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Vitamin D, Parathyroid Hormone Levels and Bone Mineral Density in Community-dwelling Older Women: The Rancho Bernardo Study

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Abstract

Vitamin D (25(OH)D) increases the efficiency of intestinal calcium absorption. Low levels of serum calcium stimulate the secretion of parathyroid hormone (PTH), which maintains serum calcium levels at the expense of increased bone turnover, bone loss and increased risk of fractures. We studied the association between 25(OH)D and PTH levels, and their associations with bone mineral density (BMD), bone loss, and prevalence of hip fractures in 615 community-dwelling postmenopausal aged 50 to 97 years. Mean level of 25(OH)D and PTH were 102.0 nmol/L ± 35.0 and 49.4 ng/L ± 23.2 respectively; 49 % of women were current hormone therapy users. The overall prevalence of vitamin D insufficiency (25(OH)D < 50 nmol/L) was 2%, and prevalence of high PTH levels (> 65 ng/L) was 17.4%. In multiple linear regression analyses hip BMD was negatively and independently associated with PTH levels ($p = 0.04$), and positively and independently associated with 25(OH)D levels ($p = 0.03$). The 23 women with prevalent hip fractures had significantly lower levels of 25(OH)D and higher levels of PTH than women without hip fracture, but these associations were not independent of age. Across the entire range of values, the overall correlation between 25(OH)D and PTH was moderate ($r = -0.20$). However, after the threshold vitamin D level of 120 nmol/L, all PTH values were below 65 ng/L. Further studies are necessary to identify the optimal vitamin D levels necessary to prevent secondary hyperparathyroidism.

Keywords: Bone mineral density, Parathyroid hormone, Vitamin D, Women

Introduction

Vitamin D contributes to calcium homeostasis by increasing the efficiency of intestinal calcium and phosphorus absorption (1). Low levels of calcium in serum result in negative calcium balance, which stimulates the secretion of parathyroid hormone (PTH) (2). This compensatory secondary hyperparathyroidism maintains serum calcium levels at the expense of increased bone turnover, bone loss, and an increased risk of hip and other non-vertebral fractures (3) (4) (5) (6). Approximately ninety percent of plasma vitamin D is produced endogenously (7) after adequate ultraviolet exposure (10-15 minutes/day in the summer months). Dietary sources of vitamin D in the U.S. include fatty salt-water fish, eggs, and fortified milk. Combined vitamin D and calcium supplementation reduces the risk of hip and other non-vertebral fractures among older men and women (8) (9), but clinical trials of treatment with vitamin D alone have had mixed results (10) (11) (12) (13).

Vitamin D insufficiency, often defined as 25-hydroxyvitamin D (25(OH)D) $\leq$ 50nmol/L (14),(15), affects over 40% of individuals aged 70 and older (16) (17); even higher prevalence is found during winter and at high latitudes (18) (19) . The main causes of low 25-hydroxyvitamin D levels in older persons include inadequate sun exposure, age-related decline in the capacity of the skin to produce vitamin D (20), and possibly reduced dietary intake of vitamin D as a consequence of reduced dairy product use. In southern California, which has a sunny temperate climate year-round, vitamin D deficiency is thought to be uncommon in community-dwelling ambulatory adults and may not be considered a risk factor for osteoporosis. However, this assumption of vitamin D sufficiency has not been rigorously examined. In this paper we report the association between 25(OH)D and parathyroid hormone (PTH) levels, and their association with bone mineral density (BMD) and prevalence of hip fracture in older community-dwelling women.

Methods

Between 1997 and 2000 all surviving participants from the Rancho Bernardo Study cohort in southern California were invited to participate in a study of osteoporosis.

A total of 676 women, approximately 60% of the surviving cohort, participated. Main reasons for non-participation included having moved away, becoming too sick or too busy, or being institutionalized. Twenty of the women were unable to lie prone for the BMD measurement, and another 22 did not have adequate blood samples for measurement of 25(OH)D and PTH levels. We also excluded 19 women with creatinine clearance values < 30 ml/min. This analysis includes the remaining 615 postmenopausal women aged 50 to 97 years. All were ambulatory and gave written informed consent. The study was approved by the Institutional Review Board of the University of California, San Diego.

Participants completed a self-administered questionnaire about intake of dairy products, current smoking, alcohol use, regular physical activity, and fracture history. Current medication use, including calcium and vitamin supplementation, was ascertained by questionnaire, and was verified by examination of pills and prescriptions brought to the clinic. Postmenopausal hormone therapy (HT) was defined as current estrogen or estrogen plus progestin use at the time of the visit. Height and weight were measured in women wearing light clothing and no shoes. Body mass index (BMI) was calculated as body weight (in kilograms) divided by height (in meters) squared. Bone mineral density was measured at the total hip by dual energy x-ray absorptiometry (Hologic QDR model 1000; Hologic Inc., Bedford, MA). Bone densitometers were calibrated daily using a calibration standard, with measurements maintained within the manufacturers' precision standards of ≤ 1.5%. Non-vehicular accident hip fractures occurring after age 45 were classified as osteoporotic. Ninety-five percent of self-reported hip fractures were confirmed by examination of radiology reports.

Blood was collected in tubes that were protected from sunlight, and serum was stored at –70^{o} C within 30 minutes of processing. Serum 25(OH)D was measured by High Performance Liquid Chromatography (HPLC) (Vitamin D research laboratory, Dr. Michael Holick, Boston University). The limit of detection was 12.5 nmol/L and reference range was 25-130 nmol/L. The assay has an intra-assay coefficient of variation of 8% and an inter-assay coefficient of 12%. Intact PTH values were determined in the

same laboratory using a chemiluminescence assay kit (Nichols Institute Diagnostics, San Juan Capistrano, California). This assay has both intra- and inter-assay coefficients of variation of 6% and a reference range of 10-65 ng/L. Serum creatinine levels were measured by Smith Kline Beecham clinical laboratories. Creatinine clearance was calculated by the modified Cockcroft-Gault formula [140 minus age (in years)] multiplied by weight (in kg) divided by [72 x serum creatinine (mg/dl)] and multiplied by 0.85 (correction factor for females) (21).

Data analyses

SPSS (SPSS Inc., SPSS Base 11 for Windows User's Guide) and SAS (SAS Institute SAS User's Guide, Version 8.2) were used for analysis. Vitamin D insufficiency was defined as 25(OH)D level ≤ 50 nmol/L (14) and vitamin D deficiency was defined as 25(OH)D level < 30 nmol/L (22). Results were expressed as mean ± 95% confidence interval (CI) or percentages, and were compared using the Student *t* test, one-way analyses of variance (ANOVA), or Chi-square tests, as appropriate. Multivariate linear regression models were carried out to assess the independent associations between 25(OH)D and PTH levels with total hip BMD, as well as BMD at the femoral neck and trochanter, using both forward and backward approaches. Risk factors previously associated with BMD in this cohort (age, BMI, use of thiazide [yes/no], thyroid medication [yes/no], alcohol intake [≥ 3/week], exercise [≥ 3/week], current smoking [yes/no], calcium and vitamin D supplementation, and current hormone therapy use) were included one at a time and in combinations, until an optimal regression model was achieved. Because both 25(OH)D and hormone therapy enhance calcium absorption from the gut, an interaction term between HT and 25(OH)D was initially included in the multivariate models. The interaction term was not significant (p value > 0.1), and further analyses were performed without it. All statistical tests were two-tailed, and statistical significance was defined as $p < 0.05$.

Results

On average, the 615 postmenopausal women in this study were aged 74.6 ± 10.0 (range 50-97) years, (Table 1). Their mean levels of 25(OH)D and PTH were 102 nmol/L ± 35.0

(range 10.0-337.0) and 49.4 ng/L ± 23.2 (range 6.0-288.0), respectively. Approximately half of all women were current HT users (mean years of use was 19.8, range 5-52 years), one-fifth reported thyroid hormone use, and 16 % reported use of thiazide medication. Use of vitamin D supplements or calcium supplements was reported by 29.3 and 55.4%, respectively. Women who used vitamin D supplements had higher levels of 25(OH)D (111.3 nmol/L versus 98.0 nmol/L , $p < 0.001$) than non-users. Most women (171 of 180) who took vitamin D supplements also took calcium supplements.

Age-adjusted 25(OH)D and PTH levels varied with season in which they were sampled. Winter (December 21st - March 20th) was characterized by lower levels of 25(OH)D, while higher levels were observed in fall (September 21st – December 20th) (95.6 nmol/L versus 114.3 nmol/L, $p= 0.001$). Lower levels of PTH were found in fall and higher levels were found in spring (March 21st - June 20th) (46.4 ng/L versus 52.3 ng/L, $p=0.04$). The associations between season and vitamin D and PTH levels were independent of HT.

The overall prevalence of vitamin D insufficiency, defined as 25(OH)D levels equal or less than 50 nmol/L was 2%. Only 6 women (1 %) had levels of 25(OH)D indicative of vitamin D deficiency according to the classical criterion of less than 30 nmol/L. Prevalence of PTH levels greater than 65ng/L was 17.4%. Vitamin D and PTH levels were inversely associated ($r = -0.20$, age adjusted linear regression $\beta = - 0.31$, $p < 0.001$). As shown in a scatter plot (Figure 1), no women with 25(OH)D levels greater than 120 nmol/L had PTH levels above 65 ng/L. Serum 25(OH)D levels were lower and PTH levels were higher at older ages (p for trend < 0.001 and 0.03, respectively) (Figure 2).

Table 2 shows the association of 25(OH)D, PTH, and other risk factors with total hip BMD. Age and BMI each made a substantial contribution to the variance in hip BMD (R^2 of 0.08 and 0.12, respectively). For every year of age there was a decline of 0.005 gm/cm^2 in hip BMD ($p < 0.001$), and for every unit increase of BMI there was an increase of 0.013 gm/cm^2 in BMD ($p < 0.001$). Women who used HT had total hip BMD 0.06 gm/cm^2 higher than women not using HT ($p < 0.001$). PTH levels ($p = 0.04$) and

alcohol intake (p = 0.01) were each negatively and independently associated with BMD, while 25(OH)D levels (p = 0.03) and use of thiazides (p = 0.02) were each positively and independently associated with BMD. Neither dietary calcium intake or calcium supplementation were independently associated with BMD in the multivariate model, but use of calcium plus vitamin D supplements was positively, although marginally, associated with hip BMD (p=0.05). The season when blood samples were collected, regular exercise, and current smoking were not associated with hip BMD. Results were similar in analyses using BMD at femoral neck or trochanter as the outcome (data not shown).

There were 23 women (3.7%) who experienced a hip fracture. In unadjusted analyses they had much lower levels of 25(OH)D (87.4 versus 102.3 nmol/L, p=0.04) and somewhat higher levels of PTH (55.2 versus 49.3 ng/L, p=0.23) than women who did not have a hip fracture. These associations were not independent of age or other risk factors.

Discussion

Consistent with other reports, we found an inverse correlation between 25(OH)D and PTH (19) (23) (24), and 25(OH)D levels declined and PHT increased with age (25) (26) (27). Although only 2% of these older women had vitamin D insufficiency according to the classical definition, serum levels of PTH indicative of hyperparathyroidism were present in about 18%. This suggests that the existing criterion for vitamin D insufficiency may be too low.

In these ambulatory community-dwelling women, we found that 25(OH)D levels were independently and positively associated with hip BMD, similar to results of other studies of Caucasian postmenopausal women (28) (29) (30). The negative and independent association of PTH levels with BMD is also in accord with other studies (31) (32) (33). PTH and 25(OH)D levels did not account for a large portion of the variation on BMD in this cohort. However, we believe that 25(OH)D and PTH levels are clinically relevant because secondary hyperparathyroidism can be prevented, unlike intractable risk factors for bone loss, such as increasing age.

While the overall correlation between 25(OH)D and PTH was moderate, we observed a threshold effect, with PTH levels below 65 ng/L in every woman who had 25(OH)D levels equal or greater than 120 nmol/L. In accord with other studies (34) (35), the findings of this study suggest that secondary hyperparathyroidism could be prevented in most or all individuals by increasing serum 25(OH)D to at least 120 nmol/L year-round. Such an increase can be achieved with 1,000 IU/day supplementation with vitamin D_3 , which is comfortably below the level of 2,000 IU/day, the maximum intake where no adverse effects would be expected (34) (36).

Winter is mild in southern California, with mean temperatures in January of 57.4^{o} F and with an average of 12 days of clear sky every month; nevertheless there was substantial seasonal variation in 25(OH)D levels. Fall market the highest 25(OH)D level, consistent with the accumulation of 25(OH)D during the summer and the 3-week half life of vitamin D (37) (38). There was little seasonal variation for PTH, probably reflecting the overall adequate values of 25(OH)D. However, the associations between 25(OH)D and PTH with BMD observed here were independent of season of sampling.

Both vitamin D and HT increase intestinal calcium absorption (39). Recent findings from the Women's Health Initiative indicate that HT may not be safe for long-term therapy, and women may be discontinuing HT as a result. Those who discontinue estrogen use may experience secondary hyperparathyroidism due to decreased calcium absorption. It is important to redefine the amount of vitamin D intake necessary to maintain the desirable level of PTH, and minimize the possibility of further bone loss. Clinical trials would be helpful to confirm the appropriate dosage of vitamin D for prevention of secondary hyperparathyroidism and its long-term adverse effects on bone.

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Table 1. Descriptive characteristics of the 615 postmenopausal women, Rancho Bernardo, CA, 1997-2000.

	Mean, SD	Range
Age (years)	74.6 ± 10.0	50.0 -97.0
BMI (kg/m^2)	24.9 ± 4.1	15.3 - 45.7
Serum 25(OH)D (nmol/L)	102.0 ± 35.0	10.0 – 337.0
Serum parathyroid hormone (ng/L)	49.4 ± 23.2	6.0 - 288.0
Hormone therapy (years) among current users	19.8 ± 11.0	5.0 - 52.0
Alcohol intake (mg/week) among drinkers	100.8 ± 69.3	10.0 - 422.3
Calcium from supplements (mg/day)	927.8 ± 607.7	200.0 - 5700.0
	%	
Hormone therapy (current)	49.0	
Exercise (≥3 times per week)	70.0	
Alcohol intake (≥3 times per week)	43.4	
Cigarette smoking (current)	6.7	
Thyroid hormone use	21.2	
Thiazide use	15.8	
Vitamin D supplement use	29.3	
Calcium supplement use	55.4	

Table 2. Multiple regression of 25(OH)D and PTH with total hip BMD, R^2 change, and amount of variance explained by the entire model, Rancho Bernardo, CA, 1997-2000.

Independent variables	β	*P* value	R^2 change
Age (years)	-0.005	< 0.001	0.08
BMI (kg/m2)	0.013	< 0.001	0.12
Current hormone therapy	0.061	< 0.001	0.04
Alcohol intake (≥3x/week)	-0.025	0.01	0.007
Thiazide use (yes/no)	0.032	0.02	0.006
Vitamin D + Calcium supplements	0.013	0.05	0.04
25(OH)D (nmol/L)	0.001	0.04	0.005
Parathyroid hormone (ng/L)	-0.001	0.03	0.005
All variables in the model			0.342

Note: Season when blood was collected, exercise, thyroid hormone replacement, and smoking (current vs. non-current; ever vs. never) were not associated with hip BMD and did not enter the model.

Figure 1. Serum 25(OH)D and Parathyroid Hormone Levels. Rancho Bernardo, CA, 1997-2000.

Figure 2. Serum 25(OH)D and Parathyroid Hormone Mean Levels (± 95% CI), by Age Group. Rancho Bernardo, CA, 1997-2000.

Figure 1.

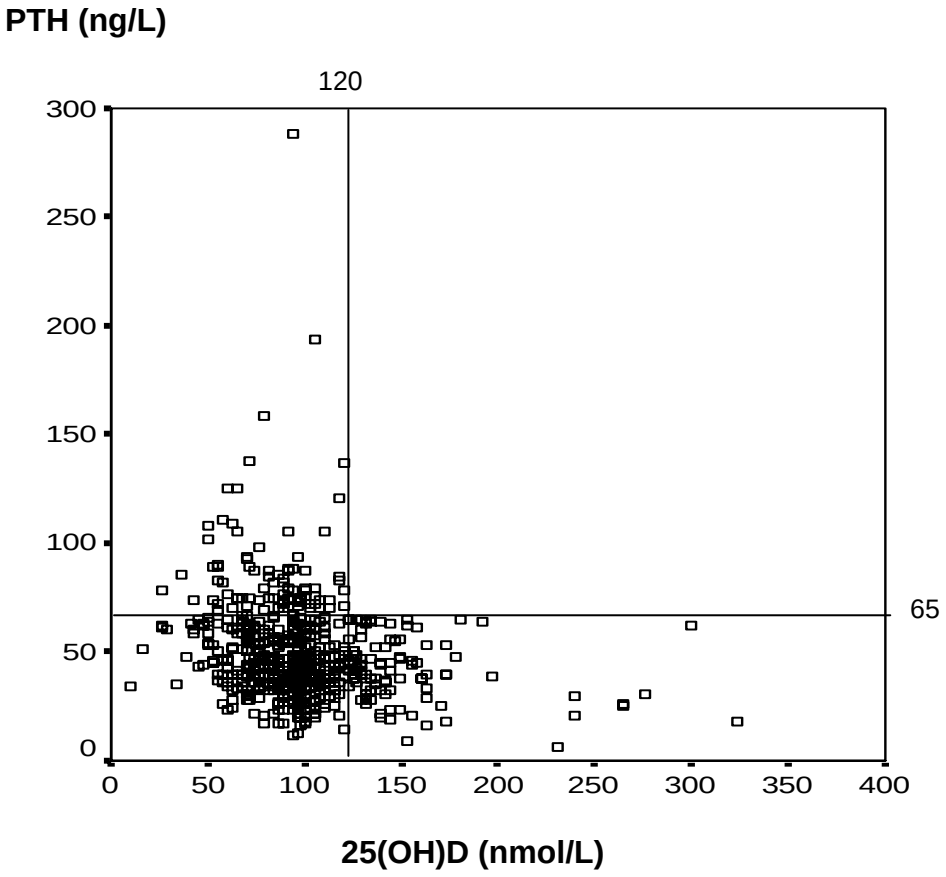
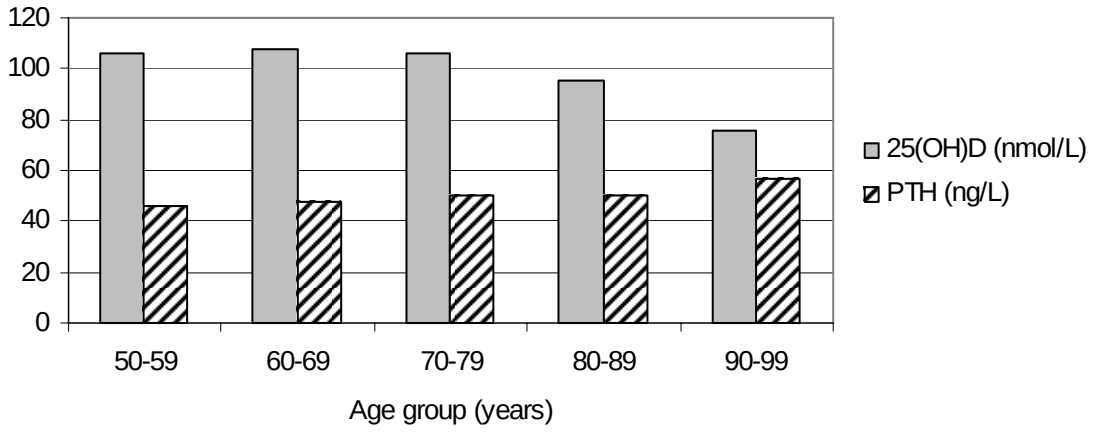

PTH (ng/L)
120
300
250
200
150
100
50
0
65
0
50
100
150
200
250
300
350
400
25(OH)D (nmol/L)

Figure 2.



Note: P for trend < 0.001 for 25(OH)D and P for trend = 0.03 for PTH