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A Study on the Association of Hypertension and Hyperparathyroidism in Diabetic Chronic Kidney Disease Patients

Authors
Piyush Saxena[1], Raju Kumar[2], Arvind Gupta[3]
[1]Assistant Professor, Deptt of Medicine, MLN Medical College, Allahabad, UP INDIA
Email- *doc.piyush.saxena@gmail.com*
[2]Resident, Deptt of Medicine, MLN Medical College, Allahabad, UP INDIA
[3]Professor, Deptt of Medicine, MLN Medical College, Allahabad, UP INDIA
Corresponding Author
Dr Piyush Saxena
Assistant Professor, Deptt of Medicine, MLN Medical College, Allahabad, UP INDIA
Email- *doc.piyush.saxena@gmail.com*, Mob- 09450110720

Abstract
Introduction: *Prevalence of hypertension is high in diabetic CKD patients. Hypertension is one of the important risk factors for cardiovascular diseases in uremic patients. cardiovascular diseases are the most important etiologies causing mortality and morbidity in these patients.. Left ventricular hypertrophy is also found in many CKD patients; its contributing factor other then hypertension is unsolved issue. Hyperparathyroidism and vitamin D can be the others.*
Aims & Objectives: *To study the association of Hypertension and Hyperparathyroidism in patients of diabetic CKD. To study the association of Hypertension and vitamin D levels in patients of diabetic CKD. To study the association of Hyperparathyroidism and vitamin D with Left ventricular hypertrophy in patients of diabetic CKD.*
Results: *Out of 90 cases ;The mean serum PTH was 202.37±66.4 pg/mL in prehypertensive group 207±82.7 pg/mL in the patients with stage I Hypertension and 350.5±140.5 pg/mL in the patients with Stage II Hypertension showing significant correlation (P =0.000) between Hypertension and iPTH levels.When cases were stratified according to iPTH quartiles (<150,150-299 ,300-449 ,>450 pg/ml) Systolic Blood Pressure(P =0.0000),and Diastolic Blood Pressure (P =0.000) were found to be significantly correlating with iPTH. Also there is significant relation (P=0.027) between vitamin D levels and development of left ventricular hypertrophy. However no correlation between left ventricular Hypertrophy and i PTH levels was found (P=0.706).*
Conclusions: *In this study, we could show a significant relationship between hypertension severity and serum i PTH level in diabetic CKD patients. While no association between Hypertension and vitamin D deficiency was found .Left ventricular hypertrophy was significantly related with serum vitamin D levels. However no correlation between left ventricular hypertrophy and i PTH levels was found.*
Keywords: *CKD, Hypertension, LVH, Hyperparatyhyroidism, Diabetes, Vitamin D*

Introduction

Chronic kidney disease (CKD) is one of the most common and potentially devastating complications of diabetes. Fifty percent of people with diabetes have CKD.[1] It is also important to recognize that people with CKD are among those at highest risk for cardiovascular (CV) morbidity and mortality, and that interventions to lower CV risk remain the most important priority in this population[2]. HTN is the most common cardiovascular disease (CVD) risk factor [3.]. Prevention of HTN is possible, and early detection and treatment can reduce the incidence of complications including stroke, CHD, heart failure, and kidney disease. [4] several factors have been known responsible for hypertension in CKD patients including water and sodium retention due to disturbance in elimination capacity of the kidney, increased activity of renin-angiotension-aldosterone system and sympathetic nervous system, high serum level of vasoconstrictor endothelin-1, and low serum level of vasodilators.[5,6] One of the aetiologies in the development of hypertension in haemodialysis patients is probably high intracellular calcium, due to the secondary hyperparathyroidism. High intracellular calcium increases peripheral artery resistance and probably causes hypertension due to constriction of arteriolar smooth muscles.[7]

Chronically increased plasma intact parathyroid hormone (PTH) concentration and/or intracellular calcium concentration ([Ca2+] i) may be of relevance in the genesis of high blood pressure. This hypothesis is based on observations that hypertension in uremic patients with secondary hyperparathyroidism is associated with increased PTH and intracellular calcium concentrations. [8]

vitamin D deficiency, is a substantially prevalent condition in patients with type 2 DM. [9] Vitamin D receptors (VDRs) are present on a large variety of cell types, including myocytes, cardiomyocytes, pancreatic beta-cells, vascular Endothelial cells, neurons, immune cells, and osteoblasts.[10]Vitamin D deficiency seems to predispose to hypertension, diabetes and the metabolic syndrome, left ventricular hypertrophy, congestive heart failure, and chronic vascular inflammation. [10,11]

The pathogenesis of LVH in ESRD is multifactorial, and arterial hypertension, hyperparathyroidism, severe anemia, hypoalbuminemia, chronic volume overload,[12] and sympathetic over activity,[13] have been implicated as causative mechanisms responsible for LVH in these patients. An increased prevalence of cardiac structural abnormalities, such as left ventricular hypertrophy (LVH), has been observed in vivo[14] and functional properties of the heart might be affected by the hyperparathyroid condition as well[15.]

Materials and Methods

The present study was a single point cross sectional case control study, mainly centered on diabetic chronic kidney disease patients. There detailed history and physical examination (with an accurate measurement of blood pressure –systolic, diastolic) was taken .They were investigated for baseline characteristics including diabetic profile, iPTH, vitamin D levels and 2 D echo. All patients of diabetes mellitus and chronic kidney disease admitted in our hospital were taken as cases. Patients having Severe anaemia ,Coronary artery disease Cardiomyopathies Valvular heart disease Previous parathyroidectomy, Connective tissue diseases. were excluded from the study. Age and sex matched volunteers as controls from the hospital were taken to minimize possibility of any bias. They were screened for the absence of diabetes, hypertension and chronic kidney disease. Blood pressure was measured with one calibrated manometer in the supine position. The participants with hypertension were divided based on the stage of hypertension according to the definition of Joint of National Committee for hypertension VII. In all patients, fasting blood sample was taken was analyzed for Complete hemogram (HB,TLC ,DLC,ESR) Serum Urea , Serum Creatinine, Serum calcium, serum phosphate Diabetic profile (Blood sugar fasting, post prandial blood sugar and HbA1c)serum calcium, phosphorous, PTH,

and vitamin D. Other investigations are USG abdomen for kidney size and echotexture. Urine examination, 2D Echo (for Left ventricular mass), X-Ray chest and ECG.

Statistical Analyses

Comparisons between the two groups were done using the t test or the chi-square, where appropriate. For comparision between various groups of I PTH and stages of hypertension with various covariables ANNOA was applied. A multiple linear regression model was applied to show serum PTH as independent predictors of systolic and diastolic blood pressure. Data analysis was carried out using the SPSS software (Statistical Package for the Social Sciences, version 17.0, SPSS Inc, Chicago, Ill, USA). *P* values less than .05 were considered significant.

Results

In this single point cross sectional study 140 subjects were studied of which 90 cases were having T2DM and chronic kidney disease and 50 age and sex matched healthy controls who were non hypertensive, non diabetic, non CKD patients admitted for some other illness healthy controls were taken.(Table No.1)

Out of 90 cases; 22 had JNC pre Hypertensive stage, 26 had JNC stage I hypertension and 30 had JNC stage II Hypertension. The mean serum PTH was 202.37±66.4 pg/mL in prehypertensive group 207±82.7 pg/mL in the patients with stage I Hypertension and 350 ±140.5 pg/mL in the patients with Stage II Hypertension showing significant correlation (*P =0.000)* between Hypertension and iPTH levels while no correlation (p=0.61) was found between hypertention and Vitamin D. (Table no. 2).

When cases were stratified according to iPTH quartiles (<150,150-299,300-449,>450 pg/ml) Systolic Blood Pressure (*P =0.0000*), and Diastolic Blood Pressure (*P =0.000)* were found to be significantly correlating with iPTH (Table No. 3). This was also proved by scatter diagram between iPTH and Systolic Blood Pressure (Figure No.1) and between iPTH and Diastolic Blood Pressure. (Figure No.2)

Also there is significant relation *(P=0.02)* between vitamin D levels and development of left ventricular hypertrophy. However no correlation between left ventricular Hypertrophy and i PTH levels was found *(P=0.706).*(Table No.4 & 5)

In the multiple linear regression model, serum PTH was a positive and significant predictor of systolic blood pressure (sig. = 0.017) and diastolic blood pressure (sig. = 0.050) when compared to oher co variables (vitamin D ,serum urea).(Table No.6)

Table no.1 The baseline characteristics of cases and controls

Characteristics	Cases	Controls	p value
Age(years)	55.44±12.32	54.28±12.58	0.59
Hb(g/dl)	8.62±1.29	11.09±1.27	0.001
Urea(mg/dl)	124.54±65.47	36.34±10.21	0.0001
Creatinine(mg/dl)	5.03±2.58	0.91±0.24	0.0001
Calcium(mmol/l)	1.08±0.35	1.11±0.07	0.55
Phosphorus(mg/dl)	5.02±0.93	3.36±0.82	0.0001
iPTH(pg/ml)	247.63±124.3	29.55±8.88	0.0001
FBS(mg/dl)	183.86±50.83	90.1±8.56	0.0001
PPBS(mg/dl)	241.33±66.44	116.9±11.96	0.0001
HbA1c(%)	7.64±0.85	5.81±0.24	0.0001
Vitamin D	20.66±5.97	25.4±7.49	0.0001

Table no.2 Relation Between JNC VII Stages Of Hypertension with Vitamin D (ng/ml) and iPTH (pg/ml) (mean ± S.D)

JNC VII Stages of hypertension	iPTH (pg/ml)	Vit D (ng/ml)
Normotensive(n=12)	161.2±63.8	18.74±4.32
Pre-hypertensive(n=22)	202.37±66.4	21.13±6.76
Stage1 HTN (n=26)	207±82.7	21.39±7.23
Stage 2 HTN (n=30)	350.5±140.5	21.3±4.98
p-value(ANOVA)	0.000	0.610

Table no.3 Correlation Between iPTH with systolic blood pressure And Diastolic Blood Pressure (mean ± S.D)

iPTH (pg/ml)	SYSTOLIC BLOOD PRESSURE(mm of Hg)	DIASTOLIC BLOOD PRESSURE(mm of Hg)
<150(N=23)	135.9±25.9	83.3± 11.6
150-299(N=46)	145.1± 22.02	88± 12.01
300-449(N=15)	166.8± 15.96	102.13± 7.5
≥450 (N=6)	193.3± 11.8	108.7± 6.9
p-value(ANOVA)	0.000	0.000

Table No.4 .Relation of vitamin D (ng/ml) and LVH (left ventricular hypertrophy) in cases

Vitamin D level (ng/ml)	Number of cases	LVH present	LVH absent
< 20 (deficiency)	56	43(77%)	13(23%)
20-30(insufficiency)	23	15(65%)	8(35%)
>30(sufficiency)	11	4(36%)	7(64%)

χ^2=7.2 df=2 p= 0.027

Table5. Relation of iPTH Levels(pg/ml) and LVH (left ventricular hypertrophy)

iPTH levels (pg/ml)	Number of cases	LVH present	LVH absent
<150	23	12(52%)	11(48%)
150-299	46	35(76%)	11(24%)
300-449	15	11(73%)	4(27%)
>450	06	06(100%)	0(0%)

χ^2—7.04 df—3 p—0.706

Figure 1: Scatter diagram showing correlation between iPTH And Systolic Blood Pressure

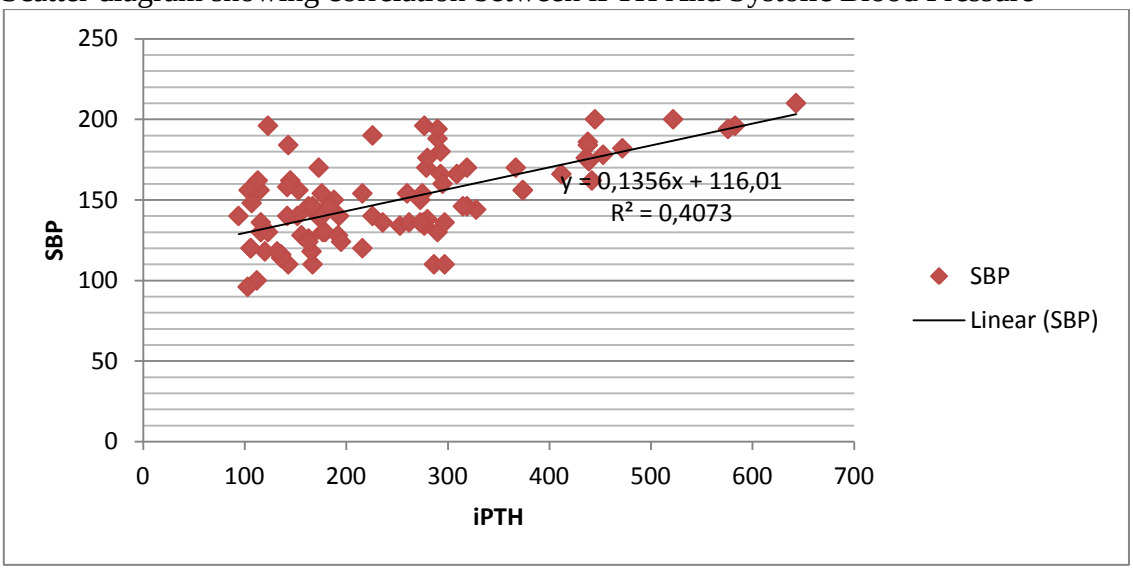

Figure 2 : Scatter diagram showing correlation between iPTH And Diastolic Blood Pressure

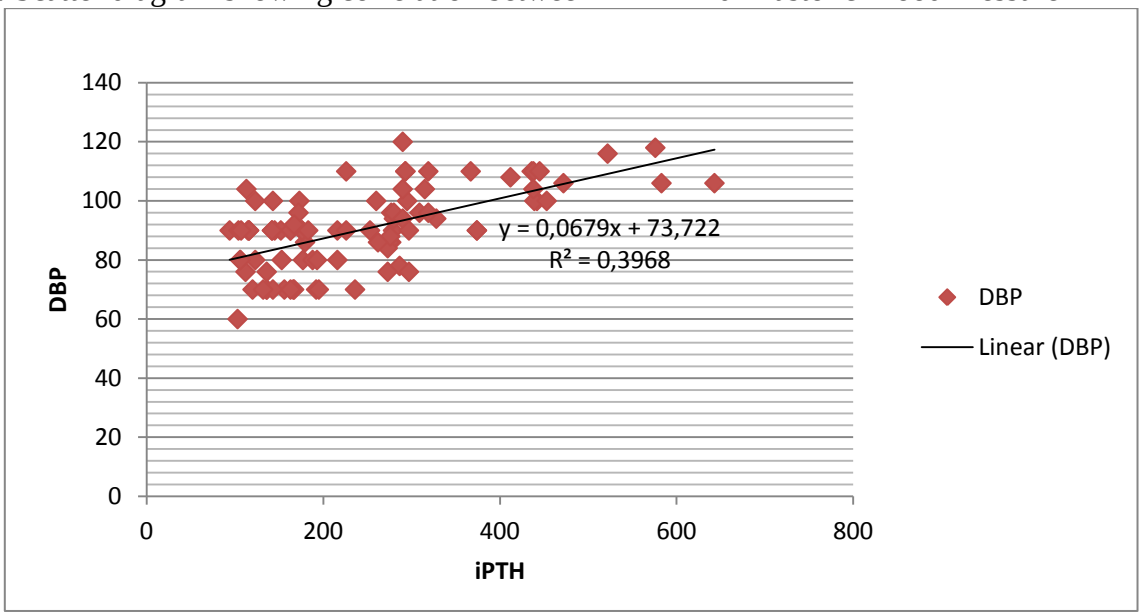

Table No.6. Multiple Linear Regression With iPTH As Dependent Variable

Coefficients

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-211.164	78.349		-2.695	.008
	VIT.D	-2.913	1.674	-.140	-1.740	.085
	SBP	1.775	.732	.377	2.424	.017
	DBP	2.874	1.444	.310	1.990	.050
	S.UREA	-.054	.153	-.028	-.353	.725

Dependent Variable: iPTH

Discussion

In the study the mean ages of cases were strongly correlating (p=0.007) with the various JNC VII stages of hypertension proving the well known fact for age being one of the most important risk factor for hypertension. These results were in accord to study by Anderson GH.et al.[16] in 2009 on 4800 patients and they found increased age to be associated with a significant increase in the prevalence of hypertension and especially of systolic hypertension.

In this study it was found that patients with T2DM were having lower Vitamin D levels than those without. 74% of the controls (non diabetics) were having Vitamin D levels more than 20 ng/ml while this percentage was only 48% in the case group i.e. the diabetics. There was significant difference (p= <0.0001) in the mean serum Vitamin D levels between diabetics and the non-diabetics. This suggested that the Vitamin D levels were significantly lower in the case group with more of the patients with hypovitaminosis D. Pietschmann et al.[17] and Isaia et al.[18] showed in their respective studies that an association exists between low circulating concentrations of Vitamin D and the prevalence of diabetes and impaired glucose tolerance.[116,117]Similar results were found in studies of Pittas et al.[19],and Gagnon et al.[20] in their respective studies. while some studies were not consistent with our finding like Suzuki et al.[21] concluded that mean Vitamin D levels

concentration in T2DM patients was not statistically different from normal population. This may be due to smaller sample, geographical and weather effects.

In the study The JNC VII stages of hypertension were strongly correlating (p=0.000) with I PTH .When the iPTH levels were stratified into quartiles then also the systolic blood pressure (p=0.000) and diastolic blood pressure (p=0.000) were having statistically significant correlation. this finding was consistent with The Tromsø study,[22] by Rolf Jorde et al on 10419 subjects, and studies of Helmut Schiffl et al[23]., and Sedighi et al[24]. showing association between hypertension and hyperparathyroidism.

In our study no correlation (p=0.61) was found between hypertention and Vitamin D. which was consistent with The Ranch Bernardo Study by Jared P. Reis et al[25], on 1070 patients and studies of Andrew St John et al.[26], M. B. Snijder et al[27]**.,** R Chan et al.[28] in which parathyroid hormone but not calcitriol remained a significant predictor of mean blood pressure.

In Our study of no relation between vitamin d levels and hypertension (p=0.61) is not consistent with findings of Pfeifer et al.[29] and study of Alexandra Jungert et al[30]. probable causes can be , firstly we did not measure 1,25-(OH)2-D levels, the most biologically active form of vitamin D, which may have given us more precise information on the biological pathway for its putative effects on blood pressure. Second, our study consisted of moderate sample size of only 90 patients, which decreased the probability of detecting a significant association between serum vitamin D and blood pressure. Third the use of a single measurement of serum 25OHD and PTH May reflects only recent exposure rather than long-term exposure.

In our study a significant correlation between vitamin d levels and left ventricular hypertrophy was found with P=0.027 and df=2 . This finding was consistent with Natalya Bodyak et al[31] in their study on rats that in the Dahl salt sensitive mice model, and Osman Kuloğlu et al.[32] in their study of Serum 25-hydroxyvitamin D levels association with aortic distensibility and left ventricle hypertrophy(p<0.001) in newly diagnosed type 2 diabetes mellitus patients.

In this study no significant correlation was found between I PTH and LVH (p=0.706) which was not accordance with previous studies[71-73] by F. N. Saleh et al.[33], Al-Hilali et al[34] ,and A. Azak,et al[35].This may be due to small sample size of the study and ethinic variations in the study group.

Conclusion

In Diabetics CKD Patients Prevalence of Vitamin D deficiency was significantly higher. Prevalence of Vitamin D deficiency was significantly higher in diabetic patients as compared to non diabetics. The mean serum Vitamin D levels were lower than the non-diabetic non CKD group showing significant association with diabetes. There is significant association between Vitamin D deficiency and Left ventricular hypertrophy. There is significant association between hypertension and Left ventricular hypertrophy. While there is no association between hyperparathyroidism and Left ventricular hypertrophy. There is a inverse correlation between iPTH levels and vitamin D levels. There is significant association between hypertension and age. There is significant association between hyperparathyroidism and systolic blood pressure. There is significant association between hyperparathyroidism and diastolic blood pressure. There is no association between Hypertension and vitamin D deficiency.

Limitations

We did not measure 1,25-(OH)2-D levels, the most biologically active form of vitamin D, which may have given us more precise information on the biological pathway for its putative effects on blood pressure. Our study consisted of moderate sample size of 140 patients which decreased the probability of detecting a significant association between serum 25OHD and blood pressure. Patient's compliance was questionable at certain times.

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