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CORRELATION OF VITAMIN D_3, PARATHYROID HORMONE AND SERUM CALCIUM AND LEFT VENTRICULAR HYPERTROPHY IN ESSENTIAL HYPERTENSION

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ABSTRACT

Objective: To study and correlate vitamin D_3, Parathyroid hormone (PTH) and serum calcium (Ca++) in left ventricular hypertrophy of essential hypertension **Study Design:** Case-control study. **Subjects and Methods:** A sample of 187 normal controls and 189 diagnosed essential hypertension cases were studied. Blood pressure, Echocardiography, Serum vitamin D, Ca++, PO^{4-}, PTH, calcitonin, alkaline phosphatase (ALP), blood urea, serum creatinine, serum Na+, serum K+, urinary Ca++ and urinary PO^{4-} were determined. Data was analyzed on SPSS 22.0 and GraphPad Prism. **Results:** Essential hypertension with LVH showed significantly low serum vitamin D_3 ($P<0.05$). Serum Ca++, PO^{4-}, PTH, Calcitonin, Na^+ and urinary Ca++ and PO^{4-} were elevated ($P<0.05$). Vitamin D_3 ($r= -0.458$, $p=0.0001$), and urinary PO^{4-} ($r= -0.458$, $p=0.0001$) showed negative correlation with LVH. **Conclusion:** LVH in essential hypertension occurs due to vitamin D deficiency caused by raised serum calcium, serum Na+ and serum Parathyroid hormone which increased myocardial contractility and protein synthesis.

KEYWORDS: Parathyroid hormone, Vitamin D_3, Calcium, left ventricular hypertrophy Essential hypertension.

INTRODUCTION

Essential hypertension is a common clinical entity which increases the work load of left ventricle (LV). As the after load of LV is exaggerated, so the compensatory remodeling phenomena simulataneusouly result in left ventricular hypertrophy (LVH). LV contractility is dependent on serum calcium (Ca++). Ca++ homeostasis is regulated by vitamin D and parathyroid hormone axis.[1,2] Clinically, the LVH is an independent risk factor of cardiac related morbidity and mortality in essential hypertension subjects.[3,4] It is now established fact that the LVH is compensatory physiological response which eventually becomes pathological. The prevalence of LVH has increased proportionately to the severity of systemic hypertension.[5,6] Approximately 95% cases of systemic hypertension are of unknown etiology termed as the Essential hypertension. It is multifactorial in origin, the genetic, environmental, dietary habits, and personality is additive factors. A large number of Pakistan populations are suffering from essential hypertension.[7] LVH may lead to cardiac failure in long term.[8,9] The underlying mechanisms of LVH are not established. Whether LVH occurs due to long standing systemic hypertension or because of non-hemodynamic systemic factors which might adversely affect the compensatory myocardial hypertrophy still remains controversial and debatable.[5,10,11] Recently, much research has pointed towards the association of vitamin D with LVH through parathyroid hormone (PTH) and Ca++ metabolism. Vitamin D deficiency is highly prevalent in Pakistan.[10,11] Subjects of essential hypertension are reported of showing abnormal homeostasis of serum and urinary calcium excretion and PTH in the presence of prevalent Vitamin D deficiency.[10,11] A previous study reported probability of altered Ca++ homeostasis causes LVH.[10] Ca++ homeostasis is regulated through PTH and Vitamin D. Levels of both PTH and Vitamin D vary in the subjects of essential hypertension.[12] Previous studies reported on the association of LVH caused by hyperparathyroidism with a concomitant rise in systemic blood pressure.[3,13,14] However, the cause effect relationship of PTH and vitamin D is not clear and needs further research.[15] One proposed mechanisms of PTH causing LVH is through

increased cytosolic free Ca++ in essential hypertension.[13-15] Vitamin D is essential for the physiological functioning of PTH and provides intracellular Ca++ for myocardial contractility. Thus vitamin D increases the cardiac contractility and affects PTH which in turn does the same through receptor binding mechanisms.[12] With this background scenario, the association of LVH with vitamin D, PTH and serum Ca++ homeostasis needs further research. As the Vitamin D, PTH and Ca++ are modifiable; hence the LVH may be prevented if it is proved they do play role in myocardial hypertrophy. The cardiovascular morbidity and mortality may be prevented simply through modification of vitamin D and Ca++ supplements. The present research was conducted to determine the Vitamin D, PTH and Ca++ in subjects with essential hypertension with evident left ventricular hypertrophy. The purpose of present research was determining the association of Vitamin D, PTH and Ca++ with LVH as non-hemodynamic modifiable risk factors in subjects suffering from essential hypertension presenting at our tertiary care hospital.

SUBJECTS AND METHODS

The present study was conducted at the Department of Medicine and Cardiology, Liaquat University of Medical and Health Sciences, Jamshoro, Sindh. The study was conducted from July 2015 to August 2016. Prior ethical approval of research proposal was obtained from the Research committee board of institute. A population of 187 normal age and gender matched controls and 189 diagnosed subjects of essential hypertension (cases) were included according to criteria. Systemic hypertension was defined according to the JNC VII criteria. Exclusion criteria were the secondary hypertension, Diabetes mellitus, Acute and Chronic kidney disease (CKD), liver disease, heart failure, coronary artery disease and angina pectoris. Study subjects were handled according to the ethical principles of institute as per "Declaration of Helsinki". Each subject was communicated for the purpose of study, harm and or benefits. Volunteers were asked for signing the consent form. Physical examination was performed by house physician followed by a Consultant Physician. Blood pressure was measured after a five minutes reset in supine position by both palpatory and auscultatory methods. Echocardiography was performed by a senior cardiologist (2.5 MHz cardiac probe) (Model SSA 270; Toshiba, Japan). LV thickness (LVH) was measured by Devereux's formula.[16] Volunteer subjects were asked for blood sampling. All blood samples were obtained from Ante cubital vein under strict aseptic measures. Serum 25-hydroxy vitamin D3, serum Ca++, serum PO^{4-}, serum PTH, serum calcitonin, alkaline phosphatase, blood urea, serum creatinine, serum Na+, serum K+, urinary Ca++ and urinary PO^{4-} were performed at the Diagnostic and Research Laboratory of Liaquat University of Medical and Health Sciences. Biochemical assays were performed as per standard methods on the Roche chemistry analyzer. Serum 25-hydroxy Vitamin D_3, PTH and calcitonin were performed by ELISA assay kit. Data was analyzed on SPSS 22.0 and GraphPad Prism. Data was analyzed by student t-test, Chi square test and Pearson`s correlation. Data was analyzed at 95% confidence interval ($p \leq 0.05$).

RESULTS

Study subjects were age and gender matched as denoted by non-significant P-value (table 1 and 2). Cases of essential hypertension showed significantly low serum 25-hydroxy vitamin D_3. Serum Ca++, serum PO^{4-}, serum PTH, serum Calcitonin and serum Na^+ were found elevated in cases of essential hypertension. Loss of urinary Ca++ and urinary PO^{4-} was increased in cases compared to controls (P= <0.05). Table 1 shows the results of biochemical findings of cases and controls. LVH showed negative correlation with 25-hydroxy vitamin D_3 (r= -0.458, p=0.0001) and urinary PO^{4-} (r= -0.458, p=0.0001).

Table 1. Age and Biochemical findings of study subjects (n=376)

	Groups	Mean	SD	P-value
Age (years)	**Controls**	52.74	7.43	0.56
	Essential Hypertension	53.41	5.94	
Systolic BP (mmHg)	**Controls**	126.0	11.0	0.0001
	Essential Hypertension	156.0	23.0	
Diastolic BP (mmHg)	**Controls**	69.0	19.0	0.0001
	Essential Hypertension	91.0	33.0	
25- hydroxy-D_3 (ng/dl)	**Controls**	35.01	11.63	0.0001
	Essential Hypertension	22.06	13.62	
Serum Calcium (mg/dl)	**Controls**	9.24	0.78	0.002
	Essential Hypertension	10.15	0.38	
Serum Phosphate (mg/dl)	**Controls**	3.39	0.63	0.001
	Essential Hypertension	3.78	0.40	
Serum PTH (pg/ml)	**Controls**	39.55	17.88	0.0001
	Essential Hypertension	53.67	8.68	
Serum Calcitonin (pg/ml)	**Controls**	6.71	2.36	0.01

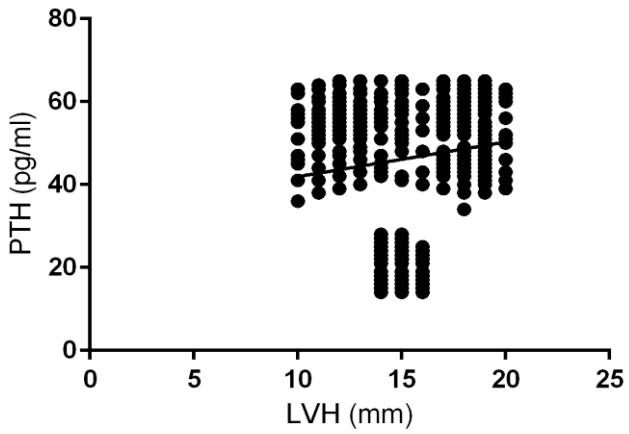
	Essential Hypertension	7.95	2.09	
Urinary Ca++ (mg/24hours)	**Controls**	176.99	79.24	0.0001
	Essential Hypertension	279.17	183.41	
Urinary PO4-- (mg/24hours)	**Controls**	548.79	110.29	0.0001
	Essential Hypertension	486.54	195.45	
Seruma Na+ (mmol /L)	**Controls**	138.48	7.29	0.001
	Essential Hypertension	145.63	10.08	
Seruma K+ (mmol /L)	**Controls**	4.11	0.32	0.056
	Essential Hypertension	4.04	0.24	
Alkaline Phosphatase (IU/L)	**Controls**	160.12	28.60	0.001
	Essential Hypertension	176.87	50.32	
Blood Urea (mg/dl)	**Controls**	30.75	10.86	0.43
	Essential Hypertension	29.86	10.78	
S. Creatinine(mg/dl)	**Controls**	1.00	0.22	0.79
	Essential Hypertension	0.90	0.32	
LVH (mm)	**Controls**	13.89	1.49	0.0001
	Essential Hypertension	17.36	2.58	

Table 2. Gender and microalbuminuria distribution

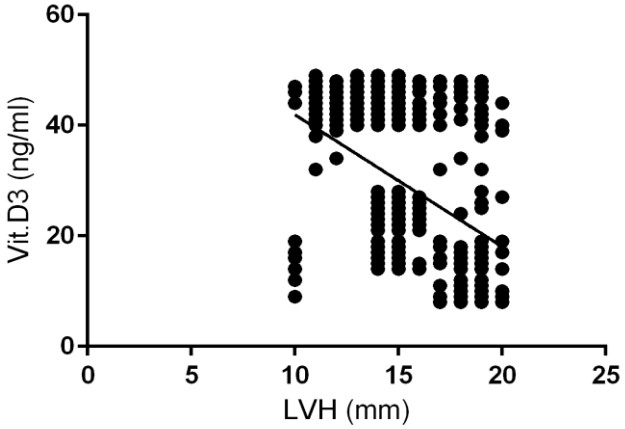
	Group A. Controls	**Group B. Cases**	**X^2 –value**	**P value**
Male	114	120	0.25	0.67
Female	73	69		

Table 3. Pearson`s correlation of LVH study subjects

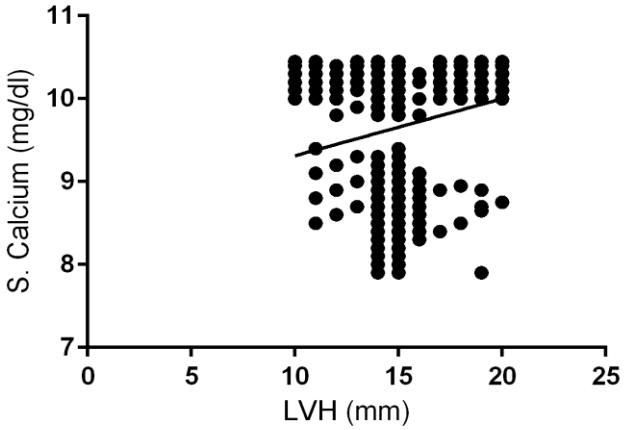
	LVH (mm)	
	r-value	**p-value**
Age (years)	0.130	0.012
25-OH-D3 (ng/dl)	-0.458	0.0001
Serum Calcium (mg/dl)	0.246	0.0001
Serum Phosphate (mg/dl)	0.296	0.0001
Serum PTH (pg/ml)	0.145	0.005
Calcitonin (pg/ml)	0.060	0.243
Urinary Ca++ (mg/24hours)	0.263	0.0001
Urinary PO4-- (mg/24hours)	-0.165	0.001
Seruma Na+ (mmol /L)	0.127	0.013
Seruma K+ (mmol /L)	-0.041	0.426
Alkaline Phosphatase (IU/L)	0.199	0.0001
Blood Urea (mg/dl)	-0.010	0.840
S. Creatinine(mg/dl)	-0.001	0.970



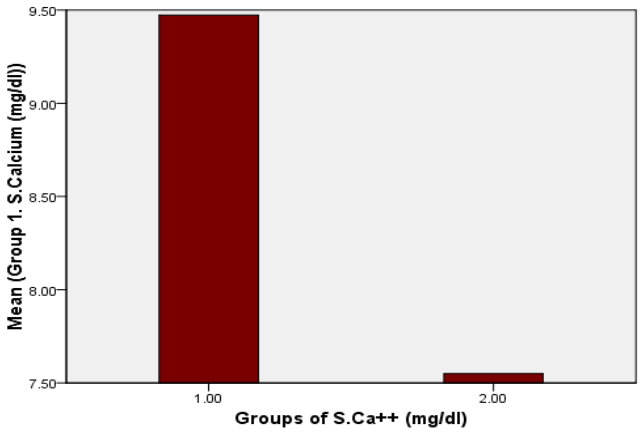
Graph 1. Scatter plot showing correlation of LVH and serum PTH (r = 0.145, R^2 = 0.021, Y = 0.834*X + 33.60, F= 8.05, p = 0.0049)



Graph 2. Scatter plot showing correlation of Vitamin D and LVH (r = -0.458, R^2 = 0.210, Y = -2.385*X + 65.78, F= 99.39, p < 0.0001)



Graph 3. Scatter plot showing correlation of serum calcium and LVH (r = 0.246, R^2 = 0.062, Y = 0.06884*X + 8.624, F= 24.13, p < 0.0001)



DISCUSSION

The present is the first study reporting on the association of Vitamin D, Parathyroid hormone and serum Ca++ in LVH of patients with essential hypertension. The present study found a significant correlation of vitamin D, PTH and Ca++ with LVH pathophysiology in essential hypertension. LVH patients revealed Vitamin D_3 deficiency with rise in serum PTH, Ca++, PO^{4-}, calcitonin and Na^{+} and increased urinary Ca++ and urinary PO^{4-}. The present findings are in keeping previous studies.[12,17,18] Vitamin D (r= -0.458, p=0.0001) and urinary PO^{4-} (r= -0.458, p=0.0001) showed negative

correlation while serum PTH, serum Ca++ and serum PO^{4-} were positively correlated. Negative correlation of increased urinary Ca++ excretion is in agreement with previous study.[19] A previous study[20] reported decreased bone mass density in female hypertensive patients, the problem may be due to the increased serum PTH levels as noted in the present study. Finding of raised serum PTH level in essential hypertension are consistent with previous studies.[10,12] Some of previous studies[12,20,21] have reported high serum vitamin D in essential hypertension, which is in disagreement with present study. It was reported high serum vitamin D may be due activation of renal 1- 25-hydroxylase enzyme which h is under control of PTH.[12] The finding of low vitamin D in LVH is in agreement with previous studies.[21,22]

Such controversial results are because of different study designs, different ethnicity, geographical and environmental factors, different laboratory techniques and reference ranges, low study sample size and research bias. Different laboratory methods for measuring the PTH and vitamin D (range 8 to 44 ng) have been reported for such discrepancy.[23,24] The association of high PTH with low vitamin D in essential hypertension is considered as a compensatory response to urinary calcium losses.[12,18] A previous study[26] reported concomitant increased serum PTH and urinary Ca++ and high serum Na+ in patients with essential hypertension, the findings are consistent with our present study. It is suggested to be the result of excessive dietary salt (NaCl) intake or secondary to a defective urinary Na+ loss which leads to excessive Ca++ excretion.[9,15,25-27] Given our finding of raised PTH and low vitamin D in LVH patients of essential hypertension is a finding consistent with previous studies.[9,15,25-27] A previous study has reported inverse association of serum PTH and vitamin D, but such compensatory phenomenon occurs to a certain limit of vitamin D, at which a farther decrease in serum PTH is noted.[28] The LVH was noted in present study, the finding is in agreement with previous studies.[3,29] However, the exact pathophysiology of this association is controversial and debatable. Ongoing research is being conducted on other factors such as Chronicity of high BP, increased sympathetic tone, hyperparathyroidism and increased rennin and angiotensin.[10,29,30] The present study reports positive association of LVH with serum PTH and serum Calcium. Previous studies reported the LVH is induced by PTH through its effect on the myocardial cells.[31,32] One suggested mechanism how does PTH cause LVH is the fact that the PTH increases intracellular Ca++ levels in cardiac myocyte through G protein and L-type calcium channels. Increased intracellular Ca++ may increase protein synthesis through some gene expression within the myocytes.[33] Evidence of regression of LVH in post operative hyperparathyroidism is a commonly observed complication.[30,34] A previous study[30] reported high LV mass in primary hyperparathyroidism patients with normal BP. The findign of positive correlation of PTH and LVH of present study is in agreement with Bauwens et al[10] They reported similar findings in LVH of essential hypertension patients. The present study suggests the essential hypertension alters serum PTH, serum Ca++, urinary Ca++, urinary PO^{4-} and vitamin D deficiency; these factors are responsible for the induction of LVH pathophysiology. Hypercalciuria, hyperphosphaturia and hypernatremia are major ionic imbalances which play role in LVH induction. Increased PTH levels might induce myocardial hypertrophy due to increased protein synthesis. The major limitations of present are; sample size, particular ethnicity and geographical area and dietary habits. However, the strength of study is because of its prospective design and normal control subjects.

CONCLUSION

Left ventricular hypertrophy of essential hypertension occurs due to vitamin D deficiency. Elevated serum calcium, serum Na+ and serum Parathyroid hormone increase myocardial contractility and *de-novo* protein synthesis; these results in ventricular hypertrophy. However underlying molecular mechanism remains to be elucidated and needs further research.

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