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Decreased blood lead levels after calcitriol treatment in hemodialysis patients with secondary hyperparathyroidism

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ABSTRACT

Objective: Secondary hyperparathyroidism (SHP) is characterized by high bone turnover, which may, in turn, result in increased release of lead from bone stores. This study investigated the effects of intravenous calcitriol on blood lead (BL) levels in patients with SHP.
Methods: Intravenous calcitriol therapy was administered for 16 wk to 28 patients who were on maintenance hemodialysis (HD) and had intact parathyroid hormone (iPTH) plasma levels of >300 pg/mL. Blood was drawn at baseline and every 4 wk for 16 wk to determine the levels of iPTH; bone remodeling markers, including bone-specific alkaline phosphatase (bAP) and type 5b tartrate-resistant acid phosphatase (TRAP); and BL.
Results: Of the 28 patients, 25 responded to calcitriol therapy; they exhibited significant decrements in serum iPTH levels by the end of 4 wk of therapy and thereafter. After 16 wk of therapy, these patients had significant reductions in serum iPTH levels ($p<0.01$) and significant and parallel decreases in the levels of bAP ($p<0.01$), TRAP ($p<0.01$), and BL ($p<0.01$). Further analysis showed a significant positive correlation between the levels of BL and serum iPTH ($r=0.34$, $p<0.01$) and BL and serum TRAP ($r=0.22$, $p<0.05$). However, there was no significant correlation between the levels of BL and serum bAP.
Conclusion: Elevated levels of BL and serum bone remodeling markers, which are common features of SHP, can be effectively suppressed by calcitriol therapy. This indicates that hyperparathyroidism not only accelerates bone remodeling but may also enhance bone lead mobilization in patients on maintenance HD.

Introduction

Secondary hyperparathyroidism (SHP) is characterized by an imbalance in the bone remodeling process, with resultant uncoupling of osteoclastic bone resorption and osteoblastic bone formation. It is one of the most common causes of renal osteodystrophy in patients who are undergoing long-term dialysis [1]. In this patient population, SHP is characterized by hyperplasia of the parathyroid glands and increased parathyroid hormone (PTH) secretion, which stimulates bone demineralization and leads to high bone turnover osteodystrophy.

Population-based studies have demonstrated associations between increased body lead burden and deterioration of renal function [2]. After lead is absorbed, it is cleared from the bloodstream within approximately 35 days [3]; however, it takes years to decades to clear lead from bone [4]. Thus, blood lead (BL) levels only reflect recent exposure. During physiological states in which bone turnover increases, such as lactation, pregnancy, and menopause, the increased release of lead from bone stores into the bloodstream may result in the incorporation of lead, instead of calcium, into bone [5]. In addition to affecting renal function, lead may directly influence the activity of osteoclasts and osteoblasts by interfering with signaling [6,7], leading to exacerbated bone loss and osteoporosis in the elderly [8].

The histomorphological changes revealed by bone biopsy are the gold standard for diagnosis of renal osteodystrophy. However, because of technical difficulties and a lack of testing facilities, several serum bone markers are used to measure changes in bone turnover more conveniently [9]. Type 5b tartrate-resistant acid phosphatase (TRAP) is an osteoclastic enzyme that is released in the process of bone resorption; it is an excellent marker of bone resorption, because the enzyme is unique to osteoclasts [10]. Similarly, bone-specific alkaline phosphatase (bAP), an enzyme produced by osteoblastic cells, is a marker of bone formation [11].

To date, few studies have examined the impact of SHP, a state of high bone turnover, on the mobilization of lead from bone. We designed a

Abbreviations: 1,25$(OH)_2D_3$, 1,25-dihydroxyvitamin D_3; $Al(OH)_3$, aluminum hydroxide; ALP, alkaline phosphatase; BL, blood lead; CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; HD, hemodialysis; IL-6, interleukin-6; iPTH, intact parathyroid hormone; bAP, bone-specific alkaline phosphatase; Pi, inorganic phosphorus; PTH, parathyroid hormone; SHP, secondary hyperparathyroidism; TRAP, type 5b tartrate-resistant acid phosphatase.

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prospective study to investigate the beneficial effects of 16 wk of calcitriol therapy on BL levels in patients with SHP who were on maintenance hemodialysis (HD). We also looked for relationships between BL levels and serum levels of intact PTH (iPTH), TRAP, and bAP to explore the role of osteoclasts and osteoblasts in bone lead mobilization.

Methods

Subjects

Patients with chronic renal failure ($n=28$; 14 men and 14 women; mean age 57.8 ± 8.1 y) who underwent maintenance dialysis therapy at two nephrology units (Tri-Service General Hospital and Cardinal Tien Hospital) were prospectively investigated. The study protocol was in accordance with the principles of the Helsinki Declaration and approved by the Human and Ethics Committees of the respective institutions. Patients were included in the study if they were aged ≥18 y, had stable chronic renal failure (survival of ≥6 mo without active cardiovascular, cerebrovascular, hepatological, infectious disease, cancer, pregnancy, previous parathyroidectomy, previous transplant, or estrogen replacement therapy), underwent maintenance HD three times a week, and had SHP. Patients had undergone HD for a mean of 8.2 ± 3.6 y. SHP was defined by symptomatic osteodystrophy (bone and joint pain and muscular weakness) and a serum iPTH level of >300 pg/mL. All patients underwent regular HD using a high-flux polysulfone membrane and a dialysate containing 1.25 mM calcium, with calcium carbonate serving as the phosphate binder. None of the patients had occupational exposure to lead; iron deficiency; history of calcitriol therapy during the previous 3 mo; or plasma calcium, phosphorus, or aluminum levels higher than 11.0 mg/dL, 6.0 mg/dL, or 1.0 μM, respectively. The control group consisted of 25 HD patients whose serum iPTH levels were less than 300 pg/mL. They were matched for sex, age, and HD duration against the study group and were also prospectively followed.

Calcitriol treatment

To achieve effective and safe suppression of PTH levels, initial low-dose intravenous calcitriol (1-μg vials; Abbot Laboratories) was administered through an effluent needle at the end of each HD session for 16 wk. If serum levels of calcium, phosphorus, and calcium–phosphorus products remained within the acceptable range, calcitriol dosage was adjusted according to the changes in serum alkaline phosphatase (ALP) and iPTH levels, which were monitored monthly [12]. Blood was obtained for laboratory tests at baseline and every 4 wk during the 16-wk calcitriol treatment. All blood samples were collected approximately 44 h after the HD session. Calcitriol administration was interrupted in the event of any of the following situations: serum PTH levels of ≤300 pg/mL, calcium-phosphate product of >75, serum phosphate level of >7.0 mg/dL, and serum calcium level of >10.5 mg/dL [13]. Aluminum hydroxide [$Al(OH)_3$] was administered only to patients whose serum phosphate level could not be maintained at <7.0 mg/dL despite administration of the maximum allowable dose of calcium carbonate. Patients with serum iPTH levels of <300 pg/mL at the end of the study period were categorized as responders ($n=25$).

Blood measurement

Analysis of serum biochemical parameters

Blood samples were collected and microcentrifuged before measurement. Serum was separated from the blood samples within 1 h of collection and stored at −30 °C until analysis. Levels of inorganic phosphorus (Pi), total calcium, albumin, blood urea nitrogen, creatinine, ferritin, serum iron, and total ALP were determined with an autoanalyzer (AV 5,000 Chemistry analyzer; Olympus, Tokyo, Japan). High-sensitivity C-reactive protein (CRP) was measured using an ultrasensitive solid phase enzyme-linked immunosorbent assay (ELISA; DRG instruments GmbH, Marburg, Germany). The serum 1,25-dihydroxyvitamin D3 [$1,25(OH)_2D_3$] level was determined using a radioreceptor assay (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). The serum iPTH concentration was measured using an iPTH immunoassay (Nichols Institute diagnostics, San Juan Capistrano, CA, USA), which is a two-site immunoradiometric assay for the measurement of the biologically intact 84-amino-acid chain of PTH. Serum levels of interleukin-6 (IL-6) were measured by ELISA (R&D Systems, Minneapolis, MN, USA).

Analysis of BL concentrations

Blood samples were stored at 4 °C until further analysis, which was performed within 2 wk of obtaining the sample. The BL levels were measured using a graphite furnace atomic absorption spectrophotometer (AAS). All specimens were analyzed three times, and the average was obtained when the relative standard deviation was less than 5% [14].

Analysis of serum bone markers

To measure serum type 5b TRAP activity, 14G6 monoclonal antibody was used to capture TRAP. TRAP substrate (7.6 mM *p*-nitrophenyl phosphate in 0.1 M sodium acetate/0.05 M sodium tartrate, pH 6.1) was then added to wells containing the samples and antibody. The plate was then incubated for 60 min at 37 °C. The reaction was stopped by the addition of 50 μL of 3 N sodium hydroxide, and absorbance was read at 410 nm on a BioRad 550 Microplate Reader [10]. Serum bAP was measured using ELISA (Quidel, San Diego, CA, USA; normal values for women aged 25–44 y, 11.6–29.6 IU/L; women aged >45 y, 14.2–92.7 IU/L; men aged >25 y, 15–40.3 IU/L).

Statistical analysis

All data are reported as means and standard deviations (SD). Statistical analysis was performed using the *t* test for paired or unpaired

Table 1
Comparison of biochemical parameters before and after 16 wk of intravenous calcitriol treatment in 25 secondary hyperparathyroidism patients.

	SHP ($n=25$)		Control ($n=25$)	
	Wk 0	Wk 16	Wk 0	Wk 16
$1,25(OH)_2D_3$, pg/mL	14.6 ± 11.4[b]	19.56 ± 12.8[c]	17.8 ± 8.6	16.9 ± 8.9
iPTH, pg/mL	697.0 ± 313.6[b]	195.7 ± 63.0[d]	182.4 ± 72.4	191.4 ± 82.3
Blood lead, μg/dL	6.76 ± 3.48[a]	3.71 ± 2.04[d]	4.14 ± 2.68	4.03 ± 2.74
TCa, mg/dL	9.58 ± 0.62	9.66 ± 0.64[c]	9.52 ± 0.42[e]	9.61 ± 0.49
iCa, mg/dL	4.77 ± 0.28	4.87 ± 0.30[c]	4.75 ± 0.18[e]	4.81 ± 0.21
Pi, mg/dL	5.03 ± 0.56	5.15 ± 0.52[d]	4.87 ± 0.48[f]	4.91 ± 0.51
AP, IU/L	250.2 ± 84.8[a]	103.6 ± 21.4[d]	106.2 ± 18.5	112.4 ± 19.8
bAP, U/L	56.84 ± 21.47[a]	26.26 ± 6.48[d]	28.42 ± 8.64	27.53 ± 9.87
TRAP, U/L	4.99 ± 1.77[a]	2.01 ± 0.41[d]	2.21 ± 0.65	2.19 ± 0.69
Albumin, g/dL	3.96 ± 0.36	4.01 ± 0.38	3.98 ± 0.32	3.97 ± 0.34
Hct, %	30.3 ± 3.3	31.1 ± 2.9	30.7 ± 3.5	30.3 ± 2.9
Serum iron, μg/dL	84.8 ± 32.4	82.5 ± 38.3	78.6 ± 36.2	81.7 ± 34.8
Ferritin, μmol/L	382.3 ± 190.5	367.5 ± 203.3	332.6 ± 158.3	341.7 ± 164.3
IL-6, pg/mL	7.68 ± 3.62	6.35 ± 2.78[c]	6.48 ± 2.92	6.39 ± 2.49
CRP, mg/dL	1.38 ± 2.02[b]	0.72 ± 1.12[d]	0.67 ± 1.01	0.65 ± 0.95
BW, kg	59.8 ± 9.8	60.1 ± 10.2	60.8 ± 9.7	60.7 ± 9.8
BMI, kg/m^2	22.96 ± 3.18	23.02 ± 3.21	23.19 ± 3.18	23.12 ± 3.24

AP, alkaline phosphatase; BMI, body mass index; BW, body weight; bAP, bone-specific alkaline phosphatase; CRP, C-reactive protein; iCa, ionized calcium; iPTH, intact parathyroid hormone; Pi, inorganic phosphate; SHP, secondary hyperparathyroidism; TCa, total calcium; TRAP, type 5b tartrate-resistant acid phosphatase.

[a] $p<0.05$.
[b] $p<0.01$, vs. wk 0 control.
[c] $p<0.05$.
[d] $p<0.01$, vs. wk 0 SHP.
[e] $p<0.05$.
[f] $p<0.01$, vs. wk 16 SHP.