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25-hydroxyvitamin D and Parathyroid hormone levels and their associations with left ventricular hypertrophy in a sample of hypertensive patients in Erbil-Iraq

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Abstract
Background and objectives: Conflicting reports support or refute an association between vitamin D deficiency with high levels of parathyroid hormone and left ventricular hypertrophy in hypertension. The objective of this study was to explore the associations of 25-hydroxyvitamin D and parathyroid hormone with left ventricular hypertrophy among a sample of hypertensive patients in Erbil-Iraq.
Patients and methods: This is a cross sectional study, including 120 patients (52males and 68 females) with essential hypertension attended the consultation unit of Rizgary Teaching Hospital from March 2015 to September 2015. Patients were classified into two groups, patients with left ventricular hypertrophy (n=70) and those without left ventricular hypertrophy (n=50).Serum 25(OH) D and parathyroid hormone concentrations were measured and studied in relation to left ventricular hypertrophy
Results: The mean age (±SD) of the patients was 53±11 years. Based on the results of the echocardiographic examination, left ventricular hypertrophy was present in 70 patients (58.3%) of whom 42 patients (60%) were female. Age, blood pressure and history of hyperlipidemia show statistically significant differences between the two groups (p= 0.007, 0.001, and 0.002, respectively). The mean of 25(OH) D level was lower while the mean of PTH level was higher in left ventricular hypertrophy patients compared to those without left ventricular hypertrophy (P<0.001).
Conclusions: Our results suggest that low serum vitamin D and high PTH levels are associated with left ventricular hypertrophy in hypertensive patients in Erbil city-Iraq.

Keywords: Vitamin D; Parathyroid hormone; left ventricular hypertrophy

1. Introduction
Vitamin D deficiency or insufficiency is a common condition that affects up to one-half of otherwise healthy middle aged to elderly population [1]. Limited cutaneous syntheses due to inadequate sun exposure and inadequate dietary intake are the principle causes of low 25(OH) D levels. Although a consensus regarding the optimal level of serum 25(OH) D has not yet been established, most experts define vitamin D deficiency as a 25(OH) D level of <20 ng/ml, vitamin D insufficiency as 21 to 29 ng/ml and the optimal concentration of 25(OH) D is at least 30 ng/ml [2].
Although vitamin D deficiency involves mainly musculoskeletal system, growing evidence suggests that vitamin D affects the cardiovascular system also [3].
Chronic vitamin D deficiency causes secondary hyperparathyroidism, which in turn may mediate many of the detrimental CV effects of inadequate vitamin D levels [4]. The threshold for elevation of parathyroid hormone (PTH) is a 25(OH) D level of < 30 ng/ml. There is an association between increased PTH levels and increased left ventricular mass. The possibility of a causal relationship is strengthened by studies where PTH appears to have chronoscopic, inotropic as well as hypertrophic effects on cardiomyocytes [5]. The reference range for serum PTH is 11-65 pg/ml [6].
Left ventricular hypertrophy (LVH) is a major maladaptive response to chronic pressure overload and an important risk factor in patients with hypertension [7]. Pathophysiological investigations suggest a link between low vitamin D levels and LVH, possibly mediated by parathyroid hormone [8]. Up to our knowledge, there was no previous study done regarding the same subject in Erbil-Iraq.
The aim of this study was to assess the associations of 25-hydroxyvitamin D and parathyroid hormone with left ventricular hypertrophy in hypertensive patients.

2. Patients and Methods
This cross-sectional study was conducted in Rizgary teaching hospital between March 2015 and September 2015. A total of 120 consecutive patients presenting with essential hypertension, aged ≥ 18 years and of both genders were enrolled in the study. All patients were assessed by a detailed history, physical and echocardiographic examinations. Blood samples were taken to measure the serum level of 25 (OH) vitamin D and parathyroid hormone for each patient.
The exclusion criteria were patients with secondary hypertension (diabetic nephropathy, polycystic kidney disease, renovascular hypertension, Cushing syndrome, thyroid disease), chronic renal failure or liver disease, patients with

primary hyperparathyroidism, any H/o diabetes, malabsorption, osteomalcia or osteoporosis, patients on medications like anticonvulsants, glucocorticoids and vitamin D supplements.

Based on recommendations of the Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8) [9], hypertension was defined as systolic blood pressure ≥140 mmhg and diastolic blood pressure ≥ 90 mmhg for adults aged 18 years and less than 60 years, and systolic blood pressure ≥ 150 or diastolic ≥ 90 in general population ≥ 60 years. Blood pressure measurements were taken with a mercury sphygmomanometer. Measurements were made to the nearest 2 mmhg, in the sitting position with the arm supported, and repeated after 5 minutes' rest if the first recording is high. The mean of two measurements was taken at each visit.

Transthoracic echocardiographic examinations were performed in the left lateral position. Standard M-mode, 2-Dimensional and Doppler echocardiography's were performed using (Brand: GE, Vivid E9, Model 2009) echocardiography machine. All diameters were measured according to established standards of the American Society of Echocardiography [10]. LV mass (LVM) was calculated according to the Devereux formula[11]: LVM=1.04[(LVDd + IVSth +PWT) ^{3} – (LVDd) ^{3}]-13.6.Thereafter, LV mass index (LVMI) was obtained by the following formula: LVM/body surface area (g/m$^{2)}$ [11]. In the presence of LVH, the LVM exceeds 134 grams in men and 110 grams in women per meter square body surface area (m^2 BSA).

Based on the results of the echocardiographic examination, the study sample was divided into two groups; Group I, patients with LVH (n=70) and Group II, those with non- LVH (n=50).Serum 25(OH) D and PTH concentrations were measured in both groups.

The data were collected by interviewing the patients using a questionnaire designed by the researchers. The questionnaire included information about socio-demographic data, hypertension, risk factors like hyperlipidemia, IHD, obesity, family history, history of smoking and alcoholism.

Ethical considerations

The study protocol was approved by the ethics committee of the College of Medicine of Hawler Medical University. This study was conducted by using an informed verbal consent from the patients prior to participation in the study. The purpose of the study was carefully explained to each patient.

Statistical analysis of data

Data were analyzed using the statistical package for social sciences (SPSS, version 19). Student's t test for two independent samples was used to compare means. A 'P' value of ≤ 0.05 was considered as statistically significant.

3. Results

One hundred and twenty participants with essential hypertension were included in this study, 68 (56.6%) of them were females. The mean age (±SD) of the patients was 53±11 years. The mean of serum 25(OH) D and PTH levels for the entire group were 7.9 ng/ml and 80.6 pg/ml, respectively. Other characteristics of the study population were shown in Table 1.

Vitamin D deficiency / insufficiency was present in 100 patients (83.3%), 63 patients (63%) of them with LVH. High serum level of PTH was present in 66 patients (55%), 54 patients of them (81.8 %) with LVH, as shown in Table 2.

Based on the results of the echocardiographic examination, left ventricular hypertrophy was present in 70 patients (58.3%), 42 patients (60%) of them were females.

The mean serum 25(OH) D level in patients with LVH (5.56±4.9 ng/ml) was low compared to those with non- LVH (11.29±8.3 ng/ml), while the mean serum PTH level in patients with LVH (94.33pg/ml) was high compared to those with non-LVH (60.38±21.1) (P<0.001). The mean serum calcium level for the entire group was (9.02±0.29) mg/dl and there was no statistically significant association with LVH in this study (P=0.984), as shown in Table 3.

In addition, other statistically significant differences were found between the two groups in terms of socio-demographic and clinical variables. Those include age, blood pressure (systolic and diastolic) and history of hyperlipidemia. The mean age of patients with LVH (55.5±10) was high compared to those without LVH (49.3±11) (P=0007). The mean systolic and diastolic blood pressures of patients with LVH (155.9 ±43.9 and 95.5±9.9, respectively) were high compared to those without LVH (143.87±17.11 and 91.93, respectively) (P=0.001and 0.024, respectively).When further analysis was performed with adjustments to these two factors, the same correlations between low vitamin D levels and high PTH levels with LVH were observed and remain significant. Patients with LVH had statistically significant history of hyperlipidemia (P=0.002), as shown in Table 4A and B.

4. Discussion

In the present study, the mean of serum 25(OH) D level was low (7.9 ng/ml) while that of PTH was high (80.6 pg/ml) for the entire group. 83.3% of the participants in our study had low vitamin D level. This percentage is rather high.Vitamin D deficiency is much more prevalent than previously recognized even in sunny countries [12].

Recent clinical studies showed that low levels of vitamin D are associated with a higher prevalence of hypertension and LVH [13]. Vitamin D insufficiency was present in 86% of a study sample (including hypertensive patients) in Brazil [14]. There were several reasons responsible for this deficiency in our group study. The prevalence of vitamin D deficiency increases in areas away from the equator because of increased atmospheric filtering of Ultraviolet B (UVB) radiation caused by the oblique angels of the sun's rays at higher latitudes [15]. This is very important if we know that up to 95% of the body's vitamin D requirement comes from the synthesis in the epidermis on sun exposure [16]. Modern human cultures produce less vitamin D cutaneously, in part because of increasingly indoor lifestyles, using sunscreens and by other sun avoidance strategies [17]. Wearing "Hejab" in Islamic societies may be another cause.

Vitamin D deficiency predisposes to up-regulation of rennin-angiotensin-aldosterone system and hypertrophy of both left ventricle and vascular smooth muscle cell.[3] Human studies indicate that vitamin D inhibits rennin synthesis, which may lower blood pressure [18]. Krause *et al* [19]. showed that increased exposure to UVB radiation in a tanning bed 3 times per week for3 months lead to a 180% increase in 25(OH) D levels and a 6-mm hg reduction in both systolic and diastolic pressures. Another study showed that a single dose of 100,

000 IU of vitamin D reduced systolic BP by a mean of 14-mmhg [20]. On the other hand, secondary hyperparathyroidism due to chronic vitamin D deficiency is associated with increase in blood pressure which eventually lead to LVH [5, 6]. the threshold for elevation of PTH is a 25(OH) D level of <30ng/ml. Further decreases in serum 25(OH) D levels will result in proportionally higher PTH levels. The results of this study are in parallel to other studies in confirming what has been previously mentioned [14, 15].

In this study, LVH was present in 70 patients (58.3%). The range of LVH in patients with essential hypertension is 12%-70%, depending largely on the measurement technique used [7]. The result in this study is within the expected above range.

The main findings of this cross-sectional study were that serum 25 (OH) D and PTH levels were significantly associated with left ventricular hypertrophy in our hypertensive patients. The findings of this study were consistent with prior studies [15-17]. those studies have shown a relationship between vitamin D deficiency and adverse cardiac changes, especially LVH. Moreover, vitamin D supplementation regresses both LVH and LV dysfunction in other studies [21].

Other statistically significant differences were found between the two groups that include age and blood pressure. The mean age of patients with LVH was high compared to those without LVH (P=0.007). Elderly was mentioned as one of the risk factors for vitamin D deficiency [15]. PTH level increases also with age and was a significant predictor of LVH in males older than 59 years and females younger than 60 years in some studies [22]. This relationship can be explained for females but not for males. As we have mentioned previously, there were many studies correlating PTH level with elevated BP [14, 22]. Hellstorm *et al* (1958) first described the association between elevated serum PTH level and hypertension in individuals with hyperparathyroidism [23]. A recent data from NHANES (2003-2006) study found that PTH was positively correlated with BP, and that SBP and DBP were higher in the highest quintile of PTH than in the lowest quintile [24]. The study suggested that PTH might modulate the relationship between vitamin D status and BP. The role of PTH in regulating mineral metabolism is well recognized. Increase in PTH could be indicative of other disorders such as hypercalcemia. The serum calcium level in the present study was not elevated in both groups and did not show any statistically significant association.

5. Conclusions

The results of this study suggest that low serum vitamin D and high PTH levels are associated with left ventricular hypertrophy in hypertensive patients in Erbil city-Iraq.

Conflicts of interest

The authors report no conflicts of interest

Table 1: Basic characteristics of study population.

Variable	Unit	Mean	S.D	Minimum	Maximum
Age	year	53	11	30	80
BMI	Kg/m^2	27.54	4.3	21.7	45.9
SBP	mmHg	151	18	110	200
DBP	mmHg	94	9.88	70	135
HT duration	year	3.96	4	0.1	17
BS	mg/dl	113.75	28.49	79	125
BU	mg/dl	30.47	7.9	16	49
SC	mg/dl	0.81	0.2	0.4	1.3
Cholesterol	mg/dl	201.24	38.9	100	338
TG	mg/dl	180.14	109.14	78	770
LDL	mg/dl	113	28.53	70	220
HDL	mg/dl	36.91	7.5	22	66
Vitamin D	ng/ml	7.9	7.06	2.2	43.75
PTH	pg/ml	80.67	35.19	34.7	256
S calcium	mg/gl	9.02	0.36	8.2	10.5
LVDd	mm	47.76	4.31	37	65
LVSd	mm	29.91	5.87	15	38
EF	%	65.93	8.32	50	90
IVS	mm	12.19	2.29	9	18
PW	mm	11.60	2.20	8	18
LA	mm	32.85	4.65	25	43
LVM	g	216.7	60.18	127	388
LVMI	g/m^2	117.82	31.99	72	225
RWT		0.49	0.11	0.29	0.97

Table 2: Association of LVH by vitamin D, PTH & calcium (by categorical evaluation)

Variables		LVH by echo						P value
		Not present		Present		Total		
		Frequency	%	Frequency	%	Frequency	%	
Vitamin D	Deficiency	33	37.9%	54	62.1%	87	100%	0.347
	Insufficient	4	30.8%	9	69.2%	13	100%	
	Sufficient	13	65%	7	35%	20	100%	
PTH	Normal	39	72.2%	15	27.8%	54	100%	<0.001*
	Increased	12	18.2%	54	81.8%	66	100%	
Calcium	Hypocalcemia	7	41.2%	10	58.8%	17	100%	0.522
	Normal	43	41.7%	60	58.3%	103	100%	

* Statistically significant

Table 3: Association of LVH by vitamin D, PTH & calcium (mean ±SD)

	LVH by echo	N	Mean	Std. Deviation	P value
Vitamin D	Not present	50	11.29	8.32	<0.001*
	Present	70	5.56	4.90	
PTH	Not present	50	60.38	21.13	<0.001*
	Present	70	94.33	35.98	
CA	Not present	50	9.02	0.29	0.984

* Statistically significant

Table 4 A: Association of some variables with LVH.

Variables		LVH by echo						P value
		Not present		Present		Total		
		Count	Row N %	Count	Row N %	Count	Row N %	
Smoking	No	37	46.25%	43	53.75%	80	100%	0.052
	Yes	12	30%	28	70%	40	100%	
Alcohol	No	50	43%	65	56.5%	115	100%	0.061**
	Yes	0	0%	5	100%	5	100%	
hyperlipidemia	No	27	57%	20	42.6%	47	100%	0.002*
	Yes	23	31.5%	50	68.5%	73	100%	
F History of IHD	No	43	43%	57	57%	100	100%	0.532**
	Yes	7	35%	13	65%	20	100%	
BMI	Normal	19	48.7%	20	51.3%	39	100%	0.280
	Overweight & obese	31	38.3%	50	61.7%	81	100%	

*statistically significant ** Fisher's exact test

Table 4B: Comparison between the means of the two study groups regarding basic characteristics, clinical variables, and echocardiographic parameters.

LVH by echocardiography (N=53)					
Variables	Group I (LVH) N=70		Group II (Non-VH) N=50		p
	Mean	SD	Mean	SD	
Age	55.5	10.1	49.35	11.4	0.007
BMI	27.85	4.17	27	4.59	0.369
SBP	155.9	43.9	143.87	17.11	0.001
DBP	95.5	9.9	91	9.3	0.024
S Cholesterol	207.73	33	191.5	45	0.055
TG	183.95	113.7	177.6	106.8	0.78
LDL	116.7	26.9	107.4	30.2	0.122
HDL	36.72	8.11	37.2	6.5	0.764
LVDd	47.08	4.29	48.77	4.19	0.054
LVSd	27.93	6.1	32.87	3.9	<0.0001
EF	68.2	8.9	62.52	5.81	0.0006
IVS	13.77	1.43	9.82	0.78	<0.0001
PW	13.09	1.51	9.37	0.62	<0.0001
Left atrium	33.68	4.99	31.6	3.81	0.027
LVM	250.35	52.16	166.22	26.87	<0.0001
LVMI	135.3	29.05	91.6	12.11	<0.0001
RWT	0.56	0.08	0.38	0.05	<0.0001

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