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## Optimal vitamin D status and serum parathyroid hormone concentrations in African American women<sup>1,2,3</sup>

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### Abstract

**Background**—Optimal vitamin D status for the prevention of osteoporosis has been inferred from examinations of the serum 25-hydroxyvitamin D [25(OH)D] concentration below which there is an increase in serum parathyroid hormone (PTH).

**Objective**—The objectives of the study were to ascertain whether a threshold for serum 25(OH)D exists below which serum PTH increases and whether persons with 25(OH)D above this threshold have lower rates of bone loss than do persons with 25(OH)D below the threshold.

**Design**—The relation of serum 25(OH)D to serum PTH was analyzed in 208 African American women studied longitudinally for 3 y. These healthy women in midlife were randomly assigned to receive placebo or 800 IU vitamin D<sub>3</sub>/d; after 2 y, the vitamin D<sub>3</sub> supplementation was increased to 2000 IU/d. Both groups received calcium supplements to ensure an adequate calcium intake. A systematic literature review found a wide range of threshold values in part due to varied calcium intake.

**Results**—A Loess plot suggested a breakpoint between 40 and 50 nmol/L for serum 25(OH)D. A line-line model was fitted to the data, and it showed a spline knot at 44 nmol/L. A heuristic approach verified that PTH does not decline as rapidly when the serum concentration of 25(OH)D is >40 nmol/L as when it is <40 nmol/L. We found no significant difference in rates of bone loss between persons with 25(OH)D concentrations above and below 40 nmol/L.

**Conclusion**—Although a threshold for 25(OH)D can be identified, we suggest that it should not be used to recommend optimal vitamin D status.

### Keywords

African Americans; vitamin D; parathyroid hormone; PTH; osteoporosis; calcium intake; secondary hyperparathyroidism

### INTRODUCTION

The purpose of calcium intake in midlife is to replace the calcium lost through excretion so that the loss does not have to be offset from the skeleton (1). There is general agreement that

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JFA, the principal investigator, designed and supervised the study and wrote the manuscript; SAT, the co-investigator, was responsible for medical supervision of the study participants; SP, the study statistician, was responsible for the data and statistical analyses and contributed to the writing of the manuscript; MF contributed to the data and statistical analyses, to the literature review, and to the writing of the manuscript; JKY, the laboratory director, was responsible for the biochemical assays. None of the authors had a personal or financial conflict of interest.

an intake of 1000–1500 mg Ca/d should be recommended for white postmenopausal women (2,3). There is insufficient information to make a definitive recommendation for other ethnic groups.

Vitamin D is necessary for active intestinal absorption of calcium. Vitamin D is an atypical nutrient in that it is primarily obtained from sunlight via its interaction with the skin rather than from food. The current recommendation for vitamin D intake is 10  $\mu\text{g}/\text{d}$  for women aged 50–70 y (4). This quantity is sufficient to prevent vitamin D deficiency (rickets and osteomalacia), but the optimal vitamin D status for bone health would maximize bone mass and reduce the occurrence of osteoporosis.

Many investigators have estimated optimal vitamin D status by examining the relation between serum 25-hydroxyvitamin D [25(OH)D], which is the best estimate of vitamin D status, and serum parathyroid hormone [PTH] 5–49]. The concept behind these estimates is that there is a threshold for serum 25(OH)D below which secondary hyperparathyroidism (and bone loss) occurs. The serum concentration of 25(OH)D below which PTH begins to rise has been estimated to be between 25 and 122 nmol/L (5–49). The wide range of these estimates may be related to the varied ethnicity and ages of the populations studied, varied calcium intake, the presence of illness that may affect PTH concentrations in the elderly, renal insufficiency, and lack of standardization of assays for 25(OH)D. Moreover, whereas the overall shape of scatter plots of PTH and 25(OH)D reported in the literature are remarkably similar, no consensus exists as to the ideal form of the mathematical relation between PTH and 25(OH)D.

Most of the reported studies are also limited because they are cross-sectional in design. We recently completed a prospective study of the effect of vitamin D supplementation on bone loss in healthy, postmenopausal, African American women (5). African Americans were selected for study because they have low serum 25(OH)D concentrations because of the low cutaneous synthesis of vitamin D that is due to their greater skin pigmentation (23,50). A calcium intake of 1200–1500 mg/d was ensured in these women by the provision of calcium supplements. In this report, we examine the relation between serum 25(OH)D and PTH to ascertain whether evidence exists for a threshold of serum 25(OH)D below which PTH begins to rise in calcium-sufficient African American women in midlife. We explored whether such a “threshold” was useful in predicting bone loss in this population.

## SUBJECTS AND METHODS

### Subjects

Healthy, ambulatory, postmenopausal African American women who were not taking hormone replacement therapy were recruited. All subjects were assessed with a medical history and a physical exam that was performed on site by a physician. A cohort of 208 healthy, postmenopausal, African American women aged 50–75 y met the entry criteria and were enrolled in the study.

All participants provided written informed consent. The trial was approved by the Institutional Review Board at Winthrop University Hospital.

### Study protocol

All subjects received calcium supplements after assessment of their dietary calcium to ensure a total calcium intake of  $\approx$  1200–1500 mg/d. The participants were randomly assigned to receive daily either 20  $\mu\text{g}$  (800 IU) of oral vitamin D<sub>3</sub> or a matched placebo. At the end of the 24-mo period, the dose of vitamin D<sub>3</sub> was raised to 50  $\mu\text{g}/\text{d}$  (2000 IU/d). Subjects were seen on-site every 3 mo. Study drug and calcium supplements were dispensed every 3 mo. A food-frequency questionnaire for calcium and vitamin D intakes was completed by participants with

the assistance of a nurse at each visit to assess the supplemental calcium requirement (total daily intake of 1200–1500 mg). In addition, a 3-d dietary log was filled out by subjects at baseline and 24 mo, and it was analyzed by using NUTRITIONIST PRO software (version 1.2.207; First Data Bank Inc, San Bruno, CA). A fasting blood sample was collected for analysis of serum 25(OH)D and PTH at baseline and at 3, 6, 12, 18, 24, 27, 30, and 36 mo. The participants were advised to take the study drug every day at bedtime. The calcium supplements were provided as calcium carbonate (Major Pharmaceutical, Livonia, MI); each tablet contained the equivalent of 600 mg elemental calcium.

Vitamin D<sub>3</sub> (20- and 50- $\mu$ g capsules) and matched placebo capsules were custom-manufactured for the study (Tishcon Corp, Westbury, NY). Three batches of the study drug were prepared; one was supplied at the beginning of the study, and the others were supplied annually thereafter.

### Laboratory tests

Serum PTH was measured by using the Allegro intact-PTH immunoassay [Nichols Institute Diagnostics, San Juan Capistrano, CA (5,51)]. The intraassay CV was 5.2% and the inter-assay CV was 9.0%. Serum 25(OH)D was measured by using a radioimmunoassay (RIA) kit (DiaSorin Inc, Stillwater, MN; 5, 52). The intraassay CV was 4.1%, and the interassay CV was 7.0%.

### Models used in the statistical analysis

To ensure that the data were examined with the fewest a priori assumptions about the shape of the curve that described the relation between serum 25(OH)D and PTH, the Loess method was used. The Loess method is a technique for determining the shape of the function that best summarizes the scatter plot between 2 continuous variables (53). The method does require the input of a “smoothing parameter,” which is the fraction of the data that is used around each point. An algorithm for choosing an optimal value for the smoothing parameter according to objective criteria, described by Hurvich and Simonoff (54), was used in this analysis. As described below, the Loess analysis suggested either a line-line model or an exponential decay model. So that the putative threshold would not depend on the model chosen, various models and techniques were used to produce converging evidence for a threshold.

The second approach used, the line-line or spline model, of 2 straight lines joined at a “knot,” was previously used in the analysis of the data on the relation between PTH and 25(OH)D [PTH–25(OH)D] (22,37). A repeated-measures regression model implemented in SAS PROC MIXED software (version 9.1; SAS Institute, Cary, NC) was used to test whether the line-line model provides a statistically better fit than does the simple linear regression model in ascertaining whether a specific 25(OH)D concentration exists.

Finally, the exponential decay model was also used in the analysis below because it was visually suggested by the results of the Loess analysis. This model is included here also because of precedent: it has been used by several researchers to model the PTH–25(OH)D relation (7). Another, more heuristic technique identifies a threshold by comparing changes in PTH from before treatment to after treatment with 25(OH)D in cohorts determined by baseline 25(OH)D (55). There should not be any significant change in PTH in those patients who began the study with 25(OH)D above the threshold. Conversely, the existence of a threshold implies significant PTH change in patients with 25(OH)D below this point. Paired *t* tests were used to quantify the significance of PTH change.

The longitudinal design of the current study has several advantages. First, our longitudinal data set allows us to examine the influence of serum 25(OH)D on PTH at various time points and

doses and also to study the influence of the change in PTH on the change in PTH at those points. Second, because we are measuring each patient as many as 9 times over 36 mo, we are able to generate a correlation between PTH and 25(OH)D and then to use that information in the modeling process. Having multiple observations per patient also allows us to model changes in bone mineral density over time and at the same time to automatically control for extraneous factors (eg, age or weight differences between participants) that may influence the rate of bone loss measured in the group as a whole. Third, we can merge the observations at each time point into a much larger set ( $n = 1240$ ) of measurements of PTH–25(OH)D pairs and examine the effect of variation in 25(OH)D on PTH. This study takes particular advantage of this third point. We did not use data collected at baseline (a time when patients were not yet reliably calcium replete) in the mathematical analysis of the Loess, line-line, or exponential decay models. The repeated-measures or longitudinal structure of our data set required that we incorporate the correlation between observations in individual patients into the analyses. This was done by implementing the line-line models by using SAS PROC MIXED. To establish the linear component of the association between PTH and vitamin D, Pearson correlation coefficients were computed for various time points and changes between time points. Independent  $t$  tests were used to analyze the group differences in continuous baseline values. Paired  $t$  tests were used to analyze differences over time. Nonparametric methods such as Spearman's correlation coefficient were used to confirm parametric results. Fisher's exact test and the chi-square statistic were used for establishing the significance of the relation between categorical variables. Model parameter estimates and their SEs were generated by the use of maximum likelihood functions. The significance threshold for all hypothesis tests was set at  $\alpha = 0.05$ . Alternative hypotheses were 2-sided.

### **Systematic review of literature reporting a parathyroid hormone–25-hydroxyvitamin D threshold**

We report below a summary of the PTH–25(OH)D relation literature. Included studies satisfied the following criteria: inclusion in Ovid Medline between 1 January 1995 and 15 December 2005; English language; human-subject studies that had the key words *parathyroid hormone*, *PTH*, *calcidiol*, or *hydroxyvitamin D*. This search yielded almost 500 abstracts. We then scanned these abstracts to determine whether they specifically discussed a relation between PTH and 25(OH)D, eg, correlation, association, and regression. This scanning identified 44 such publications (5–49), which dealt mainly with normal subjects or subjects seeking care at an osteoporosis center and specifically discussed the bivariate relation between various vitamin D concentrations by examining the relation between PTH and 25(OH)D. Of the 44 publications, 29 provided an estimate of “optimal” 25(OH)D or of a 25(OH)D threshold by examining the relation between 25(OH)D and PTH. One of these 29 publications found no evidence for a threshold after log transformation of the data (48). Another of the 29 publications (31) provided a separate estimate for each sex and is considered as having 2 separate thresholds. Our own data (5), subjected to the analyses reported below, produced a 31st threshold. Fifteen of the reported thresholds used the DiaSorin RIA for the 25(OH)D assay, and 15 used a more heterogeneous set of assays. These included mainly in-house competitive protein-binding (CPB) assays or Nichols Automated Chemiluminescence Assays (Nichols Advantage, San Clemente, CA). We wished to evaluate the reported thresholds as a linear function of other population parameters such as mean serum 25(OH)D and calcium intake. Because of the variability introduced by the inconsistent assay methods, this analysis was done in several ways. We first confined the data set to those DiaSorin RIA–based studies with reported dietary calcium intake. Because only 12 such studies had been identified, we then relaxed the inclusion criteria to allow into the regression analyses the 17 studies that used both DiaSorin and non-DiaSorin assays and that reported dietary calcium intake. A sensitivity analysis incorporating a series of hypothetical CPB-to-RIA conversion factors allowed us to examine the potential effect of including non-DiaSorin assays in the regressions. The results did not differ

qualitatively when the different sets of studies were used, and thus the results presented below use the maximal set of those 17 studies that report all necessary data. In all analyses, each data point was weighted proportionally to the sample size of that study. A second weighting scheme using weights proportional to the inverse of the SEM of reported 25(OH)D was also tried. This produced very similar results, and therefore only the weighting by sample size is reported.

The 30 publications summarized in Table 1 and analyzed below represent a collective sample of 14 577 patients. The sub-sample of 16 DiaSorin RIA-based studies represent a collective sample of 8093 patients. The sample of 18 publications with dietary calcium information represents a collective sample of 7176 patients.

## RESULTS

### Baseline characteristics of postmenopausal African American women

The baseline characteristics and demographic profile of the population were reported previously (5). The mean age of the participants was 60 y. Mean body mass index (BMI; in  $\text{kg}/\text{m}^2$ ) was  $29.8 \pm 4.6$ . The dietary intakes of vitamin D and calcium were generally low— $184 \pm 181$  IU/d and  $759 \pm 582$  mg/d, respectively, in the 2 groups. At baseline,  $\approx 47\%$  of the women were taking supplemental calcium or multivitamins. The baseline demographic profile did not differ significantly between the 2 groups. The baseline serum 25(OH)D ranged from 10.8 to 99.7 nmol/L, and the mean concentration was  $45.1 \pm 18.8$  nmol/L. At enrollment, 67% of the women had serum concentrations of 25(OH)D  $< 50$  nmol/L, and 95% had concentrations below 80 nmol/L. The highest serum PTH was 126.7 pg/mL, and the mean concentration was  $41.5 \pm 19.5$  pg/mL. Eleven percent of the women had serum concentrations of PTH  $> 65$  pg/mL.

### Negative correlation between parathyroid hormone and 25-hydroxyvitamin D

Data from the studies that examine the relation between PTH and 25(OH)D almost always find a significant negative correlation in the range of  $-0.15$  to  $-0.45$ . We, too, observed this result. In our sample of 208 women who entered the study with baseline measurements, we noted a statistically significant negative linear correlation between PTH and serum 25(OH)D. This relation expresses itself in various ways. For example, the correlation between the 3-mo changes from baseline in PTH and 25(OH)D is negative ( $r = -0.30$ ,  $P < 0.0001$ ;  $n = 163$ ), as is the correlation between the 12-mo changes in PTH and 25(OH)D ( $r = -0.40$ ,  $P < 0.0001$ ;  $n = 164$ ). The correlations between these 2 variables at baseline ( $r = -0.18$ ,  $P < 0.01$ ;  $n = 204$ ), 3 mo ( $r = -0.23$ ,  $P < 0.01$ ;  $n = 163$ ), 12 mo ( $r = -0.26$ ,  $P < 0.001$ ;  $n = 164$ ), and 36 mo ( $r = -0.22$ ,  $P < 0.005$ ;  $n = 152$ ) are also negative. Finally, incorporation of all 1240 available PTH–25(OH)D pairs yields a result of  $r = -0.23$  ( $P < 0.01$ ). The equivalence between the Pearson correlation and a simple linear model indicates that there is, at least as a first approximation, a significant inverse relation between serum PTH and 25(OH)D.

### Loess model results

The Loess model results are depicted in Figure 1. The Hurvich and Simonoff (54) selection method for using the Akaike Information Criteria resulted in a smoothing parameter of 0.6. A heuristic inspection of the smoothed data indicated a “natural” break point between  $\approx 40$  and  $\approx 50$  nmol/L. Note that the linear fit (thin solid line) is outside the 95% CI boundaries (light dashed lines), which indicates a relative lack of fit for the linear model. This result is confirmed more formally in the mixed-model analysis of variance implementation of the line-line model below.

## Line-line results

The Loess model results suggest that a 2-slope spline model will fit the data. The mixed model discussed above estimates the threshold to be 44 nmol/L. The slope regressing PTH on 25(OH)D of the first segment is different from zero (slope =  $-0.44$ ,  $P = 0.0001$ ). The slope of the second segment ( $-0.05$ ) does not differ significantly from zero ( $P > 0.05$ ), and the difference between the slopes of the first and second segments is highly significant ( $P = 0.0001$ ), which indicates a change in the rate at which PTH increases as 25(OH)D drops below 44 nmol/L. Most important, the nonlinear threshold model is significantly better than the simple straight line ( $P < 0.0001$ ).

Figure 1 indicates that our study data are consistent with a model with a threshold of  $\approx 40$ – $50$  nmol/L. A series of statistical models gives converging evidence that a threshold value of  $\approx 44$  nmol/L fits the data. At this value,  $R^2$  was increased to 6.9%; this was higher than the  $R^2$  of any other threshold model and was a significantly better fit than the linear model ( $F_{1,184} = 24.3$ ,  $P < 0.0001$ ).

These results were obtained after adjustment for the correlation structure between the multiple measurements obtained from each subject. A mixed-model analysis of variance was used to compare the incremental contribution of using a knot and a simple linear model. A model with a knot of 44 nmol/L and an “unstructured” correlation structure were found to fit the data by using the minimum Akaike Information Criteria in conjunction with the criterion, imposed for model simplification, that the slope after the threshold not differ significantly from zero. (When this restriction is relaxed, the threshold with the best fit is 40 nmol/L. But the slope of the regression line after 40 nmol/L does not differ clinically or significantly from the slopes after 44 nmol/L.)

Several authors have used an exponential decay model to model the PTH–25(OH)D relation. Figure 1 also indicates that this curve should fit the data. Indeed, it is difficult to visually distinguish the 2 curves (not shown). In a graph of the exponential decay model, a plateau appears between 40 and 50 nmol/L. The actual fitted equation is

$$\text{PTH} = 33 + 33 \times \exp[-0.045 \times 25(\text{OH})\text{D}] \quad (1)$$

These parameters are almost identical to those reported by Chapuy et al (7) in a publication commonly cited by others who are using an exponential decay model. Although the fit of the line-line and the exponential models is almost identical from a statistical perspective, we suggest that the line-line model has several advantages over the exponential model. First, the shape of the Loess model result is most similar to that of the line-line model. Second, the line-line model allows for further decline in PTH beyond the threshold; it is expected that “megadoses” of vitamin D will further suppress PTH. Finally, the line-line model allows for a clear-cut determination of the threshold point, whereas the exponential model does not.

The threshold estimate of 40–50 nmol 25(OH)D/L is confirmed by noting that the maximal ratio of PTH change in patients below the threshold to the change in patients above the threshold occurred—ie, the difference between the change in PTH (baseline to 1 y =  $-13.4$ ) in patients with  $< 42$  nmol 25(OH)D/L at baseline and the change in PTH (baseline to 1 y =  $-2.8$ ) in patients with  $> 42$  nmol 25(OH)D/L at baseline was greatest—when 42 nmol 25(OH)D/L was used as the threshold. Patients with 25(OH)D concentrations below this point did not show clinically and statistically significant changes as a result of their treatment with vitamin D<sub>3</sub>. Finally, there were highly significant differences via paired *t* tests in the change in PTH from baseline to 1 y in those active patients who began the study with a 25(OH)D value  $< 42$  nmol/

L. Conversely, the group with 25(OH)D concentrations > 42 nmol/L did not experience any significant change in PTH. Threshold values close to 42 nmol 25(OH)D/L had similar statistical characteristics.

### Systematic review of the literature on optimal 25-hydroxyvitamin D concentrations

Data from the systematic literature review are summarized in Table 1. The reported studies included subjects with age ranges from 10 y old to the elderly; some studies include both men and women. When the earlier studies were performed, the CPB assay was still in use. Most recent studies used RIAs, in particular the DiaSorin assay. BMI was generally not reported, although it is a determinant of serum PTH (56). Dietary intakes of calcium and vitamin D were generally below those recommended by the Food and Nutrition Board. Surprisingly, the calcium or vitamin D intake was not even reported in some studies. In no study did estimated vitamin D intake approach the currently recommended intake. The estimated optimal serum concentration of 25(OH)D varied from 25 to 122 nmol/L. The highest estimates were reported for either CPB (57) or Nichols Advantage (58) assays, both of which give inappropriately high values for serum 25(OH)D. Indeed, the 4 highest thresholds were all from studies that used the CPB assay. Half of the studies provided estimates of  $\leq 50$  nmol/L for optimal 25(OH)D and a third (10 studies) provided estimates between 40 and 50 nmol 25(OH)D/L.

Although the variability in threshold estimates is multifactorial, varied calcium intake and vitamin D status appear to be 2 of the more significant factors. A cross-tabulation of dichotomous dietary calcium intakes (above and below 1000 mg/d) with dichotomous thresholds (above and below 50 nmol/L) indicates that a lower calcium intake is associated with a higher reported threshold (chi-square test: 7.6;  $P < 0.02$ ). The Pearson correlation between these 2 variables of  $-0.62$  ( $P = 0.01$ ;  $n = 18$ ) confirms this inverse relation. A univariate analysis of all 30 studies (31 reported thresholds) documents the effect that mean 25(OH)D has on the reported threshold. A highly significant ( $P = 0.001$ ) Pearson correlation of 0.55 indicates the linear association between these 2 variables. The following linear equation implies that there is an almost one-to-one increase in the computed threshold for each 1-nmol/L increase in the mean 25(OH)D concentration.

$$\text{Study threshold} = 19.1 + 0.82 \times \text{mean study 25(OH)D} \quad (2)$$

Part of the variability in these estimates can also be explained by the fact that different models and methods were used to estimate the threshold. These varied from the sophisticated mixed-model approach to a naïve, intuitive, visual approach (5,20,25,26).

Multiple regression analysis suggests that serum 25(OH)D and dietary calcium influence the reported threshold independently; together they account for  $\approx 67\%$  of the variance in reported thresholds among the 18 available studies. The overall model  $P$  value was 0.0003 ( $F_{2,15} = 15.1$ ), and the contribution of dietary calcium to the prediction of the threshold remained significant even after control for serum 25(OH)D. Partial  $P$  values were both  $< 0.01$ . Because calcium intake was not reported in 13 studies, conclusions based on dietary calcium are only suggestive.

A nonsignificant negative correlation of  $-0.27$  was found between PTH and dietary calcium in the 18 studies with reported dietary calcium intakes. Recently, Steingrimsdottir et al (46) reported a calcium intake  $\times$  optimal 25(OH)D interaction for an effect on PTH, which we are able to confirm through our literature review. We found that, in those studies with 25(OH)D of  $> 50$  nmol/L, calcium intake did not affect PTH. But in those studies with a mean 25(OH)D of  $< 50$  nmol/L, dietary calcium was inversely related to PTH: within this subset, PTH was

6 pg/mL lower in the set of studies with dietary calcium > 800 mg/d than in the studies with dietary calcium < 800 mg/d (interaction  $F_{1,14} = 3.5$ ,  $P = 0.08$ ).

## DISCUSSION

Our data suggest that a serum concentration of 40–50 nmol 25(OH)D/L is needed to prevent a rise in PTH concentrations in calcium-sufficient African American women in midlife. We reviewed the English-language literature that reported a threshold estimate and found that most estimates clustered between 40 and 50 nmol/L or 70 and 80 nmol/L. Indeed, almost half of the studies in our literature review reported a threshold  $\leq 50$  nmol/L and one-third reported thresholds between 40 and 50 nmol/L, findings that are consistent with the value we observed. Thus, we take exception to the statement of Dawson-Hughes et al (59), “These estimates of the threshold serum 25(OH)D vary widely but there is a cluster in the 75–80 nmol range.” A equally evident cluster is found between 40 and 50 nmol/L.

The variability in the estimates for the 25(OH)D threshold may be explained by ethnic differences in calcium economy, the extent of vitamin D insufficiency, different calcium intakes, inaccuracy of 25(OH)D assays, the age and health of the populations studied, and the mathematical analyses used. We studied only African American women. Our findings may not be generalizable to other ethnic groups. It should be noted that osteoporotic fractures are less common and bone density is higher in African American women than in women of other races/ethnicities, despite the lower serum 25(OH)D of African Americans (60). Heaney (61) estimated that African American women require 300 mg/d less calcium intake than do white women.

Most of the studies examining optimal vitamin D status do not control for calcium intake. Consideration of optimal vitamin D intake without knowing calcium intake is problematic. In each study in which the calcium intake exceeded 1000 mg/d, the estimated optimal serum 25(OH)D was  $\leq 50$  nmol/L. It is of interest that the most recent Cochrane Database of Systematic Reviews concluded that, whereas vitamin D with calcium marginally reduced hip and other nonvertebral fractures, no effect was seen when vitamin D was given alone (62). Again, the interaction between vitamin D status and calcium intake should be considered in making nutritional recommendations.

Our population had a mean age of 60 y, whereas several of the studies from the literature were done in the elderly. Renal function declines with aging, and higher concentrations of 25(OH)D are needed to prevent a rise in serum PTH in the elderly (48). Indeed, a number of studies have documented secondary hyperparathyroidism in the elderly, and calcium with vitamin D supplementation has prevented fragility fractures in some (but not all) studies. Moreover, the effect of vitamin D effects on muscle may help prevent falls in the elderly, thereby reducing fracture risk (63).

Another cogent argument against recommending a vitamin D intake based mainly on a threshold derived from the scattergram of PTH versus 25(OH)D comes from our study (5). Using various models and techniques, we were able to consistently show a threshold value in our data. Despite our finding a threshold of 40–50 nmol 25(OH)D/L, those participants above and below the putative threshold did not differ significantly in loss of bone mineral density. Another analysis attempted to associate the rate of change in bone mineral density with 25(OH)D; no correlation was found between serum 25(OH)D and rates of bone loss (5).

The whole concept of a specific threshold is suspect because such a threshold may be partly an artifact of the reported serum 25(OH)D. In a global survey, Lips et al (57) found a wide range of mean serum concentrations of 25(OH)D across and within continents. Because the threshold is directly related to the observed serum 25(OH)D, it is not surprising that there is



similar wide variability in reported thresholds across the 30 studies that we reviewed. Identifying a single optimal 25(OH)D value among this variability is problematic. Furthermore, the average reported correlation across the 25 studies that reported a correlation between PTH and vitamin D was  $-0.30$ . Thus, serum 25(OH)D “explains”  $\approx 9\%$  of the variance in PTH. A wide range in reported thresholds is found, because these thresholds are calculated from a wide range of populations, assays, and statistical techniques all applied to a weak biological phenomenon (ie, a linear  $r^2$  of 9%). The wide variability in threshold estimates is another reason for caution in using that concept in making dietary recommendations for heterogeneous populations.

There are 2 reasons for trying to identify a threshold. One reason has to do with the slope *above* the threshold. Several of the studies suggested that PTH concentrations *above* the threshold may continue to drift down with increased vitamin D (A Arabi et al, unpublished observations, 2004; 64, 65). A second reason for estimating a threshold has to do with the PTH concentrations *below* this point. Our theoretical concern is with the latter. As did Vieth and Fuleihan (66) and Heaney (67), we ultimately reject the clinical utility of the threshold as a way of identifying optimal vitamin D, but we first rigorously establish the statistical reality of such a point. Note that the slope of the line below the threshold is almost 10 times as big as the slope of the line above the threshold. The fact that it drifts down very slowly is not nearly as important as is the observation that, as vitamin D is reduced below the threshold, PTH increases much more rapidly. The potential conclusion that such a threshold may have implications for optimal vitamin D concentrations is one that we ultimately reject.

Finally, it must be stated that the establishment of an optimal vitamin D intake should also consider the noncalcemic effects of vitamin D that are believed to influence the prevention of some cancers, type 1 diabetes, heart disease, and falls in the elderly (17,68). It is quite possible that African Americans (and others) may require less vitamin D for skeletal health but may require greater intake for prevention of these noncalcemic disorders. Vitamin D status and calcium intake recommendations should not be made independently but must be considered together.

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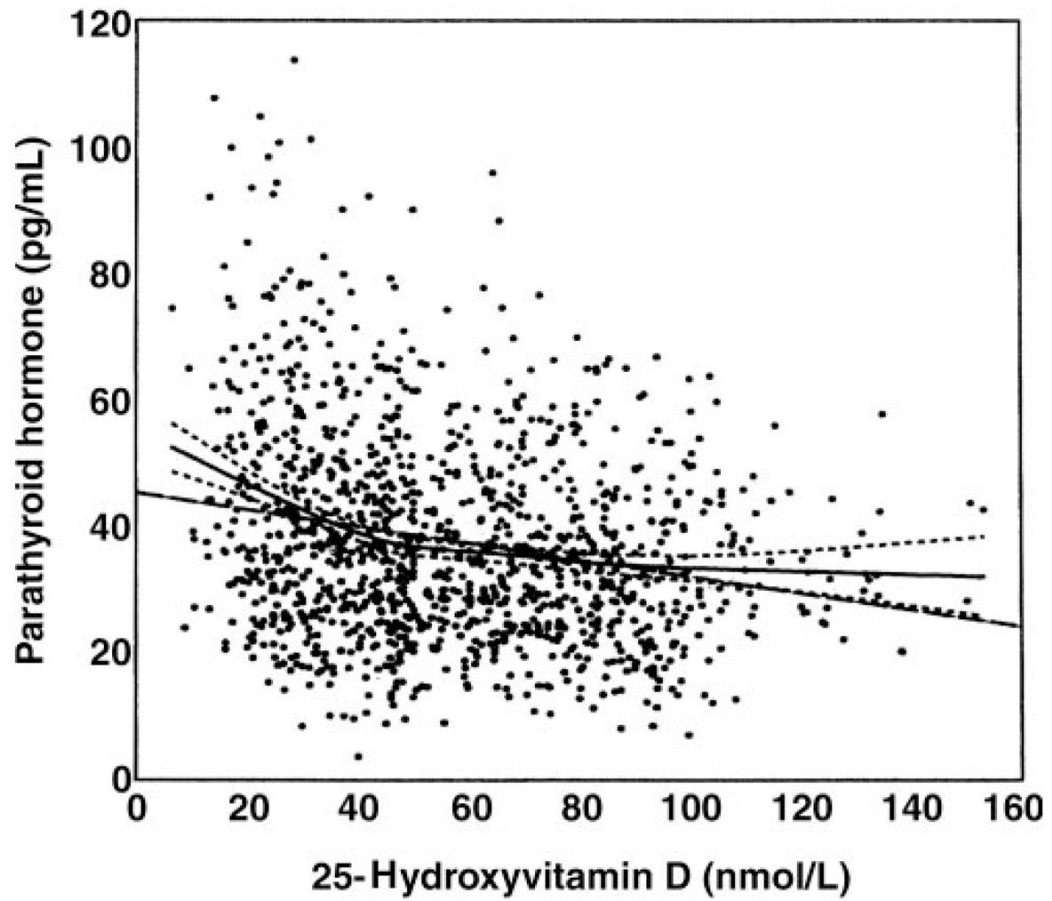
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**FIGURE 1.** Loess plot (solid line) and 95% CI of the Loess plot (dotted lines) of parathyroid hormone as a function of 25-hydroxyvitamin D.  $n = 124$ . The linear regression line (- - -) is outside the 95% CI for 25-hydroxyvitamin D concentrations <30 or >110 nmol/L.



Reference	n	Health of population	Sex	Age	Optimal 25 (OH)D	25(OH)D	PTH	Correlation <sup>2</sup> PTH plateau	Dietary vitamin D	Dietary calcium	25(OH)D assay method	Assay manufacturer <sup>3</sup>	
Thomas et al (47)	290	Other <sup>15</sup>	M/F	62.0 ± 19.0	37.5	37.5 ± 22.5	46.8 ± 44.4 <sup>5</sup>	NA	NA	7.5 ± 7.3	NA	CPB	Nichols
Vieth et al (48)	1741	Other <sup>16</sup>	M/F	56.9 ± 14.8	73 <sup>17</sup>	52.5 ± 22.0 <sup>8,13</sup>	40.4 <sup>8</sup>	NA	29.5 <sup>17</sup>	NA	NA	RIA	DiaSorin

<sup>1</sup> RIA, radioimmunoassay; CPB, competitive protein binding; IDS, Immuno Diagnostic Systems; NA, not available.

<sup>2</sup> Correlation between PTH and 25(OH)D.

<sup>3</sup> DiaSorin, Stillwater, MN; IDS, Boldon, United Kingdom; Nichols Advantage, San Clemente, CA.

<sup>4</sup>  $\bar{x} \pm SD$  (all such values).

<sup>5</sup> For some studies with subgroups, the mean  $\pm$  SD was reported only for each subgroup for some variables; in these cases, the weighted mean was computed and the overall SD was estimated from the pooled variance.

<sup>6</sup> For a few studies, the correlation was computed but not reported; in these cases, the correlation was estimated from the reported sample size and *P* value.

<sup>7</sup> For a few studies, the mean age was not reported; in these cases, it was estimated by taking the average of the minimum and maximum ages.

<sup>8</sup> Outila et al (38) inferred the optimal vitamin D status from concentrations of PTH above the mean; Cheng et al (8) simply confirmed higher PTH values below the value reported by Outila et al.

<sup>9</sup> Not specified in the report.

<sup>10</sup> For a few studies, the mean was estimated from the provided graphic—eg, box plot or bar graph.

<sup>11</sup> Elderly patients (homebound, nursing home residents, and ambulatory).

<sup>12</sup> Median.

<sup>13</sup> Estimated from the range.

<sup>14</sup> Inpatients on general medical wards and healthy outpatients.

<sup>15</sup> Inpatients on general medical wards.

<sup>16</sup> Patients with thyroid disease or osteoporosis.

<sup>17</sup> The threshold was not detected after log transformation, and Vieth et al concluded that there is no threshold.