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Authors

Kantorovich, V
Gacad, MA
Seeger, LL
et al.

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Bone Mineral Density Increases with Vitamin D Repletion in Patients with Coexistent Vitamin D Insufficiency and Primary Hyperparathyroidism*

VITALY KANTOROVICH, MERCEDES A. GACAD, LEANNE L. SEEGER, AND JOHN S. ADAMS

Burns and Allen Research Institute and Division of Endocrinology, Diabetes, and Metabolism, Cedars-Sinai Medical Center, University of California School of Medicine (V.K., M.A.G., J.S.A.), Los Angeles, California 90048; and Department of Radiological Sciences, Center for the Health Sciences, University of California School of Medicine (L.L.S.), Los Angeles, California 90095

ABSTRACT

Two hundred and twenty-nine consecutive subjects, 202 women and 27 men, referred for evaluation of osteoporosis or low bone mineral density (BMD) had serum measurements of immunoreactive PTH (iPTH) and 25-hydroxyvitamin D (25OHD) performed. Fifteen individuals (mean age $\pm$ SE, 75 ± 2.4 yr) had depressed serum 25OHD (<15 pg/mL) and concomitantly elevated (>65 pg/mL) iPTH levels. After successful treatment of vitamin D insufficiency in all subjects, iPTH remained inappropriately high or frankly elevated in 5, describing a 2.2% prevalence rate of coexistent primary hyperparathy-

roidism and vitamin D insufficiency in our population. Despite persistent primary hyperparathyroidism, normalization of serum 25OHD levels in these 5 subjects increased their BMD at an annual rate of 6.3% and 8.2% in spine and hip, respectively. Our results suggest that coexistent vitamin D insufficiency can obscure the diagnosis of primary hyperparathyroidism and, when treated effectively, can result in substantial short-term gains in BMD despite persistence of the inappropriate production of PTH. (*J Clin Endocrinol Metab* 85: 3541–3543, 2000)

POSTMENOPAUSAL osteoporosis is the most commonly encountered metabolic bone disease affecting women in the United States today (1). Effective therapies are currently available that increase bone mass and lower fracture risk (2). However, therapeutic efficacy is predicated upon the treatment of underlying metabolic disturbances, such as hyperparathyroidism, hyperthyroidism, and vitamin D insufficiency. In fact, definitive resolution of hyperparathyroidism (3) or vitamin D insufficiency (4) can result in significant and rapid gains in bone mineral density (BMD). Silverberg and colleagues (3) demonstrated a 3–4% annualized increase in BMD at the spine and hip in patients with primary hyperparathyroidism within only months of parathyroidectomy and normalization of the PTH concentration. We have observed similar increases in BMD after normalization of serum 25-hydroxyvitamin D (25OHD) levels in previously vitamin D-depleted subjects with low BMD (4).

Both primary hyperparathyroidism and occult vitamin D deficiency are relatively common disorders. Primary hyperparathyroidism has an estimated prevalence of 100 cases/100,000 normal population (5). The prevalence of hypovitaminosis D has been reported to be as high as 32% in healthy, free-living, postmenopausal women during the winter months (6) and up to 54% in the homebound elderly pop-

ulation (7). In a recent retrospective study of 237 patients who attended a specialty osteoporosis practice, 17% of the osteoporotic patients had 25OHD levels below 37.4 nmol/L (15 ng/mL) (6).

Coexistence of vitamin D insufficiency and hyperparathyroidism is not uncommon, even in sun-rich environments that are located at relatively low latitudes (8–11). Our current report supports this finding and demonstrates that vitamin D repletion is associated with a rapid rebound in BMD even in the face of persistent primary hyperparathyroidism.

Subjects and Methods

From 1995 through 1999, 229 consecutive patients referred to the Cedars-Sinai Bone Center (Los Angeles, CA) for evaluation of osteoporosis or low BMD were followed for indexes of mineral metabolism. This group was comprised of 202 women and 27 men, with a mean age of 61 ± 11 yr. Blood was drawn from each patient, and serum calcium, albumin, 25-hydroxyvitamin D (25OHD), 1,25-dihydroxyvitamin D [$1,25-(OH)_2D$], immunoreactive PTH (iPTH), TSH, and osteocalcin levels were measured. All provided a timed (≥ 2 -h) fasting urine sample for measurement of calcium and creatinine. The serum 25OHD and $1,25-(OH)_2D$ levels were determined by competitive protein binding assays (Endocrine Sciences, Inc., Woodland Hills, CA). The serum iPTH and TSH levels were measured in immunoradiometric assays (Nichols Institute Diagnostics, San Juan Capistrano, CA). Calcium, albumin, and creatinine levels were determined spectrophotometrically. BMD of the lumbar spine and proximal femur was assessed by dual energy x-ray absorptiometry (Lunar Corp., Madison, WI); the coefficient of variation for measurement of BMD in spine and femoral neck was 1.0% and 1.2%, respectively. All patients showed a t score of less than -1.50 at the hip and/or spine, which was compatible with a diagnosis of osteopenia or osteoporosis.

Fifteen subjects (13 women and 2 men) had low 25OHD levels (10.3 ± 0.6 ng/mL; range, 5–14) and consistently elevated iPTH levels (109.2 ± 13.7 pg/mL; range, 69–252). All patients were supplemented with 1000

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Address all correspondence and requests for reprints to: Dr. John S. Adams, Burns and Allen Research Institute, Division of Endocrinology, Diabetes, and Metabolism, Cedars-Sinai Medical Center, 8700 Beverly Boulevard, Room B131, Los Angeles, California 90048. E-mail: adamsj@cshs.org.

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TABLE 1. Effects of 500,000 IU orally administered vitamin D₂ on serum markers of vitamin D balance (*upper panel*) and bone mineral density (*lower panel*) in five vitamin D-depleted subjects with coexistent primary hyperparathyroidism

Biochemistry	Normal value	Patient 1 ^a		Patient 2		Patient 3		Patient 4		Patient 5		P ^b
		Before	After	Before	After	Before	After	Before	After	Before	After	
Corrected Ca	8.5–10.3 mg/dL	11.0	10.9	10.5	10.9	9.4	8.9	8.9	8.9	10.7	10.4	0.3
25-D	15–55 ng/mL	<5	21	9	23	11	21	9	21	8	17	0.03
iPTH	10–65 pg/mL	104	59	138	83	73	95	88	110	132	175	0.4
Measurement interval (months)		2		7		13		17		4		
DEXA (gm/cm ²)												
Lumbar spine	1.196 ± 0.128 ^c	1.162	1.242	0.735	0.742	1.149	1.259	0.953	0.982	0.824	0.918	0.03
Femoral neck	0.995 ± 0.138 ^c	0.715	0.734	0.630	0.639	0.584	0.605	0.499	0.651	0.661	0.684	0.03
Measurement interval (months)		3		12		25		12		11		

^a Parathyroid adenoma removed 6 months after initial evaluation and 2 months after second DEXA.^b P value comparing difference before and after vitamin D treatment by Wilcoxon matched pairs test.^c Value for a normative population at peak bone mass.

mg elemental calcium (Os-Cal 500, SmithKline Beecham, Pittsburgh, PA) and oral vitamin D₂ (50,000 IU) was administered twice weekly for a 5-week period. Serum parameters of calcium, albumin, 25OHD, and iPTH were monitored in all subjects until 25OHD and/or iPTH concentrations returned to the normal range.

All data are expressed as the mean ± SE. Statistical comparisons were made using Wilcoxon's matched pairs test.

Results

Vitamin D replacement resulted in the normalization of iPTH and calcium levels in 10 patients, substantiating the secondary nature of their hyperparathyroidism (4). The remaining 5 patients (mean age, 78 ± 2.3 yr) had persistently elevated or inappropriately high iPTH levels after normalization of their 25OHD levels (Table 1). This finding supported the diagnosis of primary hyperparathyroidism (*i.e.* autonomous parathyroid function), bringing the prevalence of coexistent primary hyperparathyroidism and vitamin D insufficiency in our cohort of 229 patients with low bone mass to 2.2%. Primary hyperparathyroidism was confirmed pathologically in patient 1 (Table 1). In this patient progressive hypercalcemia after vitamin D replacement prompted surgical removal of a parathyroid adenoma 6 months after initial ascertainment of her serum chemistry values and 2 months after follow-up measurement of her BMD by DEXA. In all subjects vitamin D repletion resulted in a significant increase in 25OHD levels (Table 1) as well as in mean fasting calcium excretion (calcium/creatinine ratio, 0.06 ± 0.16 to 0.24 ± 0.09; *P* = 0.03). Although hypercalcemia did not develop with vitamin D repletion, frank hypercalciuria was induced in 3 previously normocalciuric individuals (fasting urinary calcium/creatinine ratio, 0.36, 0.31, and 0.60 in patients 1, 2, and 5, respectively; normal, <0.16). The other 2 subjects (patients 3 and 4; Table 1) remained normocalcemic more than 1 yr postcorrection of vitamin D insufficiency. In these two subjects the diagnosis of primary, not secondary, hyperparathyroidism was confirmed by a further rise in iPTH levels after vitamin D replacement; iPTH levels in treated vitamin D-insufficient patients with secondary hyperparathyroidism characteristically return to normal within 3 months (12), whereas persistence of an elevated iPTH concentration for 6 months or more almost always heralds the presence of pathological parathyroid tissue at surgery (13). There was no significant change in mean serum 1,25-(OH)₂D levels, and the osteocalcin concentration was not altered by vitamin D repletion in this subset of patients.

As previously described for patients with primary hyperparathyroidism (14), BMD was relatively greater in the trabecular bone-enriched lumbar spine site than in the femoral neck, which has a greater cortical bone component (Table 1). Vitamin D repletion resulted in a significant increase in BMD at both lumbar spine and femoral neck (Table 1) as well as an improvement in mean *t* scores from -1.35 ± 0.79 to -0.72 ± 0.86 at the lumbar spine and from -2.96 ± 0.38 to -2.47 ± 0.2 at the femoral neck. The mean interval between initial and final determinations of BMD was 13 ± 8 months, an interval long enough to detect a significant change in bone mass for patients with either primary (3) or secondary (4) hyperparathyroidism. A monthly rate of increase in 0.005 ± 0.002 and 0.004 ± 0.002 g/cm² at the spine and hip was

measured with a mean annual increase in BMD of 6.3% and 8.2% at these sites, respectively.

Discussion

We have shown that the currently employed vitamin D replacement regimen (500,000 IU vitamin D₂ over 5 weeks) will result in a rapid return of 25OHD levels to the normal range and significantly increase BMD in patients with low BMD and vitamin D insufficiency (4). Here we demonstrate that the correction of vitamin D insufficiency results in a significant increase in BMD at both lumbar spine and femoral neck even in the presence of persistent primary hyperparathyroidism. The mean iPTH level remained above the range of normal in four of the five patients after vitamin D repletion despite the fact that two patients experienced a fall in their iPTH concentrations. Nevertheless, the levels in all five subjects remained inappropriately elevated given the corresponding serum calcium concentration. This suggests that there was an element of remediable vitamin D insufficiency-mediated secondary hyperparathyroidism superimposed upon primary hyperparathyroidism in our study subjects before treatment. Such a mixed biochemical phenotype (*i.e.* coexistent primary and secondary hyperparathyroidism) has been previously proposed (9, 10), but changes in bone mass upon resolution of secondary hyperparathyroidism were not previously reported. The annualized rates of BMD increase in these patients (6–8%) were similar to that observed by us in the treatment of vitamin D-deficient patients without primary hyperparathyroidism (4). These results suggest that persistence of the hyperparathyroid state does not diminish the effectiveness of vitamin D replacement to increase BMD and reduce fracture risk (15).

In conclusion, our data confirm that the standard biochemical phenotype for primary hyperparathyroidism can be obscured by coexisting vitamin D insufficiency and can become evident upon adequate vitamin D replacement. Our

results also suggest that discovery and treatment of vitamin D insufficiency in patients with low bone mass and primary hyperparathyroidism are worthwhile in advance of definitive treatment of the state of primary hyperparathyroidism.

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