

## CLOSE ASSOCIATION BETWEEN PARATHYROID HORMONE AND LEFT VENTRICULAR FUNCTION AND STRUCTURE IN END-STAGE RENAL FAILURE PATIENTS UNDER MAINTENANCE HEMODIALYSIS

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**Background:** Cardiovascular risk factors are a significant burden in end-stage renal disease patients under hemodialysis and are the leading cause of death among these patients. The influence of parathyroid hormone (PTH) on myocardial function as a toxin of uremia is under more attention and evaluation because of growing evidence showing that the effects of PTH on cardiac function may be the most serious consequence of secondary hyperparathyroidism in renal failure. In this study we determined role of excess PTH in the development of left ventricular (LV) hypertrophy as well as LV ejection fraction in patients with end-stage renal disease under regular hemodialysis. **Methods:** This study is cross-sectional that was done on patients with end-stage renal disease (ESRD) undergoing maintenance hemodialysis treatment. For patients, Calcium, Phosphorus, Alkaline phosphatase and Intact PTH (iPTH) were measured. Hypertensive patients were stratified into stages one to three. Ecocardiographies for LV hypertrophy and ejection fraction (%) were done and patients stratified into normal, mild, moderate and severe LV hypertrophy. **Results:** The total patients were 73 (F=28 M=45), consisting of 58 non diabetic hemodialysis patients (F=22 M=36), and 15 diabetic hemodialysis patients (F=6 M=9). The mean age was  $46.5 \pm 16$  years. The time on hemodialysis was  $21.5 \pm 23.5$  months. The LV ejection fraction (EF%) were  $51 \pm 8$  percent. 'iPTH' of patients was  $309 \pm 349$  Pg/ml. 'iPTH' of diabetic and nondiabetic groups was  $234 \pm 265$  pg/ml and  $329 \pm 368$  pg/ml respectively. Serum alkaline phosphatase was  $413 \pm 348$  IU/L. Serum alkaline phosphatase of diabetic and nondiabetic groups were  $295 \pm 179$  IU/L and  $443 \pm 375$  IU/L respectively. Serum albumin was  $4 \pm 0.75$  g/dl. Serum albumin of diabetic and nondiabetic groups was  $3.6 \pm 0.7$  g/dl and  $4.2 \pm 0.7$  g/dl respectively. Significant inverse correlation of serum ALP with percent of LV ejection fraction and marginal positive correlation of serum ALP with LVH and also marginal correlation of serum iPTH with LVH were seen. Also significant inverse correlation between serum iPTH with percent of LV ejection fraction in non diabetic heart patients was observed. **Conclusions:** Adverse effects of secondary hyperparathyroidism on LV function and structure in this study show the role of excess PTH in the development of left ventricular (LV) hypertrophy as well as low LV ejection fraction in patients with end-stage renal disease under hemodialysis which needs more attention to control of secondary hyperparathyroidism to reduce the risk of cardiovascular morbidity and mortality in dialysis patients. **Keywords:** Hemodialysis, Left ventricular hypertrophy, Ejection fraction, Secondary hyperparathyroidism

### INTRODUCTION

Cardiovascular disease is the most common cause of death in patients with end-stage renal disease (ESRD) and accounts for much of the morbidity in this population<sup>1</sup>. Dialysis patients are subject to atherosclerosis and consequent ischemic heart disease, but myocardial dysfunction and overt heart failure also are highly prevalent. Eighty-four percent of patients have left ventricular hypertrophy (LVH), left ventricular (LV) dilatation, or low fractional shortening at the initiation of ESRD therapy, and LVH has been found in 38% of patients with chronic renal failure (CRF) prior to the requirement for dialysis<sup>1-2</sup>. The presence of LVH or LV dilatation (or both) is clearly a poor prognostic factor<sup>2-3</sup>. Parathyroid hormone (PTH) is one of the factors that has been implicated in the pathogenesis of a number of cardiovascular abnormalities seen in association with renal failure<sup>2-4</sup>. Adverse effect of excess PTH on cardiac function was first hypothesized by Selye and by Lehr<sup>2</sup>. A substantial amount of evidence now exists that suggests a role for excess PTH and the changes in ion regulation induced by PTH in the pathogenesis of uremic cardiomyopathy<sup>4,5</sup>. A direct effect of PTH on myocardial contractility has not been demonstrated in human adult myocytes, but the cellular influx of calcium induced by PTH has been shown to increase contractility in animal cells<sup>2</sup>. Indeed, myocardial and vascular cells are a target for PTH *via* specific receptors on their membranes, experimental studies have shown that PTH produces positive inotropic and chronotropic effects on isolated cardiomyocytes, which occur in association with increased intracellular calcium and cAMP activity<sup>4-6</sup>. On the other hand, PTH indirectly reduces myocardial contractility<sup>2</sup>. Albeit, the clinical significance of these effects is not fully understood, but, in the terms of LV structural changes, evidence suggests that PTH may play a role in the development of cardiac interstitial fibrosis via the permissive activation of cardiac fibroblasts<sup>6-7</sup>. There is growing evidence for a role for PTH in the development of LVH.<sup>7-9</sup> Cardiac fibrosis is known to be associated with uremia<sup>2</sup> and may contribute to diminished LV compliance and consequently

diastolic dysfunction in these patients.<sup>7-9</sup> In animal models PTH has been shown to activate fibroblasts and to promote the development of intramyocardial fibrosis which is a hallmark of left ventricular hypertrophy in chronic uraemia.<sup>6,8-10</sup> Despite the commonly seen abnormalities in serum calcium and phosphate in dialysis patients, only a few studies exist regarding the association between high serum PTH level and left ventricular function and structure in hemodialysis patients, we therefore aimed to consider the evidences regarding the role of excess PTH in the development of left ventricular (LV) hypertrophy as well as LV ejection fraction in patients with end-stage renal disease under regular hemodialysis .

## **MATERIAL AND METHODS**

This study was carried out on patients with end-stage renal disease (ESRD) undergoing maintenance hemodialysis (HD) treatment. Exclusion criteria were cigarette smoking, body mass index (BMI) more than 25, recent MI and vascular diseases as well as active or chronic infection and pericarditis or pericardial effusion in echocardiography. For patients serum calcium (Ca), phosphorus (P), Alkaline phosphatase (ALP) were measured by standard kits and Intact PTH (iPTH) with DSL-8000 kits by RIA was measured. For stratification of hypertensive patients according to the sixth and seventh report of the joint national committee on prevention, detection, evaluation and treatment of high blood pressure we stratified hypertensive patients from stage one to three<sup>11,12</sup> (stage of zero equal to no hypertension) stages of the hypertension of HD patients were considered before treatment and at the first start of hemodialysis treatment. For heart echocardiography (2D & doppler ) one single cardiologist who was unaware of the patients data performed all ecocardiographies for determination of left ventricular hypertrophy and left ventricular (LV) ejection fraction (in percent). On the base of septal thickness we stratified the patients into no LVH (septal thickness between 6-11mm), mild (septal thickness between 11-15mm), moderate (septal thickness between 15-18mm) and severe LVH (septal thickness >18mm). The LVH measurements were done at the end diastolic phase and percent of LV ejection fraction between 55to 75% was considered normal. For statistical analysis descriptive data are expressed as Mean±SD and as frequency distributions. Comparison between groups were performed by using T test. For correlations we used spearman rho and Partial correlation test after adjustment for age and duration of hemodialysis treatment . All statistical analysis were performed using SPSS (version 11.00) and statistical analysis was significance when p value< 0.05.

## **RESULTS**

The total patients were 73 (F=28 M=45) consisting of 58 non diabetic hemodialysis patients (F=22 M=36), and 15 diabetic hemodialysis patients (F=6 M=9). Tables 1 and 2 show the mean± SD of ages, the length of the time the patients have been on hemodialysis and percent of LV ejection fraction as well as lab data, tables 3, 4 and 5 show the frequency distributions of stages of hypertension, chest pain and stages of LVH. The ages of patients were 46.5±16 years. The length of the time patients have been on hemodialysis were 21.5±23.5months. The percent of LV ejection fraction (EF%) were 51±8 percent and 24% of patients had chest pain. Mean±SD of 'iPTH' of total patients was 309±349Pg/ml. 'iPTH' of diabetic group and nondiabetic group were 234±265 pg/ml and 329±368 pg/ml respectively. Serum alkaline phosphatase of total patients was 413±348 IU/L .Serum alkaline phosphatase of diabetic group and nondiabetic group were 295±179 IU/L and 443±375 IU/l respectively. Mean±SD of serum albumin of total patients was 4±0.75 g/dl. Serum albumin of diabetic group and nondiabetic group were 3.6±0.7 g/dl and 4.2±0.7 g/dl respectively. There were no significant difference of age of patients, duration of hemodialysis treatment, serum ALP and serum iPTH between two groups of diabetic and nondiabetic hemodialysis (HD) patients (p>0.05). There was a significant difference of serum albumin between two groups of diabetic and nondiabetic HD patients(p =0.002). Significant difference of percent of LV ejection fraction(EF%) in two groups was found(47±8 % versus 52±7.8 % respectively)(p =0.026). Significant difference of Ca xP products (46±19 versus 61±24 in non DM-HD patients ) between two groups was seen(p=0.037). In this study there was a significant positive correlation between hypertension with left ventricular hypertrophy(LVH) (r =0.606 p<0.001).

**Table 1: Mean  $\pm$ SD , Minimum and Maximum of age, duration of hemodialysis treatment and LV ejection fraction.**

		Age (years)	D.H.T* (months)	LV-EF**, (percent)
Total patients	Mean $\pm$ SD	51 $\pm$ 16	21.5 $\pm$ 23.5	51 $\pm$ 8
	Min	15	1	30
	Max	78	112	70
Diabetic group	Mean $\pm$ SD	58 $\pm$ 16	22 $\pm$ 23	47 $\pm$ 8
	Min	27	1	30
	Max	78	72	55
Non-diabetic group	Mean $\pm$ SD	49 $\pm$ 15.6	21 $\pm$ 24	52 $\pm$ 7.8
	Min	15	1	30
	Max	78	112	70

\*duration of hemodialysis treatment, \*\*LV ejection fraction.

**Table 2: Mean  $\pm$ SD , Minimum and Maximum of laboratory data in hemodialysis patients**

		iPTH* (Pg/ml)	ALP (IU/l)	CaxP (products)	Albumin (g/dl)
Total patients	Mean $\pm$ SD	309 $\pm$ 349	413 $\pm$ 348	58 $\pm$ 24	4 $\pm$ 0.75
	Min	10	100	18	2
	Max	2235	2438	135	6.8
Diabetic group	Mean $\pm$ SD	234 $\pm$ 265	295 $\pm$ 179	46 $\pm$ 19	3.6 $\pm$ 0.7
	Min	10	120	18	2
	Max	900	734	74	4.6
Non-diabetic group	Mean $\pm$ SD	329 $\pm$ 368	443 $\pm$ 375	61 $\pm$ 24	4.2 $\pm$ 0.7
	Min	20	100	25	2.5
	Max	2235	2438	135	6.8

\*Intact PTH

**Table 3 : Frequency distribution of stages of hypertension (HTN) in hemodialysis patients.**

Stages of HTN	Total patients		DM group*		Non-DM group	
	Number	Percent	Number	Percent	Number	Percent
0	7	9.6	0	0	7	12.1
1	7	9.6	1	6.7	6	10.3
2	40	54.8	10	66.7	30	51.7
3	19	26	4	26.7	15	25.9

\*DM=Diabetes Mellitus.

**Table 4: Frequency distribution of chest pain in hemodialysis patients**

Chest pain	Total patients		Diabetic patients		Non diabetic patients	
	Number	Percent	Number	Percent	Number	Percent
Yes	24	32.9	7	46.9	17	29.3
No	49	67.1	8	53.3	41	70.7

**Table 5 : Frequency distribution of Left ventricular hypertrophy(LVH) in hemodialysis patients**

	Total patients		Diabetic patients		Non diabetic patients	
	Number	Percent	Number	Percent	Number	Percent
No LVH	12	16.4	1	6.7	11	19
Mild LVH	34	46.6	7	46.7	27	46.6
Modrate LVH	23	31.5	6	40	17	29.3

Severe LVH	4	5.5	1	6.7	3	5.2
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Significant linear inverse correlation between hypertension with percent of LV ejection fraction was observed too ( $r = -0.197$   $p = 0.047$ ). Significant positive correlation between hypertension with Ca x P products of patients ( $r = 0.231$   $p = 0.027$ ) was demonstrated also significant inverse correlation between LVH with percent of LV ejection fraction was observed ( $r = -0.423$   $p < 0.001$ ).

Partial correlation test after adjustment for ages of subjects, duration of hemodialysis treatment and also serum albumin showed significant positive correlation between serum iPTH and serum ALP ( $r = 0.302$   $p = 0.005$ ) more over significant linear inverse correlation between serum ALP with percent of LV ejection fraction was observed ( $r = -0.359$   $p = 0.001$ ) (figure 1) too.

Significant linear inverse correlation between serum iPTH with percent of LV ejection fraction in non diabetic HD patients was found ( $r = -0.319$   $p = 0.009$ ) (Figure2). Marginal correlation of serum ALP with LVH ( $r = 0.171$   $p = 0.050$ ) was observed. Partial correlation test after adjustment for serum albumin and ALP showed significant positive correlation between serum iPTH with LVH ( $r = 0.305$   $p = 0.005$ ) in total patients. Partial correlation test after adjustment for serum iPTH, ALP, age and duration of hemodialysis treatment showed marginal correlation of Ca x P products of patients with percent of LV ejection fraction in total patients ( $r = 0.188$   $P = 0.050$ ) (figure3).

**Figure1: Significant linear inverse correlation between serum ALP with percent of LV ejection fraction ( $r = -0.359$   $p = 0.001$ ) (Partial correlation test).**

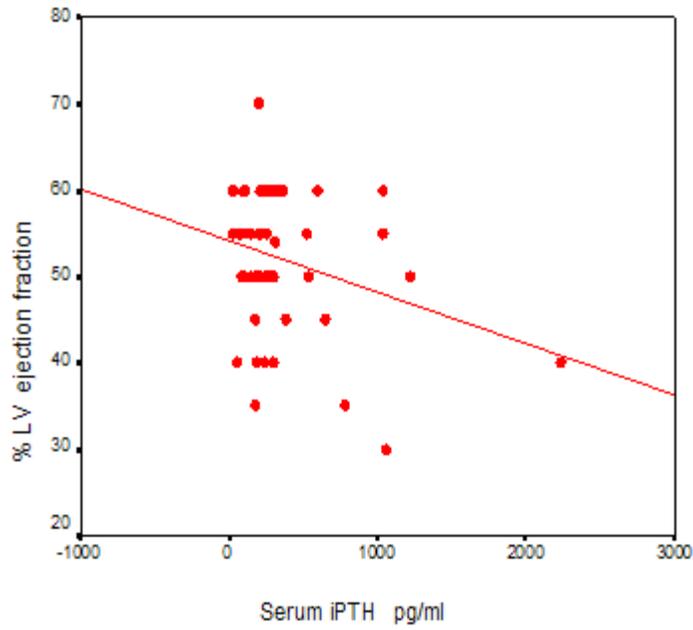
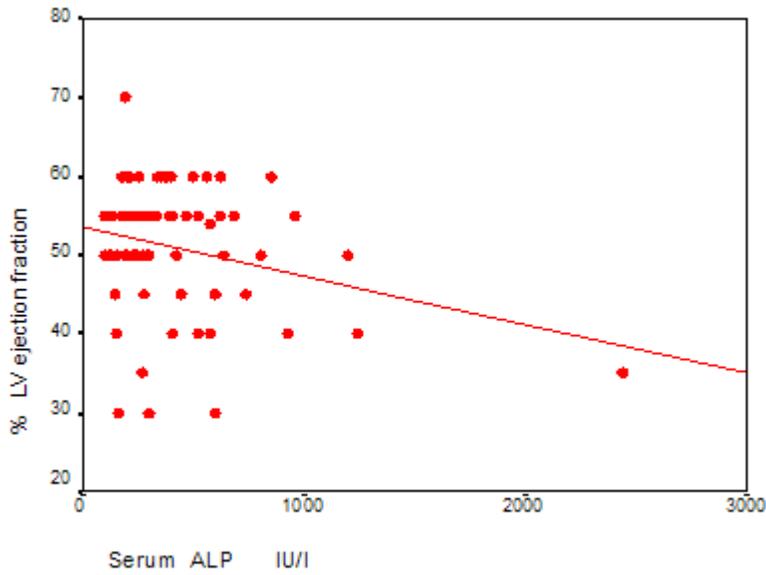
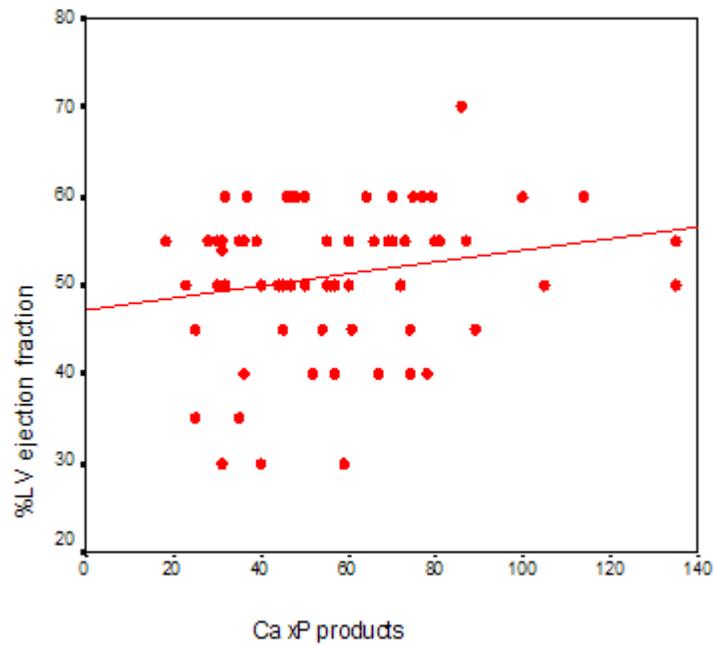


Figure2: Significant linear inverse co



relation between serum  
 iPTH with percent of LV ejection fraction in non diabetic HD patients was found too ( $r = -0.319$   
 $p=0.009$ ) (Partial correlation test).



**Figure 3: Marginal correlation of Ca x P products of patients with percent of LV ejection fraction in total patients (  $r=0.188$   $P=0.050$ )( Partial correlation test).**

## DISCUSSION

The principle findings of this study were positive significant correlation between serum iPTH with LVH, significant inverse correlation of serum ALP with percent of LV ejection fraction, marginal correlation of serum ALP with LVH, and significant inverse correlation between serum iPTH with percent of LV ejection fraction in non diabetic HD patients, marginal correlation of serum iPTH with LVH. Salem in a cross-sectional study in a random sample of 612 hemodialysis patients from 10 dialysis centers examined serum PTH and calcium levels, it was found that 25% of patients had serum PTH levels within the normal range, 25% had a PTH higher than normal (but less than three times normal), and 50% had PTH levels higher than three times normal values, diabetic patients had PTH levels lower than those of nondiabetic patients, results of this study means that hyperparathyroidism are highly prevalent in the hemodialysis population.<sup>1,3</sup> Drueke et al found that correction of severe hyperparathyroidism led to a significant improvement in cardiac performance.<sup>14</sup> Timio showed a linear relationship between serum PTH levels and LV mass in dialysis patients.<sup>15</sup> Rostand and Drueke reviewed the link between elevated PTH and cardiovascular disease in chronic renal failure patients, they found that elevated PTH was associated with left ventricular hypertrophy and increase left ventricular mass.<sup>16</sup> Kyu-Ha et al. on 62 chronic renal failure patients not yet on dialysis demonstrated that intact PTH was significantly higher in the patients group with LVH compared to without.<sup>17</sup> Strozecki et al in a study on 65 HD patients found that LV mass index was lower in normotensive HD patients<sup>18</sup>. Recently Wanic-Kossowska et al. in 59 HD patients showed positive correlation between PTH serum concentration and LV mass<sup>19</sup>. Massry has reported an association between excess PTH and a decrease in left ventricular ejection fraction<sup>20</sup>. Lowrie and Lew<sup>21</sup> in a cross-sectional study of more than 12,000 hemodialysis patients, and Foley et al.<sup>22</sup> followed 433 patients starting ESRD therapy for an average of 41 months, in both studies, they found that high alkaline phosphatase levels, a marker of hyperparathyroidism, was a significant predictor of death. In an observational study of 189 nondiabetic ESRD patients, Harnett et al. found that an elevated serum alkaline phosphatase, which correlates well with the presence of hyperparathyroidism, was a significant predictor of LVH in a subset of patients on dialysis, for patients with severe LVH, a high alkaline phosphatase was an even better predictor of LVH than was diastolic blood pressure<sup>23</sup>. In another large cross-sectional study of hemodialysis patients Block et al. showed elevated PTH was a predictor of increased mortality<sup>24</sup>. In the study of Drueke et al. a significant improvement in cardiac-function was observed after parathyroidectomy, in this research, Drueke, measured various parameters before and 1-2 weeks after parathyroidectomy in 22 hemodialysis patients with secondary hyperparathyroidism, these patients had significant cardiac dysfunction before surgery, with a mean LV ejection fraction of  $50.6 \pm 2.7\%$  as measured by radionuclide ventriculography, a significant increase in ejection fraction, cardiac index, and myocardial fiber-shortening velocity was observed postoperatively<sup>14</sup>. Hara et al. in a study on 46 hemodialysis patients, showed LV impairment was existed in 80% of hemodialysis patients, no correlation between PTH level and LV ejection fraction was existed, except in a subgroup of patients with an intact PTH level greater than 200 pg/mL, despite this, there was a significant reduction in LV mass and an improvement in LV ejection fraction after parathyroidectomy<sup>25</sup>, interestingly Nagashima et al. reported A 52-year-old woman, who was a hemodialysis patient that was admitted because of exertional dyspnea, echocardiography showed left ventricular (LV) dilatation and reduced contraction. Coronary angiography showed no fixed stenosis. She had elevated levels of parathyroid hormone as a result of secondary hyperparathyroidism with advanced renal failure. After parathyroidectomy, marked improvement of LV function following immediate decrease of blood levels of PTH was observed<sup>26</sup>. Park et al. could show that treatment of secondary hyperparathyroidism with intravenous calcitriol resulted in

significant attenuation of myocardial hypertrophy<sup>27</sup> In this study we could show the adverse effect of secondary hyperparathyroidism on LV function and structure, as well as in the studies mentioned above, suggest that the effects of PTH on cardiac function may be the most serious consequence of secondary hyperparathyroidism in renal failure. Elevation of PTH have recently been associated with increase mortality rate among dialysis patients<sup>28-29</sup>. Regardless of the implications for cardiovascular disease, however, it is accepted that secondary hyperparathyroidism should be controlled to prevent renal osteodystrophy, likewise, serum calcium and phosphate levels should be carefully regulated to assist in PTH control and avoid the complications of an elevated  $\text{Ca} \times \text{PO}_4$ . These measures may serve to reduce the risk of cardiovascular morbidity and mortality in dialysis patients. In the meantime, further clinical study into this important aspect of the care of ESRD patients is needed.

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