

## CLINICAL STUDY

## Close association between parathyroid hormone and left ventricular function and structure in end-stage renal failure patients under maintenance hemodialysis

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### Abstract

**Objectives:** Cardiovascular risk factors are a significant burden in end-stage renal disease patients under hemodialysis and cardiovascular-related diseases are the leading cause of death among these patients and are responsible for almost half of all deaths in dialysis patients. In this study we aimed to consider the role of excess PTH in the development of left ventricular hypertrophy (LVH) and LV ejection fraction in patients with end-stage renal disease under regular hemodialysis.

**Patients and methods:** This study is cross-sectional, and was done in patients with end-stage renal disease (ESRD) undergoing maintenance hemodialysis treatment. Calcium, Phosphorus, Alkaline phosphatase and Intact PTH (iPTH) were measured. Hypertensive patients were stratified into three stages. The total of 73 patients (F=28, M=45) consisted of 58 non-diabetic hemodialysis patients (F=22, M=36) and 15 diabetic hemodialysis patients (F=6, M=9).

**Results:** Significant inverse correlation of serum ALP with percent age of LV ejection fraction, marginal correlation of serum ALP with LVH and marginal correlation of serum iPTH with LVH were observed. Also significant inverse correlation of serum iPTH with percent age of LV ejection fraction in non diabetic HD 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. (Tab. 5, Fig. 3, Ref. 29.)

**Key words:** hemodialysis, left ventricular hypertrophy, ejection fraction, secondary hyperparathyroidism.

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 (1). Dialysis patients are subject to atherosclerosis and consequent ischemic heart disease, but myocardial dysfunction and overt heart failure are also 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 (1, 2). The presence of LVH or LV dilatation (or both) is clearly a poor prognostic factor (2, 3). Parathyroid hormone (PTH) is one of the factors that have been implicated in the pathogenesis of a number of cardiovascular abnormalities seen in association with renal failure (2, 3, 4), adverse effect of excess PTH on cardiac

function was first hypothesized by Selye and by Lehr (2). 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 (4, 5). A direct effect of PTH on myocardial contractility has not been demon-

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**Tab. 1. Mean±SD, minimum and maximum age, duration of hemodialysis treatment and LV ejection fraction.**

		Age (years)	DHT* (months)	EF** (%)
All pts	mean±SD	51±16	21.5±23.5	51±8
	min	15	1	30
	max	78	112	70
Diabetic group	mean±SD	58±16	22±23	47±8
	min	27	1	30
	max	78	72	55
Non-diabetic group	mean±SD	49±15.6	21±24	52±7.8
	min	15	1	30
	max	78	112	70

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

**Tab. 2. Mean±SD, minimum and maximum of lab data in hemodialysis patients.**

		iPTH* (pg/ml)	ALP (IU/l)	CaxP (products)	Albumin (g/l)
All pts	mean±SD	309±349	413±348	58±24	4±0.75
	min	10	100	18	2
	max	2235	2438	135	6.8
Diabetic group	mean±SD	234±265	295±179	46±19	3.6±0.7
	min	10	120	18	2
	max	900	734	74	4.6
Non-diabetic group	mean±SD	329±368	443±375	61±24	4.2±0.7
	min	20	100	25	2.5
	max	2235	2438	135	6.8

\* intact PTH

strated in human adult myocytes. But the cellular influx of calcium induced by PTH has been shown to increase contractility in animal cells (2). 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 (4, 5, 6). On the other hand PTH indirectly reduces myocardial contractility (2). Although, the clinical significance of these effects is not fully understood but in the terms of LV structural changes, evidences suggests that PTH may play a role in the development of cardiac interstitial fibrosis via the permissive activation of cardiac fibroblasts (6, 7). There is growing evidence for a role of PTH in the development of LVH (7, 8, 9). Cardiac fibrosis is known to be associated with uremia (2) and may contribute to diminished LV compliance and consequently diastolic dysfunction in these patients (7, 8, 9). 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 uremia (6, 8, 9, 10) 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.

### Patients and methods

This study is cross-sectional and was performed in patients with end-stage renal disease (ESRD) undergoing maintenance hemodialysis treatment. Exclusion criteria were cigarette smoking, body mass index (BMI) more than 25, recent MI and vascular diseases and active or chronic infection and also pericarditis or pericardial effusion shown by echocardiography. Serum calcium (Ca), phosphorus (P), Alkaline phosphatase (ALP) were measured by standard kits. Intact PTH (iPTH) was measured by RIA with DSL-8000 kits from USA. 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 (11, 12) (stage of zero equal to no presence of HTN) 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

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

Stages of HTN	All patients		Diabetes mellitus group		Non-diabetes mellitus group	
	No	%	No	%	No	%
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

**Tab. 4. Frequency distribution of chest pain in hemodialysis patients.**

Chest pain	All patients		Diabetic patients		Non-diabetic patients	
	No	%	No	%	No	%
Yes	24	32.9	7	46.9	17	29.3
No	49	67.1	8	53.3	41	70.7

**Tab. 5 Frequency distributions of left ventricular hypertrophy (LVH) in hemodialysis patients.**

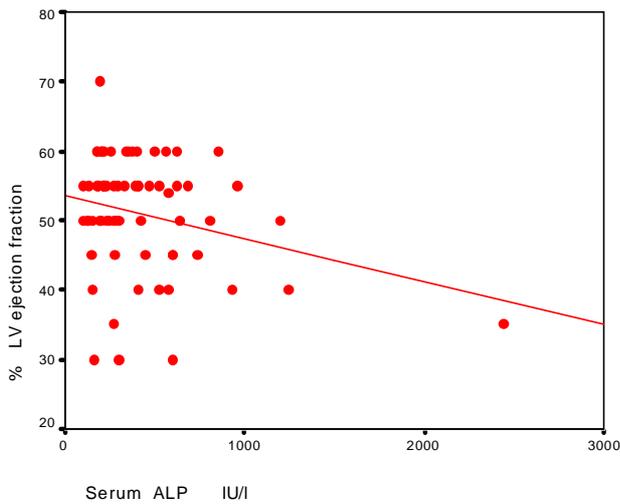
LVH	All patients		Diabetic patients		Non-diabetic patients	
	No	%	No	%	No	%
No	12	16.4	1	6.7	11	19
Mild	34	46.6	7	46.7	27	46.6
Moderate	23	31.5	6	40	17	29.3
Severe	4	5.5	1	6.7	3	5.2

data performed all echocardiographies for 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 6–11 mm), mild (septal thickness between 11–15 mm), moderate (septal thickness between 15–18 mm) and severe LVH (septal thickness >18 mm). The LVH measurements were done at the end-diastolic phase and percentage of LV ejection fraction between 55 and 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 analyses were performed using SPSS (version 11.00) and statistical analysis was significant when p value was <0.05.

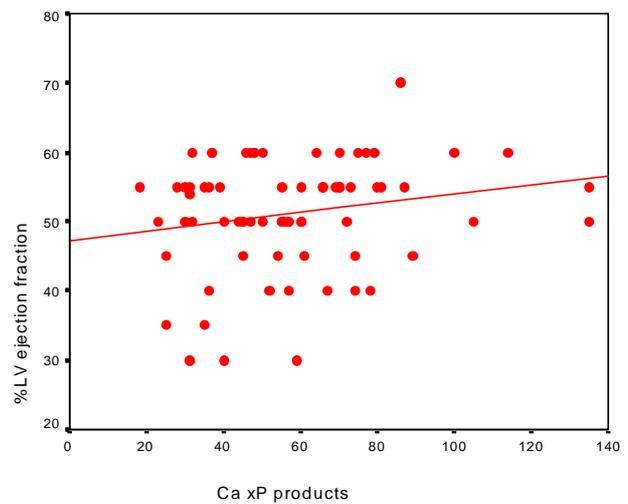
## Results

The total number of patient, 73 (F=28, M=45) consisted 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 percentage of LV ejection fraction and

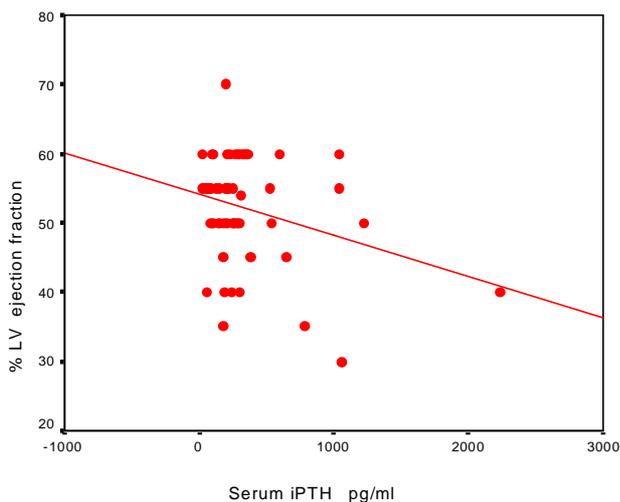
lab data. Tables 3, 4 and 5 show the frequency distributions of stages of HTN, chest pain and stages of LVH. The ages of patients were 46.5±6 years. The period the patients have been on hemodialysis was 21.5±23.5 months. The percent of LV ejection fraction (EF %) was 51±8 percent and 24 % of patients had chest pain. Mean±SD of iPTH of all patients was 309±349 pg/ml. iPTH of diabetic group and non-diabetic group were 234±265 pg/ml and 329±368 pg/ml, respectively. Serum alkaline phosphatase of all patients was 413±348 IU/L. Serum alkaline phosphatase of diabetic group and non-diabetic group were 295±179 IU/L and 443±375 IU/l, respectively. Mean±SD of serum albumin of all patients was 4±0.75 g/dl. Serum albumin of diabetic group and non-diabetic group were 3.6±0.7 g/dl and 4.2±0.7 g/dl, respectively. There were no significant differences in age of patients, duration of hemodialysis treatment, serum ALP and serum iPTH between the two groups of diabetic and non-diabetic hemodialysis (HD) patients. There was a significant difference of serum albumin between two groups of diabetic and non-diabetic HD patients (p=0.002) and significant difference of percentage of LV ejection fraction (EF %) in two groups (47±8 % versus 52±7.8 % respectively) (p=0.026) was found. Significant difference of CaxP products (46±19 versus 61±24 in non DM-HD patients) (p=0.037) was also observed. In this study



**Fig. 1. Significant linear inverse correlation between serum ALP and percentage of LV ejection fraction ( $r=-0.359$ ,  $p=0.001$ ) (partial correlation test).**



**Fig. 3. Marginal correlation of CaxP products of patients with percentage of LV ejection fraction in all patients ( $r=0.188$ ,  $p=0.050$ ) (partial correlation test).**



**Fig. 2. Significant linear inverse correlation between serum iPTH with percentage of LV ejection fraction in non diabetic HD patients was also found too ( $r=-0.319$ ,  $p=0.009$ ) (partial correlation test).**

there was a significant positive correlation between stages of hypertension and left ventricular hypertrophy (LVH) ( $r=0.606$ ,  $p<0.001$ ), and significant linear inverse correlation between stages of hypertension and percentage of LV ejection fraction observed ( $r=-0.197$ ,  $p=0.047$ ). Significant positive correlation between stages of hypertension with CaxP products of patients ( $r=0.231$ ,  $p=0.027$ ) was demonstrated. Significant linear inverse correlation between LVH with percentage of LV ejection fraction was observed ( $r=-0.423$ ,  $p<0.001$ ). Partial correlation test after adjustment for age of patients, duration of hemodialysis treatment and also serum albumin showed significant positive correlation between serum iPTH and serum ALP ( $r=0.302$ ,  $p=0.005$ ) also significant linear inverse correlation between se-

rum ALP with percentage of LV ejection fraction was observed ( $r=-0.359$ ,  $p=0.001$ ) (Fig. 1). Significant linear inverse correlation between serum iPTH with percent of LV ejection fraction in non diabetic HD patients was found ( $r=-0.319$ ,  $p=0.009$ ) (Fig. 2). 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 and stages of LVH ( $r=0.305$ ,  $p=0.005$ ) in all patients. Partial correlation test after adjustment for serum iPTH, ALP, age and duration of hemodialysis treatment showed marginal correlation of CaxP products of patients with percent of LV ejection fraction in all patients ( $r=0.188$ ,  $p=0.050$ ) (Fig. 3).

## Discussion

The principle findings of this study were positive significant correlation between serum iPTH and LVH, significant inverse correlation of serum ALP with percentage of LV ejection fraction, marginal correlation of serum ALP with LVH. Significant inverse correlation between serum iPTH with percentage of LV ejection fraction in non diabetic HD patients and marginal correlation of serum iPTH with LVH in all patients were the important findings. Salem examined serum PTH and calcium levels in a cross-sectional study in a random sample of 612 hemodialysis patients from 10 dialysis centers, 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 non-diabetic patients, results of this study demonstrated that hyperparathyroidism is highly prevalent in the hemodialysis population (13). Druke et al found that correction of severe hyperparathyroidism led to a significant improvement in cardiac performance (14), Timio showed a linear relationship between serum PTH

levels and LV mass in dialysis patients (15). Rostand and Druke 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 increased left ventricular mass (16). Kyu-Ha et al demonstrated in 62 chronic renal failure patients not yet on dialysis that intact PTH was significantly higher in patients with LVH compared to those without (17). Strozecki et al in a study in 65 HD patients found that LV mass index was lower in normotensive HD patients (18). Recently Wanic-Kossowska et al in 59 HD patients showed positive correlation between PTH serum concentration and LV mass (19). Massry has reported an association between excess PTH and a decrease in left ventricular ejection fraction (20). Lowrie and Lew in a cross-sectional study of more than 12,000 hemodialysis patients, and Foley et al in a study following 433 patients starting ESRD therapy for an average of 41 months, found that high alkaline phosphatase levels, a marker of hyperparathyroidism, was a significant predictor of death (21, 22). In an observational study of 189 non-diabetic 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 (23). In another large cross-sectional study of hemodialysis patients Block et al showed elevated PTH was a predictor of increased mortality (24). In the study of Druke et al a significant improvement in cardiac-function was observed after parathyroidectomy, in this research, Druke 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 (14). Hara et al in a study on 46 hemodialysis patients, showed LV impairment in 80% of hemodialysis patients, no correlation between PTH level and LV ejection fraction was observed, 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 (25), 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 (26). Park et al could show that treatment of secondary hyperparathyroidism with intravenous calcitriol resulted in significant attenuation of myocardial hypertrophy (27). In this study we could show the adverse effect of secondary hyperparathyroidism on LV function and structure, as well as in the stud-

ies mentioned above, suggesting that the effects of PTH on cardiac function may be the most serious consequence of secondary hyperparathyroidism in renal failure, elevation of PTH has recently been associated with increase mortality rate among dialysis patients (28, 29). 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 complications of an elevated  $\text{CaPO}_4$ . These measures may serve for reduction of the risk of cardiovascular morbidity and mortality in dialysis patients. In the meantime, further clinical study on this important aspect of the care of ESRD patients is needed.

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