CLINICAL RESEARCH STUDY

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# The Relationship Between Serum 25(OH)D and Parathyroid Hormone Levels

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## ABSTRACT

**OBJECTIVE:** Low 25(OH)D levels are associated with increased parathyroid hormone levels leading to progressive bone loss. The serum levels of 25(OH)D sufficient to keep the parathyroid hormone level at a range that will prevent bone loss are still unclear. The current study was aimed at evaluating the relationship between 25(OH)D levels and concomitant parathyroid hormone levels.

**METHODS:** The computerized laboratory database of Clalit Health Services, a not-for-profit health maintenance organization covering more than half of the Israeli population, was searched for all 25(OH)D and parathyroid hormone tests performed in 2009. Concomitant tests of parathyroid hormone and 25(OH)D were identified in 19,172 people.

**RESULTS:** Serum parathyroid hormone levels were inversely correlated with 25(OH)D levels ($r = -0.176$, $P < .001$); 25(OH)D levels less than 50 nmol/L were associated with a steep increase in parathyroid hormone levels and hyperparathyroidism, which decreased with increasing 25(OH)D levels and reached a plateau at 25(OH)D levels of 75 to 85 nmol/L. The quadratic fit with plateau model showed that parathyroid hormone stabilizes at 25(OH)D level of 78.9 nmol/L. However, after excluding 5449 people with hypercalcemia or renal failure, the parathyroid hormone plateau was attained at a significantly lower 25(OH)D cut point of 46.2 nmol/L.

**CONCLUSION:** Our data suggest that a 25(OH)D threshold of 50 nmol/L is sufficient for parathyroid hormone suppression and prevention of secondary hyperparathyroidism in persons with normal renal function. 25(OH)D levels greater than 75 nmol/L do not seem to be associated with additional change in parathyroid hormone levels.

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Vitamin D insufficiency is currently recognized as a worldwide epidemic[1,2] and has been found to be associated with increased morbidity.[3,4] It is widely accepted that vitamin D status is best assessed by serum 25(OH)D.[3,5,6] Because levels of 25(OH)D less than 25 nmol/L are associated with increased risk of rickets and osteomalacia,[5-7] there is a general agreement that this threshold defines vitamin D deficiency.[3,6] However, there is still lack of consensus on the definition of vitamin D insufficiency and on the physiologic range for its normal function. Because vitamin D controls dietary calcium absorption, even mild insufficiency of vitamin D is compensated by an increase in serum parathyroid hormone, which in turn is associated with increased bone turnover that leads to osteopenia, osteoporosis, and increased risk of fracture.[3-5] Many studies, therefore, use the relationship between serum parathyroid hormone and 25(OH)D to define the normal range of serum 25(OH)D,[4,5,7-11] and different cut points of serum 25(OH)D (37.5 nmol/L,[12] 50 nmol/L,[2,10,11,13] or 75 nmol/L[2,3,5,8]) are currently in use for insufficiency definition: According to the recently released report on Dietary

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Reference Intakes for vitamin D and calcium by the Institute of Medicine (IOM), persons are at risk of deficiency at serum 25(OH)D levels less than 30 nmol/L. Some, but not all, persons are potentially at risk for inadequacy at serum 25(OH)D levels between 30 and 50 nmol/L, and practically all persons are sufficient with serum 25(OH)D levels of at least 50 nmol/L.[14]

The lack of a well-established consensus regarding thresholds to be used has clinical implications, and some thresholds may lead to under- or overtreatment. This study assesses the optimal range of serum 25(OH)D by testing the dynamic relationship between 25(OH)D and parathyroid hormone levels.

**CLINICAL SIGNIFICANCE**

- A 25(OH)D threshold of 50 nmol/L is sufficient for parathyroid hormone suppression and prevention of secondary hyperparathyroidism.
- 25(OH)D levels greater than 75 nmol/L are not associated with additional change in parathyroid hormone levels.
- By using the threshold of 50 nmol/L, a smaller proportion of the population will be defined as vitamin D insufficient.

## MATERIALS AND METHODS

### Study Population and Data Collection

Clalit Health Services (CHS) is a not-for-profit health maintenance organization covering more than half of the Israeli population. Data on laboratory tests and demographic variables are available from a computerized database. The study population includes all CHS members for whom 25(OH)D and parathyroid hormone test results performed at the same time in 2009 were available. When more than 1 pair of results was available for the same person, the most recent tests were selected. Paired test results were included only if concomitant serum creatinine and calcium levels also were available for the case, within ± 8 weeks from the index result.

### Clinical Definitions

Primary hyperparathyroidism was defined as concomitant serum parathyroid hormone > 65 pg/mL and serum calcium > 10.5 mg/dL. Secondary hyperparathyroidism was defined as concomitant serum parathyroid hormone > 65 pg/mL and serum calcium ≤ 10.5 mg/dL. Renal failure was defined as serum creatinine > 1.5 mg/dL and hypercalcemia as serum calcium > 10.5 mg/dL.

### 25(OH)D and Parathyroid Hormone Assay

25(OH)D and parathyroid hormone were tested in different laboratories; however, more than 90% of the blood tests were performed in 4 central laboratories using the same assay for both tests. 25(OH)D was measured using the LIAISON 25-OH Vitamin D TOTAL assay (DiaSorin USA, Stillwater, Minn), a competitive 2-step chemiluminescence assay with a measurement range of 4.0 to 150 ng/mL (10-375 nmol/L), analytic sensitivity < 1.0 ng/mL (2.5 nmol/L), and functional sensitivity < 4.0 ng/mL (10 nmol/L). The intra-assay precision is up to 5%, and the inter-assay precision is up to 15%. The specificity is 104% for 25-OH vitamin D2 and 100% for 25-OH vitamin D3. Parathyroid hormone was measured using the IMMULITE200 intact parathyroid hormone (Siemens USA, New York, NY), a 2-site chemiluminescent enzyme-labeled immunometric assay with a measurement range of 1 to 2500 pg/mL and functional sensitivity of 1 pg/mL. The intra-assay precision is up to 5.7%, and the inter-assay precision is up to 9%.

### Statistical Analysis

Continuous data are presented as mean ± standard deviation, along with median and interquartile range. Spearman's correlation coefficient was used to test the relation between continuous variables, because some variables, including parathyroid hormone, presented a relatively right-skewed distribution. Continuous variables were compared between 2 groups by the unpaired Student *t* test or the Mann-Whitney test as appropriate. Logistic regression was used for testing an association between a continuous variable and a prevalence indicator.

The mean serum parathyroid hormone is graphically presented in 12 categories (almost equally spaced) of serum 25(OH)D (≤12, 12-25, 25-37, 37-50, 50-62, 62-75, 75-85, 85-95, 95-105, 105-115, 115-125, and >125 nmol/L). A quadratic model with plateau was fitted to model the relationship between serum parathyroid hormone and serum 25(OH)D levels (exact continuous values) to objectively identify the 25(OH)D level where the parathyroid hormone reaches a plateau. This model assumes that for 25(OH)D level less than certain concentration ($X_0$) the equation relating parathyroid hormone and 25(OH)D is quadratic, and for 25(OH)D levels greater than $X_0$ the equation is constant (at a value $P$). The model equations thus are parathyroid hormone = a + b[25(OH)D] + c[25(OH)D]$^2$ for 25(OH)D < $X_0$, and parathyroid hormone = $P$ for 25(OH)D ≥ $X_0$.

This model was estimated using nonlinear least squares model, as performed by the SAS NLIN procedure (SAS Institute Inc, Cary, NC). The joint point ($X_0$) need not be known for that application. All other statistical analyses were performed using SPSS 17.0 (SPSS Inc, Chicago, Ill). A $P$ value of less than .05 was considered statistically significant.

## RESULTS

### Subject Characteristics

Complete data were available for 24,109 pairs of serum parathyroid hormone and 25(OH)D test results in 20,045 CHS members who had test results in 2009. Included in the analysis are 19,172 members who fulfilled the inclusion