CKD was found to be increased with the stages of hypertension; with normotensive healthy control groups having the low prevalence of CKD and those with established hypertension were not included in the study. Since we used either microalbuminuria (ACR >3.4mg/mmol) or decreased eGFR (<60 ml/min/m^2) to define CKD, microalbuminuria was the most commonly noted marker of CKD across all of the blood pressure categories and were found more common than reduced eGFR. With the evidence of our study underlying risk factor for CKD were higher across the stages of blood pressure. In our study 51.9% of newly diagnosed hypertensive people had CKD. Furthermore, the prevalence of CKD in stage II hypertension was found to be higher i.e. 30.2% against the CKD in stage I hypertension was 21.7% among all hypertensive population. JNC 7 Report recommended that persons with hypertension and CKD or diabetes mellitus should control blood pressure below 130/80 mmHg.[21]

Our study showed that most of the study cases with newly diagnosed hypertensive patients lack regular health checks up due to lacking a routine site for health care. In addition we found that the greatest prevalence of hypertension in among those of low socioeconomic status like income, education etc again suggesting that health care facilities may be limited in this population. Our hypothesis of hypertension and CKD is supported by Cutler JA *et al*[22] and Plantinga LC *et al*.[23] In normotensive healthy control group CKD was found to

be 23.6% of all CKD population. The prevalence of CKD among the healthy control in the absence of traditional risk factor like diabetes and hypertension may be due to lack of awareness towards health, educational status, socioeconomic condition, health care facilities and so on. Moreover, we observed that different demographic factors like increasing age, sex etc and socioeconomic status like limited education, income etc also associated with both hypertension and CKD. Thus both populations i.e. with newly diagnosed hypertension as well as normal blood pressure should be in need of improving screening tool for CKD in their regular health visit.

The difference in mean value of UTP (p-Value 0.013), PCR (p-Value 0.011), MAU (p-Value <0.001) and ACR (p-Value <0.001) were statistically significant in hypertensive patients and normal healthy controls. The finding of our study is consistent with the finding of other population.[24-26]

There was no significant difference in mean value of sodium between hypertensive patients and normal healthy controls. However, the mean value of potassium was significantly different between hypertensive patients and normal healthy controls. The statistical significant difference in potassium level between hypertensive patients and normal healthy control might be due to size of the reference range (3.5 to 5.0 mEq/L) which represents a 33% change in concentration, whereas for sodium the reference range (135 to 145 mEq/L) extend over only a 7% change in concentration.[27] Our study found that mean difference of serum level of sodium and calcium was not significant. These results corroborate the findings of study by Adegoke *et al*[28] but differ from the result obtained by Morton and Abraham *et al*.[29]

Our study showed the significant mean difference of serum level of uric acid between hypertensive patients and normotensive healthy control which is corresponds with Perlstein *et al*[30] and Strasak *et al*.[31]

Hypertension is the major risk factor of CKD. Assess of CKD can be done using eGFR as a marker for Kidney dysfunction and spot urinary ACR as a marker for kidney damage. Though the CKD was also found in significant numbers among normal healthy controls, the prevalence of CKD was high among newly diagnosed hypertension. CKD awareness was low among individuals with both newly diagnosed hypertension and normal blood pressure. Thus we recommend giving appropriate hypertension and CKD education to those persons with newly diagnosed hypertension and normal blood pressure for screening and prevention of hypertension and CKD.

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