Calcif Tissue Int (1999) 64:275–279

Calcified
Tissue
International

Clinical Investigations

Calcidiol and PTH Levels in Women Attending an Osteoporosis Program

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Received: 9 February 1998 / Accepted: 1 October 1998

Abstract. We performed a retrospective study of 237 patients attending a specialty osteoporosis practice. Secondary causes for reduced bone mineral density (BMD) were evaluated in 196 postmenopausal women and 41 premenopausal women; mean age was 56 ± 13.8 years (mean ± SD). BMD was measured by dual-energy X-ray absorptiometry (DXA) (QDR 1000W/2000 Hologic). Levels of intact parathyroid hormone (iPTH), calcidiol [25(OH)D], thyroid-stimulating hormone, and 24-hour urinary calcium were measured, and serum and urine protein (SPEP and UPEP) electrophoresis were performed. Overall, 16% of our patients had 25(OH)D levels <15 ng/ml, the lowest acceptable vitamin D level without a concomitant rise in iPTH levels. Among the osteoporotic patients (T score <−2.5 SD), 17% had 25(OH)D levels <15 ng/ml and 7% <10 ng/ml. Among the osteopenic patients (−2.5 < T < −1.0 SD), 11% had 25(OH)D levels <15 ng/ml. Seventeen percent of patients with Z score ≤−1.0 SD (low range normal value) had 25(OH)D levels <15 ng/ml. Low 25(OH)D levels were inversely related to high iPTH values ($r = 0.30$, $P < 0.0001$). Hypercalciuria was present in 15% of our patients, elevations of PTH levels (>65 pg/ml, upper normal limit of assay) were present in 11.5%, and hyperthyroidism in 4%. A 25(OH)D level of <25 ng/ml in women ($n = 86$) with *no known secondary causes of low BMD* was associated with an iPTH level above 49 pg/ml. The measurement of 25(OH)D levels is recommended in the evaluation of secondary causes for reduced BMD. Supplementation with vitamin D appears needed to keep 25(OH)D above 25 ng/ml, the level required to prevent increments in iPTH levels.

Key words: Risk factors — 25(OH)D — iPTH — low BMD.

An estimated 26–38 million Americans have osteoporosis or are at risk for developing osteoporosis [1]. Measurement of low bone mineral density (BMD) by densitometry is clinically useful to identify patients who may benefit from prevention or treatment interventions for osteoporosis [2–3]. Osteoporosis is defined by WHO criteria as a T score (compared with young normal BMD values) <−2.5 SD, and osteopenia (low BMD) as a T score between −1 and −2.5 SD [3]. Once a diagnosis of low BMD is made, the clinician is faced with the task of ruling out other secondary causes for low BMD before instituting therapy. Cornerstones of therapy must include adequate calcium (Ca) and vitamin D (calcidiol [25(OH)D]) intake. Some studies have shown that low Ca intakes and low 25(OH)D levels contribute to low BMD [4–7], and studies from Europe, Scandinavia, and the United States have shown an association between low 25(OH)D levels and hip fracture [8–11].

Vitamin D deficiency (of a severity to cause rickets and osteomalacia) and low level vitamin D insufficiency [4, 12, 13] lead to elevations in parathyroid hormone levels, resulting in reduced BMD [14–20]. Definitions of 25(OH)D deficiency and insufficiency may vary considerably with seasons due to sunlight exposure [8, 15, 22, 23]. Also, the variability in the different vitamin D assays used in Europe and those that include a high performance liquid chromatography (HPLC) extraction technique may result in lower vitamin D levels than assays commonly used in the United States [4, 24, 25]. Gloth et al. [14] defined the lowest acceptable level of 25(OH)D as 15 ng/ml, based on iPTH levels as an index of 25(OH)D repletion whereas data from European studies report a lower range of <12 ng/ml and 15 ng/ml [26, 27]. Several studies have demonstrated a significant negative correlation between 25(OH)D and iPTH levels [5, 6, 14, 22, 23, 28–36]. Ooms et al. [28] found that a 25(OH)D level below a threshold of 10 ng/ml was related to an elevated iPTH level whereas others have reported levels of 14.8 ng/ml [14, 15] and 20 ng/ml [13, 16]. In patients with low 25(OH)D levels, negative relationships between vertebral BMD and PTH levels [20], and positive relationships between hip BMD and 25(OH)D levels [28] have been demonstrated.

The question arises as to what screening tests would be indicated in the workup of patients with low BMD. Some researchers start assessing patients for secondary causes for low BMD at a very low Z score (age-matched BMD values) of −2.0 SD, or between −1 and −2 SD. Other investigators believe that a Z score of −1.0 SD, a low normal value that

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is associated with an increased fracture risk, is a better indicator at which to start an evaluation, but no clear guidelines exist. Moreover, many patients are treated with antiresorptive therapy for osteoporosis without the identification of possible secondary causes for low BMD.

The aim of this study was to identify the proportion of secondary causes for low BMD in patients referred to a specialty bone clinic and to determine whether that proportion varies within the diagnostic categories based on BMD criteria.

Subjects and Methods

Patients

In a retrospective study, we examined the charts of 237 community-based women who were referred to the Skeletal Health and Osteoporosis Program at the Brigham and Women's Hospital, Boston, MA from January 1990 through December 1995. Patients were included in this study if they had bone densitometry performed at any of the three main sites—the lumbar spine (LS), femoral neck (FN), or forearm (FA)—and a workup for secondary causes of low BMD. Detailed medical histories identified the following causes for low BMD: preexisting thyroid disorders, prolactinomas, hyperparathyroidism, menstrual irregularities, premature ovarian failure, and medication use including therapy with glucocorticoids, thyroid hormone, or cyclosporine. Calcium intake was estimated from a detailed calcium questionnaire.

Biochemical Measurements

Serum and urinary calcium and creatinine and liver function were measured and serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP) were performed through the clinical chemistry laboratory (Brigham and Women's Hospital, Boston, MA). Normal urinary calcium ranges for women were <250 mg/24 hours. In the Core Clinical Research Laboratory, iPTH levels were measured by the immunoradiometric Allegro assay (Nichols Institute, San Juan Capistrano, CA). The detection limit of the assay is 1 pg/ml (normal range, 10–65 pg/ml), and the intra- and interassay coefficients of variation (CV%) in our Core Laboratory are 2% and 10%, respectively. Serum 25(OH)D was measured by a radioimmunometric assay (Incstar, Stillwater, MN). The normal range is 9–53 ng/ml, the intraassay CVs in these kits range from 8.7% to 10%, respectively, and the interassay CVs range from 12 to 14%, respectively. Serum thyroid-stimulating hormone (TSH) was measured by the Allegro HS-TSH immunometric assay (Nichols Institute). The detection limit of the assay is 0.14 ng/ml, and the intraassay and interassay CVs are 2.3% and 4.1%, respectively.

Bone Densitometry

BMD at any site, i.e., LS, FN, and FA (distal 1/3 radius), was performed with DXA (Quantitative Digital Radiography 1000W/2000, Hologic, Inc. Waltham, MA). The device was upgraded in 1993 and strict cross-calibrations were performed to ensure that BMD measurements at the various sites would be comparable. The fan-beam mode was used with the QDR-2000 device. Reproducibility of DXA in our laboratory is (CV%) 0.68% ± 0.08 at the spine and 0.98% ± 0.18 at the femoral neck in premenopausal women and 1.21% ± 0.21 at the spine and 1.74% ± 0.39 at the femoral neck in postmenopausal women [37].

Statistical Analysis

In the analysis of BMD, the LS, FN, or FA site was examined. Patients were defined as having osteoporosis if the T score was <−2.5 SD at any of the above sites, or osteopenia if $-2.5 < T < -1.0$ at any of the above sites, if there was a discrepancy among the sites; the more severe definition was applied. The relationships between BMD and serum calcium, iPTH, serum 25(OH)D, 24-hour urinary calcium levels, and dietary calcium were assessed with a Spearman correlation as the distribution of the above variables was skewed. Chi-square analysis was performed to evaluate the relationship between the presence and absence of historical risk factors. The biochemical variables were dichotomized to 25(OH)D <15 ng/ml, or ⩾15 ng/ml, based on data reported by Gloth et al. [14], and iPTH levels above or below the upper limit of the normal range measured in our laboratory (<65 pg/ml, or ⩾65 pg/ml).

For simultaneous measurements of 25(OH)D and iPTH levels, data were analyzed in 86 patients without any identifiable risk factors for BMD. Because the relationship between 25(OH)D and iPTH was nonlinear, a sigmoidal (Boltzmann) fit was applied to the data using the equation:

$$y = [A_1 - A_2]/[1 + e^{(x-x_0)/dx}] + A_2,$$

where the sigmoidal line was characterized by a set-point at x_0, the slope of the line at the set-point, the width between points (dx), a maximal iPTH value (A_1), and a minimal iPTH value (A_2). The intersection of a line drawn through the set-point and a horizontal line with a slope of zero determined the 25(OH)D level that induced a rise in iPTH values. This level corresponded to the point of greatest change in iPTH levels on the sigmoidal curve. The statistical analysis was performed with SAS software (SAS Institute, Inc., Cary, NC, USA). The data are expressed as median ± SD unless otherwise stated; $P < 0.05$ is considered significant.

Table 1. Clinical characteristics of patients in a study evaluating secondary causes for low BMD

Clinical parameter	Median[a]	Range
Serum calcium (n = 232)	9.6 mg/ml	7.8–11.7
Daily calcium intake (n = 210)	807.5 mg	200–2800
Intact PTH (n = 177)	37 pg/ml	1.9–106
25(OH)D (n = 223)	23 ng/ml	4–70
Urinary calcium (n = 151)	144 mg/day	5–593
BMD		
Lumbar spine (T) (n = 168)	−2.35 SD	−5.35–1.13
Lumbar spine (Z) (n = 168)	−1.34 SD	−4.46–1.48
Femoral neck (T) (n = 120)	−3.25 SD	−5.91–1.53
Femoral neck (Z) (n = 120)	−1.28 SD	−3.63–3.26
Forearm (T) (n = 20)	−2.34 SD	−4.91–0.64
Forearm (Z) (n = 20)	−0.38 SD	−3.15–1.22

* Data did not meet normality criteria and are expressed in medians

Results

Clinical Characteristics

There were 196 postmenopausal women and 41 premenopausal women evaluated for secondary causes of low BMD. Their median age was 56 ± 13.8 years. The characteristics of the patients studied are shown in Table 1. One patient had a low serum calcium level that corrected after accounting for the low serum albumin, and five patients taking supplemental vitamin D doses of 800 IU/day or less had 25(OH)D levels above 50 ng/ml. Eight patients had calcium intakes above 2000 mg/day at the initial visit, three of whom had had chemotherapy for breast cancer and had started empirical calcium supplementation.

Table 2. The proportion of patients with secondary causes for low BMD

Secondary causes	Percentage of patients with test abnormality (n)
25(OH)D <15 ng/ml (n = 223)	16(37)
PTH >65 ng/ml[a] (n = 177)	11.5(21)
Urine calcium >250 mg/24 hours (n = 151)	15(22)
Abnormal SPEP[b] (n = 158)	6(10)
Abnormal UPEP[b] n = (101)	6(6)
Hyperthyroidism (TSH <0.5 μU/ml) (n = 214)	4(8)

[a] Five cases of surgically proven hyperparathyroidism
[b] One case of multiple myeloma

Secondary Causes of Low BMD

Of the 196 postmenopausal women, 49 were started on hormone replacement therapy. The most common risk factor for low BMD was age-associated menopause (n = 170). Secondary causes of low BMD, present in 54% of our patients, included glucocorticoid use (⩾7.5 mg prednisone daily) in 39 patients; documented thyroid disease in 30 patients; premature ovarian failure (POF) defined as ovarian failure before 40 years of age without estrogen supplementation in 26 patients; organ transplantation (heart, lung, or kidney) in 6 patients; gastrointestinal disorders (e.g., celiac sprue, inflammatory bowel disease) in 11 patients; rheumatological disorders (e.g., rheumatoid arthritis, ankylosing spondylitis) in 7 patients; and hyperparathyroidism in 4 patients. Forty-eight percent of the women studied had no identifiable historical risk factors. The proportions of patients with osteopenia and osteoporosis at our subspecialty clinic were 33% and 61%, respectively. Seventy percent of the patients had Z scores ⩽−1.0.

Low 25(OH)D level was the abnormality most often detected, as shown in Table 2. Sixteen percent had 25(OH)D levels <15 ng/ml and 7% <10 ng/ml (below the normal assay range). Thirteen percent (n = 5) of patients with 25(OH)D levels <15 ng/ml had fractures at one or more of the sites. Elevations in iPTH (>65 pg/ml) were present in 11.5% (n = 21) of patients; 10 had secondary hyperparathyroidism with low 25(OH)D levels, 5 subsequently had surgically proven parathyroid adenomas, and 6 had inappropriately elevated iPTH levels for the degree of their asymptomatic hypercalcemia, but no further data were available. Hypercalciuria was detected in 15%. Relevant abnormalities in SPEP and UPEP were each detected in 6% of patients; one patient developed multiple myeloma and one a monoclonal gammopathy of unknown significance. Only 4% of our patients had suppressed thyroid-stimulating hormone (TSH) levels. One patient had been treated for Graves' disease with radioactive iodine and was currently receiving thyroxine therapy for hypothyroidism, six were receiving thyroxine therapy for hypothyroidism, and one was newly diagnosed to have a multinodular goiter with autonomous function.

Of the patients with 25(OH)D levels <15 ng/ml, 22% had identifiable historical risk factors for low BMD, and 11% did not, $P = 0.028$. In an analysis of 86 patients *without identifiable risk factors for low BMD* for whom data on 25(OH)D and iPTH levels were available, 25(OH)D levels were inversely related to the iPTH values, $R^2 = 0.11$, $P < 0.005$. We fitted the data to a sigmoidal (Boltzmann) curve with the following characteristics: a set-point of 22.9 ng/ml, a slope of −4.8, a maximal iPTH level of 49.1 pg/ml, and a minimum iPTH level of 29.7 pg/ml. The intersection of a line drawn through the set-point and a horizontal line with a slope 0 produced a 25(OH)D level of 24.9 ng/ml, corresponding to the point of greatest change of iPTH levels on the sigmoidal graph (Fig 1). Twenty-three percent of the patients had iPTH levels above 49 pg/ml.

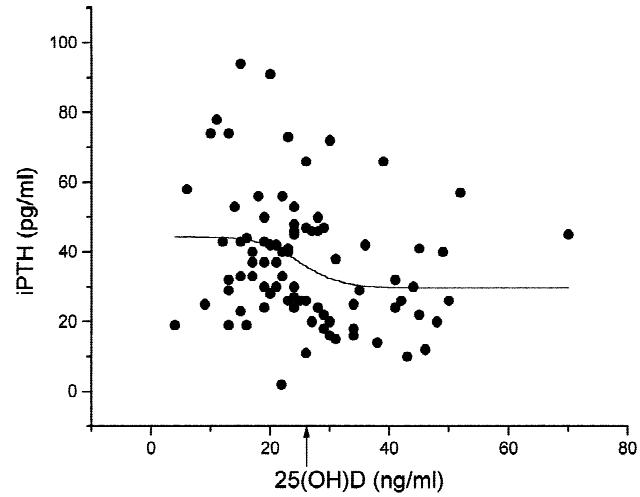

Fig. 1. The relationship between 25(OH)D levels and iPTH levels in 86 patients without known secondary causes for low BMD. A sigmoidal (Boltzmann) fit was applied to the data. Characteristics of the sigmoidal curve include a set-point of 22.9 ng/ml, a slope of −4.8, a maximal iPTH level of 49.1 pg/ml, and a minimum iPTH level of 29.7 pg/ml. Intersection of a line drawn through the set-point and a horizontal line with a slope of 0 allowed determination of the 25(OH)D threshold (24.9 ng/ml) that induced a rise in iPTH.

BMD Cutoffs and Low Vitamin D Levels

Of the osteoporotic patients (T-scores below −2.5 SD), 17% had 25(OH)D levels <15 ng/ml and 7% had 25(OH)D levels below <10 ng/ml (below the normal assay level). Of the osteopenic patients (−2.5 < T < −1.0), 11% and 4% had 25(OH)D levels below 15 ng/ml and below 10 ng/ml, respectively. Of the patients with Z scores ⩽1.0 (low range normal value), 17% had 25(OH)D levels below 15 ng/ml (Table 3). There were no statistically significant associations between 25(OH)D levels and the T-score LS, FN, and FA sites (r = 0.03, 0.03, and 0.32), respectively. Likewise, iPTH levels did not correlate to the T-score LS, FN, and FA sites (r = 0.03, −0.13, and 0.14), respectively.

Discussion

Our data show that vitamin D insufficiency, defined as a 25(OH)D <15 ng/ml [14, 29–36], as determined by a radioimmunometric assay, was the most common laboratory abnormality detected in evaluating secondary causes for low BMD in a group of community-dwelling, noninstitutionalized women referred to a specialty osteoporosis clinic. Sixteen percent of our patients had 25(OH)D levels below 15 ng/ml, including 17% of those with Z scores ⩽−1. Eight

Table 3. Proportion of patients with abnormalities in 25(OH)D levels at various BMD cutoffs

BMD	% Vitamin D <10 ng/ml (n)	% Vitamin <15 ng/ml (n)
T < −2.5[a] (n = 135)	7(10)	17(24)
−2.5 < T < −1.0[b] (n = 73)	4(3)	11(8)
Z ⩽ −1.0 (n = 156)	7(11)	17(17)

[a] WHO definition of osteoporosis
[b] WHO definition of osteopenia

percent of our patients were below the lower vitamin D threshold of 12 ng/ml (data not shown), a level characterized as vitamin D insufficiency in studies from Europe and the Netherlands [26, 27].

Another common laboratory abnormality was hypercalciuria, occurring in 22 patients (15%). Elevations in iPTH levels were present in 21 (11.5%) patients, 5 patients had primary hyperparathyroidism. Although our detection of new abnormalities in SPEP and UPEP is similar to findings of other studies identifying secondary causes of low BMD in ambulatory patients [38], the clinical relevance of these abnormalities remains unclear. Only one case of myeloma was diagnosed. Suppressed TSH levels were not common in patients using thyroid hormone replacement therapy, and only one new case of a multinodular goiter with autonomous function was detected.

The high frequency of hypovitaminosis D, detected in northeastern United States, despite fortification of milk with vitamin D, is of concern. Serum 25(OH)D levels are a more clinically available measure of vitamin D status than a bone biopsy to show increased PTH-mediated bone resorption or a defect in mineralization. Low vitamin D levels below the normal range (<10 ng/ml) and insufficient (<15 ng/ml) levels may impair mineralization of bone [4]. The relationship between vitamin D and iPTH raises concern for a PTH-mediated bone loss in this study population, even at vitamin D levels reported by many laboratories to be in the normal range. The association between vitamin D and secondary hyperparathyroidism has been demonstrated in previous studies, particularly in elderly patients (mean age 81 years) in ambulatory, homebound, and nursing home settings [5, 14–23]. Several studies have defined a critical calcidiol level of 15 ng/ml that would prevent a rise in iPTH levels, but supplementation with vitamin D to 25 ng/ml and above may be needed to prevent secondary hyperparathyroidism and thus prevent bone loss [6, 39].

On the basis of Gloth et al.'s [14] recommendation to raise the lower limit of the 25(OH)D assay to 15 ng/ml and minimize an iPTH rise, we selected 15 ng/ml as the low 25(OH)D cutoff in our analysis. Our data suggest that the 25(OH)D threshold level should be 25 ng/ml to prevent the concomitant iPTH rise (95% confidence interval for the threshold level, 12.3–33.5). The threshold is higher than previously described [4, 15, 16, 28]. Our data are supported by other studies [5, 6, 36, 39, 40]. A total dose of 800 IU/day of 25(OH)D increased baseline levels to 25 ng/ml, and these patients lost less bone than the group receiving doses of 200 IU/day with 25(OH)D levels of 17 ng/ml [6]. Chapuy et al. [5] showed that vitamin D supplementation of 800 IU daily increased 25(OH)D levels from 16 to 42 ng/ml, reduced iPTH levels by 44%, and reduced the risk of hip fracture by 43% after 18 months of therapy, compared with a placebo-treated group. In addition, therapy with calcium (1500 mg/day) and vitamin D (1000 IU/day) for 6 weeks decreased markers of bone turnover 38% and 66%, iPTH levels decreased by 10%, and 25(OH)D levels increased by 25% [40]. In a recent study, vitamin D intake of approximately 900 IU/day together with calcium achieved increments in BMD after therapy for 2 years, with reduction in nonvertebral fractures. The mean 25(OH)D level was 43 ng/ml on supplementation in this study, with iPTH levels of 31 pg/ml [39].

Limitations of our study include those associated with retrospective studies, in that we had to use preexisting data that might have been lacking some data points. Certain calciotrophic hormones, such as 1,25 dihydroxyvitamin D, were not routinely measured. Since BMD was not measured at all sites, we did not have the power to detect any association between BMD and 25(OH)D levels, and an existing relationship may actually have been overlooked [2, 41, 42]. The inability to assess any seasonal variability in vitamin D levels may reflect the fact that only initial 25(OH)D measurements ascertained from the patients' first visit were used.

Our Osteoporosis Program is a referral center, and the proportion of osteoporosis in our patient profile is definitely higher than would be expected in the general population [1]. The high percentage of our patients (70%) with Z scores ⩾−1.0 SD may also reflect some selection bias. Yet, the Third National Health and Nutrition Examination Study (NHANES III) reported an osteopenia prevalence of 54% in their noninstitutionalized US population. The prevalence of low vitamin D levels may indeed be underestimated. In fact, the proportion of patients with low vitamin D levels was comparable in the patients with Z scores ⩽−1.0 and in the osteoporotic range. Thus, it is possible to detect low vitamin D levels when BMD is in the low normal range in young women.

As health care has moved to managed care and cost containment, on the basis of the data presented herein, the measurement of 25(OH)D levels is useful in the evaluation of patients for secondary causes for low BMD. Our study agrees with the new data of several others that suggest the desirability of maintaining 25(OH)D levels above 25 ng/ml to prevent rising iPTH levels.

Acknowledgments. This work was supported in part by NIH Grant 5R01 AG12271-03 (M. S. L.), NIH NIA Grant K01 AG00666-01 (G.E.-H.F.), and an NIH National Center for Research Resources General Clinical Research Center Grant M01-RR-02635, Brigham and Women's Hospital, Boston, MA.

We thank Dr. Neville Sonnenberg for his assistance in data analysis; Dr. Lynn Kohlmeier for her thoughtful comments; Drs. Shelley Hurwitz, John Orav, and Ray Gleason, for their statistical advice; Jaylyn Olivo for her editorial advice; and Dr. G. H. Williams for overall support.

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