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The role of secondary hyperparathyroidism in left ventricular hypertrophy of patients under chronic hemodialysis

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Abstract

End-stage renal disease (ESRD) patients frequently develop structural cardiac abnormalities, particularly left ventricular hypertrophy (LVH). The mechanisms involved in these processes are not completely understood. In the present study, we evaluated a possible association between parathyroid hormone (PTH) levels and left ventricular mass (LVM) in patients with ESRD. Stable uremic patients on intermittent hemodialysis treatment were evaluated by standard two-dimensional echocardiography and their sera were analyzed for intact PTH. Forty-one patients (mean age 45 years, range 18 to 61 years), 61% males, who had been on hemodialysis for 3 to 186 months, were evaluated. Patients were stratified into 3 groups according to serum PTH: low levels (<100 pg/ml; group I = 10 patients), intermediate levels (100 to 280 pg/ml; group II = 10 patients) and high levels (>280 pg/ml; group III = 21 patients). A positive statistically significant association between LVM index and PTH was identified (r = 0.34; P = 0.03, Pearson's correlation coefficient) in the sample as a whole. In subgroup analyses, we did not observe significant associations in the low and intermediate PTH groups; nevertheless, PTH and LVM index were correlated in patients with high PTH levels (r = 0.62; P = 0.003). LVM index was also inversely associated with hemoglobin (r = -0.34; P = 0.03). In multivariate analysis, after adjustment for age, hemoglobin, body mass index, and blood pressure, the only independent predictor of LVM index was PTH level. Therefore, PTH is an independent predictor of LVH in patients undergoing chronic hemodialysis. Secondary hyperparathyroidism may contribute to the elevated cardiovascular morbidity associated with LVH in ESRD.

Key words
- End-stage renal failure
- Parathyroid hormone
- Echocardiography
- Left ventricular hypertrophy

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Introduction

End-stage renal disease (ESRD) has been associated with changes in the structure and function of the myocardium (1). A significant percentage of patients who start dialysis treatment have cardiac abnormalities, particularly left ventricular hypertrophy (LVH) (2). Likewise, approximately 70% of the patients under chronic hemodialysis treatment present LVH (2,3). Different conditions have been implicated in the pathogen-

esis of ESRD-related LVH, such as hypertension, chronic anemia, arteriovenous fistulas, concurrent ischemic heart disease, and hypoalbuminemia. These factors have independent effects, which possibly act synergistically leading to LVH and its related morbidity and mortality (4,5).

Recently, parathyroid hormone (PTH) has been identified as an important cardiotoxin in ESRD. Previous studies have supported the view that high PTH serum levels in uremic patients may cause deleterious effects in myocardium metabolism and function (4). The association between PTH levels and LVH has been reported by some investigators, with inconsistent results (6-9). The present study was therefore conducted to evaluate the independent association between intact PTH levels and the presence of LVH in end-stage stable uremic patients under chronic hemodialysis, in whom other known risk factors for LVH were not present.

Material and Methods

Subjects

Forty-one adult ESRD patients receiving renal replacement therapy with hemodialysis for at least three months were included. Patients with diabetes mellitus, severe anemia (hematocrit <20%), body mass index (BMI) <15 kg/m^2, coronary artery disease, uncontrolled hypertension, primary or secondary cardiomyopathies, known valvular heart disease or pericarditis, a history of heavy alcohol consumption associated with altered liver function tests, parathyroidectomy, and connective tissue disease were excluded. All patients who agreed to participate in this protocol signed an informed consent document. The research protocol was approved regarding its ethical and methodological aspects by the Ethics Committee in Research Procedures of Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul Medical School, accredited by the Brazilian National Research Committee, and registered at the Office for Human Research Protection (OHRP-USDHHS) as an Institutional Reviewing Bureau (IRB 00000921).

Two-dimensional echocardiography

Color Doppler echocardiograms were performed by one of the investigators (LER) using the ATL HDI 5000 (ATL Ultrasound, Bothel, WA, USA) ultrasound equipment with a 2.5-3.5 MHz transducer and harmonic imaging. Echocardiograms were performed with the patients within a maximum of 3% above the estimated dry weight (weight when normotensive and free of edema). The echocardiographic parameters studied in this protocol were evaluated according to the recommendations of the American Society of Echocardiography. For each measurement, 3-5 consecutive cardiac cycles were analyzed and the average was computed. Left ventricular mass (LVM) was calculated according to the modified cube formula proposed by Devereux et al. (10). LVM index was calculated by dividing LVM by body surface. An LVM index above 100 g/m^2 for women and above 131 g/m^2 for men was considered to indicate LVH (11).

Blood analysis

Plasma PTH measurements were carried out by a radioimmunoassay technique measuring intact PTH (Immunolite 2000, Diagnostic Products Corporation, Los Angeles, CA, USA). Intra-assay and interassay coefficients of variation for this test are 5.7 and 8.8, respectively. The patients were classified into three groups according to their plasma PTH levels: group I, PTH <100 pg/ml (low PTH levels, N = 10); group II, PTH between 100 to 280 pg/ml (intermediate PTH levels, N = 10), and group III, PTH >280 pg/ml (high PTH levels, N = 21).

Other laboratory tests were carried out by standardized clinical laboratory methods and included total alkaline phosphatases, bone-fraction alkaline phosphatase, total calcium, phosphorous, pre- and post-dialysis urea, creatinine, alanine aminotransferase, aspartate aminotransferase, albumin, total cholesterol, triglycerides, hematocrit, hemoglobin, serum iron, and serum aluminum. Bone-fraction alkaline phosphatase was measured by the thermal inactive enzyme method (12). Averaged 12-month data of urea fractional clearance and urea reduction rate were used for the biochemical evaluation of dialysis adequacy.

Other measurements

Blood pressure was evaluated by averaging the measurements obtained before hemodialysis over a period of 6 months preceding the echocardiographic examination. BMI was calculated using the formula: BMI = weight/height^2 (kg/m^2).

Statistical analysis

Data are reported as means ± SD or as percentages. Differences in echocardiographic, clinical, and laboratory variables between different PTH groups were evaluated by analysis of variance. The Tukey test was used for multiple comparisons. The association between PTH and LVM index and the other variables was evaluated by Pearson's correlation coefficient. Multiple linear regression analysis was used to evaluate the relation between PTH and LVM index, controlling for variables that may potentially influence LVM index. A two-tailed P value <0.05 was considered to be statistically significant. Statistical analysis was carried out using the SPSS Program, version 8.0.

Results

The demographic and anthropometric characteristics of the patients are presented in Table 1. Causes of renal failure were: a) hypertensive nephrosclerosis in 10 (24%) patients, b) polycystic kidney disease in 8 (20%), c) glomerular diseases in 5 (12%), d) obstructive uropathy in 4 (10%), e) Alport syndrome, chronic pyelonephritis, U-shaped kidneys and HIV nephropathy in 1 (2%) patient each, and e) undetermined etiology in 11 (24%) patients.

Laboratory variables are shown in Table 2 for the patients as a whole and stratified by PTH groups. Alkaline phosphatase levels were significantly higher in the high PTH

Table 1. Clinical characteristics of the patients as a whole and divided into groups according to parathyroid hormone levels.

Parameters	Overall group (N = 41)	Group I (N = 10)	Group II (N = 10)	Group III (N = 21)
Age (years)	45 ± 11 (18-61)	48 ± 13	48 ± 10	42 ± 11
Weight (kg)	66 ± 17 (38-114)	64 ± 18	76 ± 20	62 ± 13
Height (cm)	166 ± 11 (147-193)	167 ± 12	171 ± 12	163 ± 8
BMI (kg/m^2)	23.7 ± 4.1 (16.2-34.4)	23.2 ± 4.5	25.5 ± 3.9	23 ± 3.8
Time until echo (months)	58 ± 42 (3-186)	58 ± 44	55 ± 36	59 ± 45
SBP (mmHg)	138 ± 17 (100-174)	137 ± 16	149 ± 16	134 ± 16
DBP (mmHg)	81 ± 10 (59-103)	80 ± 10	86 ± 11	80 ± 10
Male gender (yes/no)	26/15	7/3	7/3	12/9
White/not white	15/26	7/3	8/2	10/11
Anti-hypertensive medications (yes/no)	14/27	1/9	6/4	7/14

Data are reported as means ± SD and (range) unless otherwise indicated. Groups I, II, III = low, intermediate and high serum PTH levels, respectively. BMI = body mass index; time until echo = hemodialysis time until echocardiography; SBP and DBP = systolic and diastolic blood pressure (6-month average of the pre-dialysis readings). There were no significant differences between groups (ANOVA).

group compared to the low PTH group ($P < 0.05$) and a similar trend was observed for bone-specific alkaline phosphatase ($P = 0.06$). Serum total calcium levels were significantly lower in the high PTH group, while serum phosphorous, calcium-phosphorous product, triglycerides, total cholesterol, and albumin were higher in the intermediate PTH group. Other laboratory variables did not differ among groups (Table 2).

Echocardiographic variables were not significantly different among groups. Table 3 shows the echocardiographic data for the patients as a whole and according to PTH levels. Overall, left ventricle dimensions and systolic function were within normal values, except for a slightly increased diastolic septal wall thickness.

Although dialysis time did not differ among groups (Table 1), a significant correlation between PTH level and hemodialysis time was observed in all patients ($P = 0.02$), and with a higher level of association in subgroup analysis ($P = 0.002$ for the high PTH group). Likewise, significant correlations were observed between PTH and total alkaline phosphatases ($P = 0.001$) and bone-fraction alkaline phosphatase ($P = 0.001$) in all patients and also in the high PTH group ($P = 0.001$; Table 4). As shown in Figure 1,

Table 2. Laboratory measurements.

Parameters	Overall group (N = 41)	Group I (N = 10)	Group II (N = 10)	Group III (N = 21)	P value
PTH (pg/ml)	381 ± 412	28 ± 23	148 ± 54	661 ± 408	0.0001
AP (U/l)	332 ± 275	163 ± 84	317 ± 428	420 ± 206	0.046*
Bone-AP (U/l)	286 ± 226	166 ± 122	247 ± 285	361 ± 211	0.06
Total calcium (mg/dl)	9.1 ± 1.2	9.6 ± 0.8	9.6 ± 1.4	8.7 ± 1.0	0.04*
Phosphorous (mg/dl)	5.8 ± 1.6	4.8 ± 1.7	6.6 ± 1.6	5.8 ± 1.3	0.04**
Ca x P $(mg/dl)^2$	53 ± 17	48 ± 18	63 ± 20	50 ± 14	0.08
Albumin (g/dl)	4.0 ± 0.3	3.8 ± 0.4	4.1 ± 0.3	4.0 ± 0.3	0.04*
Total cholesterol (mg/dl)	166 ± 41	156 ± 30	190 ± 56	160 ± 33	0.09
Triglycerides (mg/dl)	183 ± 117	147 ± 47	305 ± 175	144 ± 54	0.003***
Serum aluminum (µg/l)	2.7 ± 1.7	3.2 ± 1.8	3.2 ± 2.6	2.2 ± 0.9	0.23
Kt/V	1.3 ± 0.3	1.4 ± 0.3	1.2 ± 0.2	1.2 ± 0.2	0.19
URR (%)	64.5 ± 7.8	68.6 ± 9.9	60.9 ± 7.3	64.6 ± 6.7	0.12
Hemoglobin (g/dl)	9.7 ± 1.6	9.6 ± 2.0	9.6 ± 1.5	9.8 ± 1.4	0.89
Serum iron (µg%)	63 ± 20	66 ± 26	67 ± 20	62 ± 17	0.75

Data are reported as means ± SD. Groups I, II, III = low, intermediate and high serum PTH levels, respectively. PTH = parathyroid hormone; AP = total alkaline phosphatases; Bone-AP = bone fraction of alkaline phosphatase; Ca x P = calcium x phosphorous product; Kt/V = urea fractional clearance; URR = urea reduction rate. ANOVA *between groups I and III; **between groups I and II; ***between groups I and II, and groups II and III.

Table 3. Echocardiographic parameters.

Parameters	All patients (N = 41)	Group I (N = 10)	Group II (N = 10)	Group III (N = 21)
Diastolic septal thickness wall (cm)	1.2 ± 0.2	1.3 ± 0.3	1.2 ± 0.2	1.2 ± 0.2
Diastolic LV diameter (cm)	4.8 ± 0.7	4.7 ± 0.8	5.2 ± 0.5	4.7 ± 0.8
Diastolic posterior wall thickness (cm)	1.0 ± 0.2	1.0 ± 0.1	1.1 ± 0.1	1.0 ± 0.2
Systolic LV diameter (cm)	3.0 ± 0.6	3.0 ± 0.8	3.2 ± 0.5	2.9 ± 0.5
LVM (g)	204 ± 68	194 ± 50	231 ± 45	196 ± 81
LVM index (g/m^2)	119 ± 41	117 ± 39	124 ± 29	118 ± 48
LV ejection fraction (%)	68 ± 9	68 ± 10	68 ± 7	68 ± 10

Data are reported as means ± SD. Groups I, II, III = low, intermediate and high serum PTH levels, respectively. LV = left ventricle; LVM = left ventricular mass. There were no significant differences between groups (ANOVA).

a significant correlation between PTH and LVM index was observed in all patients (r = 0.34; P = 0.03). The correlation was more prominent in the group of patients who presented the most pronounced degree of hyperparathyroidism (high PTH group; r = 0.62; P = 0.003).

No significant correlations were observed between LVM index and anthropometric or clinical variables. However, a negative correlation was observed between LVM index and hemoglobin levels (r = -0.34; P = 0.03). Trends were also noted for associations between LVM index and alkaline phosphatases (r = 0.27; P = 0.08).

Multivariate analysis was performed including age, BMI, systolic blood pressure, hemoglobin, and PTH as independent variables and LVM index as dependent variable. Models were created for all 41 patients (model 1), aggregating the low and intermediate PTH groups (model 2) and in analyses restricted to the high PTH group (model 3). In this analysis (Table 5), LVM index was significantly and

Table 4. Person's correlation coefficients between parathyroid hormone and clinical parameters.

Parameters	All patients (N = 41)		Group I (N = 10)		Group II (N = 10)		Group III (N = 21)	
	r	P	r	P	r	P	r	P
Time until echo	0.36	0.02	-0.06	0.87	0.14	0.69	0.63	0.002
AP (U/l)	0.55	0.001	-0.20	0.58	0.08	0.82	0.72	0.001
Bone-AP (U/l)	0.58	0.001	-0.16	0.66	0.07	0.85	0.69	0.001

Groups I, II, III = low, intermediate and high serum PTH levels, respectively. Time until echo = hemodialysis time until echocardiography; AP = alkaline phosphatase.

Table 5. Clinical predictors of left ventricular mass index in multiple regression analysis.

Variables	Overall group (N = 41)		Group I + Group II (N = 20)		Group III (N = 21)	
	ß	P value	ß	P value	ß	P value
PTH	0.03	0.02	0.84	0.44	0.07	0.01
Hemoglobin	-6.51	0.11	-6.18	0.18	-2.78	0.71
SBP	0.34	0.35	-0.35	0.45	0.70	0.27
Age	1.08	0.10	1.04	0.22	0.72	0.48
BMI	-3.3	0.08	-4.21	0.09	-3.09	0.29
	R^2: 0.31		R^2: 0.38		R^2: 0.47	

Groups I, II, III = low, intermediate and high serum PTH levels, respectively. ß = ß coefficient; PTH = parathyroid hormone; SBP = systolic blood pressure; BMI = body mass index.

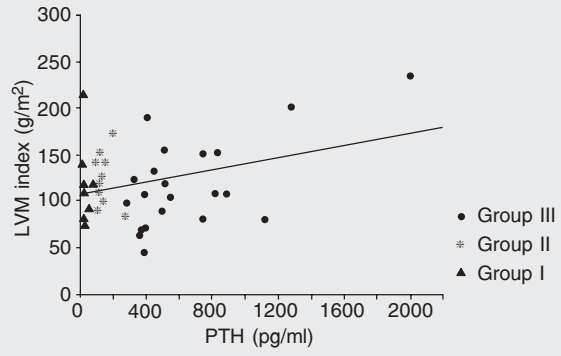

Figure 1. Dispersion diagram demonstrating the correlation between PTH levels and LVM index for all patients and for the patients divided into groups according to PTH levels. Groups I, II, III = low, intermediate and high serum PTH levels, respectively. LVM = left ventricular mass; PTH = parathyroid hormone. r = 0.34 (P = 0.03) for all patients and r = 0.62 (P = 0.003) for high PTH group (Pearson's correlation coefficient).

independently associated with PTH, both in model 1 (P = 0.02) and model 3 (P = 0.01).

Discussion

Several factors contribute to the development of LVH in patients on intermittent hemodialysis treatment, including chronic hypervolemic state, anemia, elevated blood pressure, and arteriovenous fistula (3). It has been suggested that secondary hyperparathyroidism may also play a role in the cardiovascular disease of end-stage uremia (2,7), although previous studies evaluating the role of PTH in LVH in ESRD patients have led to contradictory results (6-9).

In the present study, a well-selected sample of patients was examined. Our data indicate that LVH is positively correlated with PTH levels, particularly in patients with significant secondary hyperparathyroidism. However, this correlation does not hold true for patients with intermediate or low PTH levels. These findings were unchanged after multiple regression adjustment for other parameters involved in LVH. Interestingly, intermediate PTH levels are considered adequate for the bone remodeling processes in uremic patients (13).

Our results agree with those of Stack and Saran (14) who reported that PTH levels above 157 pg/ml correlated independently with the development of LVH. Nevertheless, contradictory findings about the role of secondary hyperparathyroidism in cardiac changes have been reported in chronic uremic patients. London et al. (6) presented contradictory results concerning the correlation between PTH levels and LVM index, describing a significant negative association. The reason for this discrepancy is not clear, but may be related in part to some methodological aspects. Firstly, PTH values were relatively higher in our patients with great variability in the group of more severe hyperparathyroidism. Secondly, London et al. (6) used a PTH radioimmunoassay technique detecting the terminal C-fragment. This technique measures predominantly inactive PTH metabolites whose excretion is reduced in renal failure (15). These metabolites have biological effects on target tissues including the heart that differ from those of intact PTH.

Anemia is considered to be an important factor in the pathogenesis of LVH, contributing to increased cardiovascular mortality in dialysis patients (16). In the overall group, we observed that hemoglobin was negatively associated with LVM index. However, in multivariate analysis, the correlation of PTH with LVM index was independent of anemia and several other potential confounding factors. Moreover, in patients on dialysis, the presence of anemia is combined with chronic volume overload and it has been shown that the use of human recombinant erythropoietin can attenuate LVH by correcting anemia (17).

High blood pressure is also strongly associated with LVH development (16,18,19). Foley et al. (18) showed that hypertension in chronic dialysis is associated with concentric hypertrophy of the left ventricle. Hypertensive hemodialysis patients have LVM indices that are significantly higher than their normotensive counterparts. However, LVM indices are similar to those of non-uremic hypertensive patients, demonstrating that inadequate blood pressure control is an important factor for the development of LVH (20). In order to avoid such an interaction, we selected for the present study only normotensive or well-controlled hypertensive patients. Among the 19 patients using antihypertensive medications, 14 were taking 1 drug and 5 were taking two drugs for blood pressure control (data not shown). Systolic blood pressure, which was included in the multivariate analysis, did not affect the association of PHT with LVH.

In the past years, there has been compelling evidence that the cardiovascular system is a major target of PTH action, suggesting

that its chronic elevation in ESRD patients adversely affects myocardial metabolism and function (4). LVH in uremic patients is not only characterized by an increased myocardial fiber mass but also by myocardial interstitial fibrosis (21). The mechanisms by which PTH induces LVH have not been completely elucidated. Studies have shown increased cytosolic calcium and/or protein kinase C activation. Expression of cardiac proto-oncogene may be enhanced, which in turn may lead to altered expression of several genes involved on cardiac structure and action and ultimately stimulate the translation of contractile and non-contractile cardiac muscle proteins leading to LVH (22). These studies also suggest that PTH has a permissive role for fibroblast activation and myocardial fibrosis. Thus, it has been observed that elevated PTH levels in ESRD cause irreversible interstitial fibrosis with collagen deposition (23). Following parathyroidectomy in animals with chronic renal failure, a reduction of collagen deposition in the myocardium is consistently observed (22). Interactions between PTH levels and cardiac abnormalities specifically related to LVH and left ventricular diastolic dysfunction were shown in patients with primary hyperparathyroidism as well (24-26). Such abnormalities were independent of plasma calcium levels and hypertension and also regressed following parathyroid mass reduction (24-27).

Since numerous factors are involved in the genesis of LVH in chronic hemodialysis patients, one should not expect that isolated interventions on specific targets will lead to complete correction of this condition. Control of these factors, however, is vital and may significantly reduce LVH related to ESRD. This can be observed in patients after successful renal transplantation (28). Moreover, it has been demonstrated that parathyroidectomy exerts a significant role in decreasing LVM index among dialysis patients with tertiary hyperparathyroidism (29).

Although several comorbidities associated with chronic renal failure may contribute to the development of LVH, the findings of the present study suggest that secondary hyperparathyroidism plays an important and independent role in this process. Based on the current state of our knowledge, patients with early renal failure should have their PTH levels monitored and kept within adequate levels, by the judicious use of routine interventions, including dietary protein restriction, the prescription of phosphate binders and the proper use of vitamin D analogs. It also seems adequate to periodically evaluate left ventricular morphological parameters and cardiac geometry by echocardiography, especially in those patients with multiple risk factors for LVH development.

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