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A Study on Association of Hypertension with Hyperparathyroidism in Non Diabetic Kidney Disease

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ABSTRACT

80 non-diabetic chronic kidney disease (CKD) cases and 40 non-hypertensive non-diabetic non CKD age matched controls were evaluated. The baseline characteristics of both groups were compared. Student't' test was applied to analyse the characteristics among the 2 groups. The cases were stratified according to JNC VII(Joint National Committee VII)stages and characteristics were analysed using ANOVA(analysis of variance).The mean intact parathyroid hormone(iPTH) of CKD cases was 385.7±287.7 pg/ml and of controls was30.8±13.4 pg/ml(t=7.780;p<0.001) thereby showing a significantly raised iPTH in cases. A statistically significant difference was observed between cases and controls in ionized calcium, phosphorus, urea, creatinine, iPTH and vitamin D. iPTH>300pg/ml independently correlated with hypertension when logistic regression was applied on the variables which showed significant association in univariate assessment with blood pressure.Since iPTH independently correlated with hypertension in non-diabetic CKD patients, reduction of iPTH could lower their blood pressure.

KEYWORDS non-diabetic chronic kidney disease , hypertension, intact parathyroid hormone

INTRODUCTION

The number of patients with chronic kidney disease worldwide is rising markedly. Cardiovascular diseases (CVD's) are the most common cause of death in patients with ESRD and, within the first year of dialysis, 55% of non-diabetic patients with hypertension carry a diagnosis of CVD. Elevated BP in dialysis patients has been associated with LVH, heart failure, and ischaemic heart disease. Mechanisms of hypertension in CKD are extracellular volume expansion,excessive renin-angiotensin system activity,sympathetic nervous system activation, aortic stiffness, asymmetric dimethylarginine elevation.

Hyperparathyroidism secondary to CKD is due to overproduction of PTH caused by several changes that occur in bone and mineral metabolism as a result of decreased kidney function . The first changes that usually occur with declining kidney function involve the deficiency of activated vitamin D and an increase in phosphorus excretion by the remaining functional nephrons. Both of these changes stimulate an increase in PTH synthesis and secretion(Tomasello, 2008)[1]. Parathyroid hormone serves to increase blood concentrations of calcium. Vitamin D acts also to increase blood concentrations of calcium. It is generated through the activity of parathyroid hormone within the kidney. Far and away the most important effect of vitamin D is to facilitate absorption of calcium from the small intestine. Vascular stiffness and calcification in CKD are highly correlated and appear to be driven by renal bone mineral disease comprising hyperphosphatemia, hypocalcemia and hyperparathyroidism together with decreased bone mineral density (Moe, Chen 2008)[2], hence contributing to hypertension. Vitamin D insufficiency is associated with increased arterial stiffness and endothelial dysfunction in the conductance and resistance blood vessels in humans, irrespective of traditional risk burden. Vitamin D normalization was found to be associated with reduction in mean arterial blood pressure (Mheid, 2011)[3].

Considering the relative importance of a number of factors determining blood pressure in CKD patients, we hereby attempt to study the association between iPTH, vitamin D, calcium, phosphate and hypertension. Thus our study shall focus on the cross-talk between the kidneys, cardiovascular system and the skeletal system.

MATERIAL AND METHODS

It was a case control observational study carried out at the department of medicine of a government medical college of Uttar Pradesh with an aim to study the association between hyperparathyroidism and hypertension in non-diabetic chronic kidney disease patients.

For this purpose a total of 120 subjects were enrolled. 80 patients of different stages of chronic kidney disease comprised the case group of study while 40 non-diabetic, non-hypertensive, non-CKD patients admitted to our hospital for treatment of other than the indicated illnesses comprised the control group of the study. Patients of diabetes mellitus, cardiomyopathy, valvular heart disease, smokers were excluded from the study. After a complete history and physical examination, patients were investigated and their characteristics were analysed. CKD staging was done using MDRD equation for calculating eGFR in patients ≥18 years and Schwartz equation in patients < 18 years.We used the Chi-square test,student t test,ANOVA and logistic regression to analyse data. Finally the Hosmer–Lemeshow test was used for assessing the goodness of fit of the logistic regression models. The statistical analysis was done using SPSS (Statistical Package for Social Sciences) version 15.0 statistical analysis software. We analysed the data in 2 ways.CKD cases were first stratified according to the PTH levels into 4 groups and their characteristics were studied. ANOVA (analysis of variance)was applied. Then logistic regression was applied on the variables that showed significant association in univariate assessment. Secondly, we stratified the cases as per the JNC 7 stages of hypertension and studied their characteristics, applied ANOVA and then logistic regression.

RESULTS

Table 1: Comparison of blood Pressure Levels in Case and Controls

SN	Parameter	cases (n=80)		controls (n=40)		Significance of difference	
		Mean	SD	Mean	SD	"t"	"p"
1.	SBP	150.5	32.0	108.2	7.2	8.233	<0.001
2.	DBP	88.8	16.8	68.9	6.7	7.211	<0.001
No. of hypertensives(as per the JNC 7 criteria)		56 (70%)		0 (0%)		χ^2=52.500; p<0.001	

Table 2: Comparison of other parameters in Case and Controls

SN	Parameter	cases(n=80)		controls(n=40)		Significance of difference	
		Mean	SD	Mean	SD	"t"	"p"
1.	Ionized calcium (mmol/L)	1.06	0.13	1.11	0.08	-2.472	0.015
2.	Phosphate(mg/dL)	5.9	1.7	3.4	0.7	8.992	<0.001
3.	Urea (mg/dL)	136.0	85.0	39.0	14.8	7.149	<0.001
4.	Creatinine (mg/dL)	7.7	5.7	0.9	0.2	7.494	<0.001
5.	iPTH (pg/ml)	385.7	287.7	30.8	13.4	7.780	<0.001
6.	Vitamin D (ng/ml)	27.4	17.6	34.8	16.0	-2.067	0.041

Table 3: Characteristics of cases stratified by categories of iPTH (n=80)

iPTH category (pg/ml)	Age (years)		Hb (g/dl)		SBP (mm Hg)		DBP (mm Hg)		S. Ca (mmol/l)		S. Phosphorous (mg/dl)		S. Creatinine (mg/dl)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
<150 (n=18)	45.61	13.62	9.22	2.59	126.7	31.4	75.4	11.4	1.09	0.10	5.26	1.51	3.29	2.48
150-300 (n=18)	45.10	14.78	9.48	1.69	153.6	26.2	93.4	13.8	1.02	0.13	5.39	1.12	5.88	3.62
300-600 (n=29)	44.45	20.63	8.92	1.62	156.7	22.5	91.5	14.0	1.03	0.14	6.32	1.87	9.39	5.02
>600 (n=13)	43.83	17.57	8.28	1.44	164.2	45.6	93.5	24.8	1.11	0.10	6.72	1.64	12.50	7.64
F (ANOVA)	0.031		1.100		5.143		5.693		2.085		3.414		11.367	
p"	0.992		0.354		0.003		0.001		0.109		0.022		<0.001	

Table 4: logistic regression table based on above table

	B	S.E.	Wald	df	Sig.	Exp(B)
SBP>140 mmHg	1.494	0.949	2.476	1	0.116	4.454
DBP>90 mmHg	-.223	0.889	0.063	1	0.802	0.800
S.Creatinine>5.6 mg/dl	1.929	0.549	12.360	1	<0.001	6.881
Constant	-1.865	0.569	10.759	1	0.001	0.155

χ^2=2.755 (df=3); p=0.431 (NS) (Hosmer&Lemeshow test); Predicted accuracy=75.0%

The equation generated through this model was as follows:

$$=\{e^{-1.865+1.495*SBP-0.223*DBP+1.929*S.Creatinine}\}/\{1-e^{-1.865+1.495*SBP-0.223*DBP+1.929*S.Creatinine}\}$$

Hosmer and Lemeshow test showed that there was no significant difference in observed and expected outcome (χ^2=2.755; p=0.431).

Table 5: Characteristics of cases stratified according to JNC-7

JNC-7 Stage	Age (years)		S. Ca (mmol/l)		S. Phosphorous (mg/dl)		S. Urea (mg/dl)		S. Creatinine (mg/dl)		iPTH (pg/ml)		Vit. D (nmol/l)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Normotensive (n=17)	41.18	16.44	1.09	0.10	5.0	1.6	94.5	58.4	5.30	5.78	223.3	244.6	35.9	12.7
Pre-hypertensive (n=7)	34.00	10.89	1.01	0.09	5.9	0.6	126.4	97.7	5.05	3.29	276.0	285.3	25.3	12.9
Stage 1 Hypertension (n=21)	43.14	18.30	1.06	0.16	5.9	1.6	115.3	44.1	8.04	5.77	403.6	263.1	25.4	18.2
Stage 2 Hypertension (n=35)	49.20	16.65	1.04	0.12	6.4	1.8	170.6	99.9	9.19	5.61	475.7	291.4	26.3	18.8
F (ANOVA)	2.121		0.877		2.802		4.176		2.446		3.645		0.836	
"p"	0.105		0.457		0.046		0.009		0.069		0.016		0.480	

Table 6: Logistic Regression table based on above table

	B	S.E.	Wald	df	Sig.	Exp(B)
Phosphorous>5 mg/dL	0.769	.581	1.752	1	0.186	2.157
Urea >90 mg/dl	1.051	.575	3.334	1	0.068	2.860
PTH>300 pg/ml	1.247	.590	4.463	1	0.035	3.481
Constant	-.897	.589	2.318	1	0.128	.408

χ^2=5.586 (df=5); p=0.349 (NS) (Hosmer&Lemeshow test); Predicted accuracy=76.3% The equation generated through this model was as follows: ={$e^{-0.897+0.769*Phosphorous+1.051*Urea+1.247*PTH}$} {$1-e^{-0.897+0.769*Phosphorous+1.051*Urea+1.247*PTH}$}

Hosmer and Lemeshow test showed that there was no significant difference in observed and expected outcome (χ^2=5.586 (df=5); p=0.349).

Age of subjects ranged from 13 to 85 years. On comparing the data statistically, no significant difference was found with respect to age of patients among cases and controls (p=0.751). In cases, majority of patients were male (68.8%), however, in controls, majority of patients were female (60%), thus showing a statistically significant difference between them (p=0.003).Thus the cases and controls were age matched but not sex matched. Mean SBP and DBP of cases patients was significantly higher as compared to controls (p<0.001). There were a total of 56 (70%) hypertensives in cases as compared to none (0%) in controls (p<0.001)(Table1). Majority of patients, 55(73.33%) were Stage V followed by those diagnosed as StageIV,19(23.75%), Stage IIIb, 2(2.5%), Stage III a, 3(3.75%) Stage II, 1(1.25%) CKD. None of the patients in the study was in stage I CKD. Mean Hb levels in controls were significantly higher as compared to cases(p<0.001). Statistically no significant difference in lipid levels was observed between cases and controls. (p>0.05).A statistically significant difference was observed between cases and controls in ionized calcium, phosphorus, urea, creatinine, iPTH and vitamin D(Table2).With increasing stage of CKD, an increase in mean iPTH was observed. With increasing iPTH levels an increase in mean values of SBP, DBP, phosphorus and creatinine was observed which was also significant statistically (p<0.05). No significant association of iPTH levels was observed with age, haemoglobin levels and calcium levels. In this first model when logistic regression was applied on the screened variables which showed significant association in univariate assessment with iPTH, only serum creatinine correlated independently with iPTH.

(Tables 3&4).No significant difference in mean age, calcium levels, creatinine levels and Vitamin D levels of patients in different JNC-7 stages was observed (p>0.05). A significant increase was observed for mean phosphorous levels, urea and iPTH levels in relation to increasing JNC-7 stage. iPTH>300pg/ml independently correlated with hypertension in this second model of logistic regression which was applied on the screened variables which showed significant association in univariate assessment with blood pressure according to JNC 7 staging(Tables 5&6) .The Hosmer-Lemeshow test showed that both the models of logistic regression had a ≥75% accuracy. In our study, we also found that except for a statistically significant relation with total cholesterol, iPTH did not correlate with LDL, HDL or triglyceride levels, the relation with total cholesterol was non-linear, with total cholesterol being maximum when iPTH was <150pg/ml and minimum when iPTH was between 150-300 pg/ml(Table7).

Also with variation in iPTH, Hb levels did not vary significantly(Table 3)

DISCUSSION

The fact that primary hyperparathyroidism is associated with hypertension and the progression of CKD results in rapid increase in PTH levels, lead researchers to investigate PTH as a culprit in causation of hypertension in CKD patients. Systolic blood pressure was found to be positively associated with PTH and this was shown in a number of studies (Young 1990[4], Morfis 1997[5], Jorde 2005[6]). Researchers have reported high blood pressure in 40 to 65% of patients with primary hyperparathyroidism (Feldstein 2010)[7].Despite variations in published data the prevalence of hypertension in patients with primary hyperparathyroidism (PHPT) is higher than in the general population regardless of age. Elevated PTH levels have also been reported in a subgroup of patients with primary hypertension (Carron 1985[8], Kurtz 1986[9], Bukoski 1988[10]). Even in our study conducted on 120 subjects of which 80 were CKD patients, an iPTH>300pg/ml was found to be independently correlating with blood pressure.

PTH's role in causation of hypertension comes from experiments using rat models of hypertension. In these models it was shown that surgical removal of parathyroid glands attenuated the development of high blood pressure **(Berthelot 1980[11],Mann 1987[12]).** The antihypertensive effects of parathyroidectomy were apparently independent to effects of serum Ca 2+ concentration because fall in B.P. persisted even during Ca 2+ replacement **(Gairard 1982[13]). Brinton and colleagues (1975[14])** suggested that renin angiotensin aldosterone system (RAAS) may play a role in hypertension associated with primary hyperparathyroidism. However **Zawada and colleagues (1980[15])** claimed that hypertension associated with hyperparathyroidism was not dependent on renin. Recent studies have shown the relationship between PTH and vascular calcification **(Tomiyama et al. 2006[16], Neves et al. 2007[17],** Toussaint et al. 2008[18]). In 2007, Neves et al. showed that high PTH levels induced bone turnover and medial vascular calcification resembling **Monckeberg's** sclerosis independent of uremia. They removed parathyroid glands from rats but infused synthetic hormone (PTH) at a supraphysiologic rate. All rats on PTH replacement developed severe aortic calcification. Pressor action of PTH was investigated and it was found that whether infused or added to isolated vascular preparations, it was without fail a vasodilator and **Hanson and Linas (1994)[19]** explained this by showing that PTH is coupled to adenylate cyclase through a cholera toxin-sensitive G protein. They further explained that in contrast, states of prolonged PTH excess may not be associated with vasodilatation because PTH induced increase of cyclic AMP is desensitized.

Hulter (1986)[20] studied the effects of chronic continuous PTH infusion in normal human subjects. Chronic PTH infusion for 12 days resulted in persistent hypercalcemia and hypertention reversible during a 4-8 day recovery period.

The finding that acute PTH infusion resulted in vasodilatation and removal of parathyroid glands resulted in improvement in blood pressure, a research began for a hypertensive factor other than PTH but produced from parathyroid gland.

Pang and Lewanczuk (1989)[21]described the presence of a circulating hypertensive factor in spontaneously hypertensive rat (SHR) plasma. Transplantation of SHR parathyroid glands into Sprague Dawley (SD) rats resulted in an increase in mean arterial pressure (MAP) and the appearance of the factor in the plasma, SD to SD transplantation had no effect on MAP or hypertensive factor activity. Infusion of PTH gave opposite effects to hypertensive factor infusion. On the basic of this they proposed that the factor be referred to as "Parathyroid hypertensive factor" or "PHF".

Ifudu et al. (1998)[22] conducted a study on 19 hemodialysis patients 1 month before total parathyroidectomy (PTx), during the first month after PTx and long term (mean 16 months) in 12 of 19 patients. In the 12 patients followed for long term there was neither a clinically nor statistically significant change in either systolic or diastolic blood pressure. They hence concluded that PTx failed to correct hypertension in hemodialysis patients.

However Pizzarelli (1993)[23] found that PTx caused a significant progressive increase in body weight and fall in blood pressure in 7 of 11 uremic patients who underwent successful PTx.

Broulik et al. (2011)[24] conducted a large study on 1020 PHPT patients and 1020 age, sex, BMI and smoking status matched controls. 726 patients from 1020 patients (69.8%) with PHPT were found to be hypertensive while only 489 from 1020 controls were hypertensive. Parathyroidectomy in hypertensive patients reduced systolic and diastolic blood pressure.

London et al. (2007)[25] suggested that arterial calcification scores were not independently associated with 25(OH)D3 and 1, 25(OH)2 D3. However nutritional vitamin D deficiency and low 1, 25(OH)2D3 could be associated with arteriosclerosis and endothelial dysfunction in patients who have end stage renal disease.

Forman et al. (2010)[26] examined the relation between plasma 25 (OH) vitamin D and elements of RAAS in 184 normotensive individuals. Although (plasma renin activity) PRA was higher among individuals with insufficient levels of vitamin D, the result was not statistically significant.

Martins et al. (2007)[27] examined the association between serum levels of 25 (OH)D and cardiovascular risk factors using data from 3rd NHANES(National Health and Nutrition Examination Survey III 1988-1994). The 25(OH)D levels were lower in women, elderly persons racial/ethnic minorities and participants with obesity, hypertension and diabetes mellitus.

In 2010, Jorde et al.[28] reported association between 25 (OH) D and blood pressure during 14 years of follow up in Tromso study, conducted on Norwegian population. Compared with those whose baseline 25 (OH) D level was > 25 ng/ml, individuals whose baseline 25 (OH)D level was < 16.6 ng/ml had an adjusted odds ratio for incident hypertension of 1.22 (95% C.I:0.87 to 1.72).

Our study comprised of 80 non-diabetic CKD patients and 40 non-diabetic, non-hypertensive, non-CKD controls. The mean ionized calcium and vitamin D levels were significantly high in control group of study patients. In CKD cases, mean phosphorus, urea, creatinine and iPTH was significantly high.

We analysed the patient characteristics in 2 ways. **In the first**, CKD cases were stratified according to the PTH levels into 4 groups and their characteristics were studied. ANOVA (analysis of variance)was applied. With increasing iPTH levels, an increase in mean values of systolic blood pressure (SBP), diastolic blood pressure (DBP), serum phosphorus and serum creatinine was found. These measurements on investigation were statistically significant. A Logistic regression model was then applied for association of iPTH levels with variables showing significant association in univariate assessment, and it was found that iPTH>300pg/ml significantly associated with only serum creatinine.

Secondly, we stratified the cases as per the JNC 7 stages of hypertension and studied their characteristics. Applying ANOVA, a significant increase was observed for mean serum phosphorus levels, serum urea and iPTH with increase in blood pressure which was in accordance with JNC 7 staging. A logistic regression model was proposed with hypertension as the dependent outcome. It was found that only iPTH>300 pg/ml independently correlated with hypertension in our CKD cases.

Thus the outcome of our study had a close resemblance with the observations and results made out by previous workers **(Young 1990[4], Morfis 1997[5], Nasri 2005[29],)**

In our study, we also found that except for a statistically significant relation with total cholesterol, iPTH did not correlate with LDL, HDL or triglyceride levels. However the relation with total cholesterol was non linear, with total cholesterol being maximum when iPTH was <150pg/ml and minimum when iPTH was between 150-300 pg/ml and this finding was somewhat in accordance with the previous studies by **Navarro (1998)[30] and Ahmadi (2012)[31]**.

Also with variation in iPTH, Hb levels did not vary significantly in our study, whereas **Memon et al. (2013)[32]** observed that small positive association existed between PTH and hemoglobin among diabetics but not among non-diabetics. The lack of association of Hb levels with iPTH was probably due to repeated blood transfusions and iron supplementation.

However the limitations of our study were small sample size and advanced CKD in majority of patients.

CONCLUSION

Our study shows that secondary hyperparathyroidism correlates with hypertension in CKD patients, hence lowering of PTH in these patients might contribute to control of blood pressure in them.

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