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Original Article

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Effect of Intravenous Active Vitamin-D Treatment on the Left Ventricular Mass Index in Chronic Hemodialysis Patients with Secondary Hyperparathyroidism

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Abstract

Objective: We investigated the effect of active D vitamin therapy on echocardiographic examination results in hemodialysis patients with hyperparathyroidism.
Materials and Methods: This prospective study involved 20 patients who undergoing HD for a total of 12 hours per week at least 6 months. Patients with serum intact parathormone level (iPTH) ≥20.8 pmol/L, phosphorus level 3.5 - 5.5 mg/dL, calcium level <9.5 mg/dL included in this study. Before and after 6 months active vitamin D treatment, left ventricular mass index (LVMI) of all patients were investigated by echocardiography.
Results: The mean age was 51.2±15.0 Ten patients were female and ten patients were male. The mean iPTH level in serum before and six months after active vitamin-D treatment were 35.97±16.41 and 24.92±13.28 pmol/L respectively (p<0.001). Before and six months after active vitamin- D treatment the mean LVMI were 294.40±103.2 gr/m^2 and 250.40±101.44 gr/m^2 respectively. LVMI was statistically significant decreased after six months treatment compared to before treatment (p<0.001).
Conclusion: Increased serum iPTH levels in patients undergoing HD decrease with active vitamin-D treatment and this results in significant reduction in LVMI. Our results show that treatment of hyperparathyroidism plays an important role in correcting LVH.
Keywords: End stage renal disease, hyperparathyroidism, vitamin D

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INTRODUCTION

Cardiovascular complications are the major cause of mortality in patients with end-stage renal disease (ESRD) (1). Increased cardiovascular risk and mortality are relatively higher particularly in young patients and pediatric age group (2). Cardiovascular diseases are caused by structural and functional disorders of the heart (left ventricular hypertrophy (LVH) and cardiomyopathy) and vascular disorders (atherosclerosis and arteriosclerosis) (3). Left ventricular hypertrophy is the most common cardiac complication in ESRD, and it is a worrying prognostic sign (4). It poses a risk for all deaths due to some reasons as well as cardiac mortality. There is evidence that high parathormone (PTH) in a secondary hyperparathyroidism-related situation that develops in chronic renal failure (CRF) is a potential cardiotoxin (3). Abnormal calcium phosphorus metabolism and hyperparathyroidism have been shown to coexist with myocardial fibrosis and myocardial hypertrophy. There are studies suggesting that these complications may be reduced by the active use of vitamin D or parathyroidectomy (5, 6).

Since serum intact parathormone (iPTH) is a correctable factor, it should be aimed to reduce the present levels to the levels accepted by guidelines in hemodialysis patients.

In our study, left ventricular mass index (LVMI), which is an LVH indicator, was measured with echocardiographic examination before intravenous (IV) active vitamin D therapy and in month 6 of treatment in patients with ESRD who regularly underwent hemodialysis and had high iPTH levels, serum calcium (Ca) level of 9.5 mg/dL, and serum phosphorus (PO_4) level of 3.5-5.5 mg/dL. The aim of the present study was to evaluate the effect of iPTH and IV active vitamin D treatment on LVMI in the short term.

MATERIALS AND METHODS

The present study was planned for echocardiographic examination in hemodialysis patients who had secondary hyperparathyroidism between 2002 and 2003 and needed treatment according to the guidelines. The study was prepared in accordance with the Declaration of Helsinki. Inclusion criteria were as follows: 18 years old and <75 years old; undergoing hemodialysis for 3 days/week (12 hours/week) for ≥6 months or longer period; no parathyroidectomy; values of serum iPTH ≥ 20.8 pmol/L (normal range in our hospital laboratory is 0.8-5.2 pmol/L), serum Ca <9.5 mg/dL, and serum phosphorus 3.5-5.5 mg/dL; not being given active vitamin D therapy (calcitriol) in the last 6 months; no findings suggesting cancer, rheumatic diseases, uncontrolled hypertension, coronary artery disease, pericardial effusion, heart failure, anemia (hemoglobin <10 g/dL), hyperthyroidism, hypothyroidism, diabetes, or any other systemic diseases; and having agreed to participate in the study. Exclusion criteria were as follows: <18 years old and >75 years old; underwent parathyroidectomy; values of serum iPTH <20.8 pmol/L, serum Ca>9.5 mg/dL, and serum PO_4 > 5.5 mg/dL; receiving dialysis for <6 months; receiving active vitamin D therapy (calcitriol) in the last 6 months; and having the above-mentioned comorbidities.

Data on anamnesis, history, etiology and comorbid diseases, treatment that was given, diet, dialyzer, heparin dose, blood flow rates, dialyzate flow rates, dialyzate Ca and potassium amounts, routine biochemistry, hemogram, blood tests including hormone levels, resting electrocardiography, and telecardiographies were obtained from the patient follow-up files.

A total of 20 (10 male and 10 female) hemodialysis patients who met the inclusion criteria were included in the study. The mean age of the group was 51.2±15.0 years. The patients were treated with hemodialysis with synthetic or semi-synthetic hemodialyzers with at least 1 m^2 surface area, 1.25 mmol/L Ca dialyzate, and standard heparin for 4 h for 3 days/week. Written informed consent was obtained from patients who participated in this study. At the beginning of the study, the mean duration of dialysis for patients was 69.85±37.72 months. IV active vitamin D was given to the patients at a dose of 2 µg for a maximum of three times a week for 6 months. The drug doses were determined by the following hemodialysis physician. All patients received a 30-35 kcal/kg/day calorie diet with 1.2 g/kg protein and poor in potassium and phosphorus. Other treatments (essential amino acid, phosphorus-binding agents, iron, and erythropoiesis-stimulating agents) were also regulated by the physician responsible for the dialysis center. No intervention was performed. Blood pressure was measured twice using a mercurial sphygmomanometer at 5-minute intervals, at full resting, from the arm without a fistula. Body mass index (BMI) was calculated as BMI=body weight (kg)/height^2 (m^2).

Table 1. Clinical and laboratory findings of patients

Age (mean±SD)	51.2±15.0
No. of patients	20
Female/male ratio	10/10
BMI (kg/m^2)	25.24±5.9
Duration of dialysis (month)	69.85±37.72
Urea (mg/dL)	166±31.97
Creatinine (mg/dL)	9.25±2.4
Calcium (mg/dL)	8.49±1.06
Phosphorus (mg/dL)	4.9±0.41
Sodium (mEq/L)	136.4±4.61
Potassium (mg/dL)	5.15±0.68
Hemoglobin (g/dL)	11.36±1.17
Hematocrit (%)	34.3±3.4

BMI: body mass index

Before hemodialysis, blood samples were obtained from the arm without arteriovenous shunt after a 12-hour fasting. Urea, creatinine, sodium, potassium, total Ca, PO_4, hemoglobin, hematocrit, and iPTH values were evaluated. The results are shown in Table 1.

iPTH was measured by the Coat-A-Count kit using an immunoradiometric assay (IRMA) technique with a pmol/L unit. The normal range is 0.8-5.2 pmol/L in our hospital laboratory. For bone regeneration rate to continue at a normal rate in patients with ESRD, it is recommended that iPTH levels are 2-9 times higher than normal (7). iPTH levels are not recommended in values below two times of the normal upper limit because of the possible increase in the prevalence of adynamic bone disease. In fact, it is stated that African-Americans are more susceptible to adynamic bone disease, and the risk of adynamic bone disease development is high in iPTH levels between 150 and 300 pg/mL (8).

Therefore, those whose PTH level was four or more times higher than normal (PTH ≥20.8 pmol/L) were included in the study. When the PTH value is converted from pmol/L to pg/mL, the coefficient is multiplied by 10.61. Two-dimensional M-mode Doppler echocardiography was used to evaluate LVMI. Echo-

Table 2. Results of the study

	Baseline	Month 6	p
iPTH (pmol/L)	35.97±16.41	24.92±13.28	0.001*
LVMI (g/m^2)	294.4±103.02	250.40±101.44	0.001*

*Statistically significant difference (p<0.05).
iPTH: intact parathormone; LVMI: left ventricular mass index

cardiography was performed on the day after dialysis. Echocardiographic measurements were performed by using a 2.5 MHz transducer probe in Vingmed System Five device. From parasternal long-axis images in two-dimensional and M-mode echocardiography, interventricular septum thickness (IVST) in diastole, posterior wall thickness (PWT) in diastole, and left ventricular end-diastolic diameter (LVEDD) were measured. Left ventricular mass (LVM) was calculated by the Devereux-Reichek formula as LVM (g)=1.04×[(LVEDD+IVST+PWT)^3–LVEDD^3]−13.6. Body surface area (BSA) (m^2) was calculated as BSA=0.007184×Height (cm)$^{0.725}$×Weight (kg)$^{0.425}$. LVMI (g/m^2) was calculated as LVMI=LVM (g)/BSA (m^2).

Statistical Analysis

Statistical analysis of all obtained data was done by Statistical Package for the Social Sciences 10.0 software (SPSS Inc., Chicago, IL, USA). For continuous variables, data with normal distribution were expressed as mean±standard deviation, and data with non-normal distribution were expressed as median (minimum-maximum). The Kolmogorov-Smirnov test was used to evaluate the parametric or non-parametric distribution of the continuous variables. Student's t-test was used for evaluation of the differences between the two groups in parametric variables. The Mann-Whitney U test was employed for non-parametric variables. A p<0.05 was considered statistically significant.

RESULTS

Intact parathomone levels of the patients (10 male and 10 female) were found to be high at 35.97±6.4 pmol/L (381.64±67.90 pg/mL) before the treatment. After a 6-month treatment, iPTH levels were 24.92±13.28 pmol/L (264.40±140.90 pg/mL). There was a statistically significant difference between pre- and post-treatment PTH values (p<0.01). Non-specific ST changes were present in four of the electrocardiograms of the patients. Telecardiograms of all patients were normal, and there was no significant valve pathology in color doppler echocardiographies. Thyroid function tests of the patients in both groups were normal, and the patient's serum magnesium level was normal. Parathomone levels and LVMI data are shown in Table 2.

When LVMI was evaluated, it was observed that there was a significant decrease in LVM. While it was 294.40±103.02 at the beginning, it was 250.4±101.44 after a 6-month IV active vitamin D therapy. The difference between the mean values of LVMI was statistically significant (p<0.001).

DISCUSSION

Approximately half of deaths in all age groups in dialysis patients are associated with cardiovascular system complications (1). Generally, cardiac complications are present when dialysis begins (9). Cardiovascular disease-induced mortality rates in patients with ESRD are higher than those in the general population (10). The rate of LVH in the adult group is 75% when the dialysis process begins (11). Left ventricular dilatation and LVH are independent risk factors for mortality in renal failure (4). Multiple factors included in the etiology of LVH include arteriovenous fistula, volume burden, hypertension, anemia, hyperparathyroidism, comorbidities, atherosclerosis, oxidative stress, and inflammation. Ganesh showed in his study on 6634 patients that iPTH level is associated with cerebrovascular and sudden deaths as well as cardiac death (12). Moreover, Amann et al. (5) showed increased fibroblast activity and cardiac fibrosis after iPTH replacement in the study group, in rats undergoing parathyroidectomy-subtotal nephrectomy. A statistically significant analysis compared with the control group provides evidence that iPTH plays a role as potential cardiotoxin. According to the Massry hypothesis, PTH levels that can lead to undesired results are considered to be uremic toxin. Parathormone is considered to have neuropathy, myopathy, hematological disorders, carbohydrate intolerance, hyperlipidemia, and cardiomyopathy-making effects (13). In vitro studies have shown that vitamin D receptors (VDRs) are present in the heart (14). Vitamin D is a hormone, and it has protective properties in the tissues. Active vitamin D (calcitriol) initiates the biological response by binding to cytoplasmic VDR (15). It regulates numerous gene transcriptions. A consequence of decreased active vitamin D due to CRF is an increase in serum levels of fibroblast growth factor 23 (FGF-23). This has been associated with LVH, cardiovascular complications, and death (16). In a myocardial autopsy study conducted by Leifheit-Nestler et al. (17), they demonstrated a strong association between increased FGF-23 expression and decreased klotho expression and LVH in patients receiving dialysis. An increase in FGF receptor 4 (FGFR4) was shown with cardiac FGF-23 level. FGF-23 is thought to cause LVH through calcineurin-activated T cell nuclear factor signaling via FGFR4. It has also been shown that serum renin and angiotensin II levels decrease after a 3-month active vitamin D treatment in hemodialysis patients (18). In the study of Drüeke examining hemodialysis patients undergoing parathyroidectomy for the first 2 weeks, the cardiac functions were demonstrated to be improved (19).

In our study, we examined the effect on LVMI after taking iPTH level under control following IV active vitamin D therapy. Although there were changes similar to concentric remodeling in the left ventricle in the comparative echocardiograms performed at the beginning and in month 6 of IV active vitamin D therapy, a statistically significant decrease was observed in LVMI, which showed LVH, following IV active vitamin D treatment (p<0.001).

The findings of our study support that secondary hyperparathyroidism contributes to the development of LVH in addition to traditional and uremia-specific factors, such as diabetes and hypertension, and shows that IV active vitamin D therapy leads to regression in LVMI.

According to the results of our study, taking iPTH under control with IV active vitamin D treatment regresses LVH and decreases the likelihood of heart failure. This situation points out the importance of phosphorus-lowering drugs, patient compliance, and nutrition as well as iPTH level for CRF in the dialysis and pre-dialysis stages.

CONCLUSION

In patients with chronic renal failure, one of the risk factors for left ventricular hypertrophy is increased parathormone levels. Given active vitamin D in patients receiving hemodialysis under appropriate conditions is an important treatment option for reduction of left ventricular hypertrophy due to secondary hyperparathyroidism.

Ethics Committee Approval: The study was prepared in accordance with the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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