# Diagnosing Hypovitaminosis D: Serum Measurements of Calcium, Phosphate, and Alkaline Phosphatase Are Unreliable, Even in the Presence of Secondary Hyperparathyroidism

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***ABSTRACT.*** ***Objective.*** To ascertain the ability of routine biochemical markers of bone turnover to predict vitamin D insufficiency.

***Methods.*** Receiver operating characteristic (ROC) analysis was used to assess the value of serum alkaline phosphatase, calcium, and phosphate concentrations in the detection of hypovitaminosis D (< 20 nmol/l) in 467 patients between 1998 and 2000 (Cohort 1). The same analysis was repeated in a subsequent group of 719 patients between 2001 and 2003 (Cohort 2), in whom values of parathyroid hormone (PTH) were also available. Samples with elevated parathyroid levels from Cohort 2 were also analyzed to determine whether, in this subset, serum levels of calcium, phosphate, and alkaline phosphatase could reliably predict hypovitaminosis D. A subset of 50 patients from Cohort 1, with serum Vitamin D < 12 nmol/l, were reviewed by case note and telephone interview to determine demographic characteristics and the prevalence of risk factors for severe hypovitaminosis D.

***Results.*** The areas under the ROC curves for alkaline phosphatase, calcium, and phosphate were all less than 0.7 (the criterion for a useful test) in both Cohorts 1 and 2. In the subset of Cohort 2 with elevated serum PTH levels (n = 337), the area under the ROC curve for calcium was 0.701 (95% confidence interval 0.643-0.758), and less than 0.7 for alkaline phosphatase and phosphate. In the 50 patients from Cohort 1 with severe hypovitaminosis D, risk factors were prevalent: 66% were vegetarian or vegan, clothing was partially or completely occlusive of sunlight (veiling) in 72%, and 60% of this cohort went outdoors less than 5 times per week. Symptoms were non-specific in the majority.

***Conclusion.*** Routine measurements of calcium, phosphate, and alkaline phosphatase are not reliable predictors of hypovitaminosis D, even when vitamin D insufficiency has been sufficient to produce a PTH response. Clinical suspicion based upon history and an awareness of risk factors should remain the gold standard for requesting serum vitamin D measurements. Inadequate sunlight exposure (through veiling and poor outdoor exposure) and poor dietary intake are highly prevalent features of hypovitaminosis D in severely affected patients. (J Rheumatol 2005;32:684–9)

*Key Indexing Terms:*
VITAMIN D ALKALINE PHOSPHATASE CALCIUM
PHOSPHATE PARATHYROID HORMONE

Vitamin D is needed to maintain calcium homeostasis, skeletal integrity, and muscle strength[1]. Vitamin D insufficiency (hypovitaminosis D) and vitamin D deficiency are associated with an increased risk of fracture due to both proximal muscle weakness leading to increased body-sway with a propensity to fall[2] and to skeletal fragility from secondary hyperparathyroidism (increased bone turnover and decreased bone density), or from the development of osteomalacia[3-5]. Furthermore, in addition to its role in bone metabolism, vitamin D also appears to have immunomodulatory effects, as suggested by a report of an inverse relationship between risk of developing rheumatoid arthritis and dietary vitamin D intake[6], and an association between vitamin D deficiency and susceptibility to tuberculosis[7].

The definition of vitamin D sufficiency, insufficiency, and deficiency is not clearly defined[1]. Different biologic effects of falling vitamin D have been detected at varying thresholds, for example a rise in parathyroid hormone (PTH) when vitamin D falls below 78 nmol/l[8], increased body sway at concentrations below 50 nmol/l[9], and reduced muscle strength below 30 nmol/l[10] and 20 nmol/l[11]. Given these thresholds, it is becoming increasingly apparent that vitamin D insufficiency of biologic importance is not uncommon.

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Non-institutionalized population based studies report prevalences of vitamin D insufficiency between 7 and 31%[8,12,13]. In postmenopausal women in Southern Europe prevalences are reported between 51% and 64%[14,15] and similarly in high risk groups, 57% of inpatients in a general medical ward[16], 54% of community based homebound elderly patients[17], and 38% of nursing home patients[17] are reported to have vitamin D insufficiency.

It is likely that the identification of vitamin D insufficiency will become increasingly important in falls and fracture prevention programs, and possibly also within the fields of autoimmunity, immunomodulation, and infection. Traditional teaching is to suspect the diagnosis of vitamin D deficiency only when routine blood tests show evidence of increased bone turnover with elevated serum bone alkaline phosphatase (ALP), and reduced serum calcium and phosphate. These markers have been reported to satisfactorily predict the presence or absence of histological osteomalacia in a cohort of young patients[18] but to be poor discriminators of histological osteomalacia in an elderly hospital population[19]. In Indo-Asian hospital patients[20] and elderly patients attending a falls clinic[21], biochemical tests were not of discriminatory value in detecting degrees of hypovitaminosis D. In the last few years assays of serum vitamin D and PTH have become routinely available in most United Kingdom NHS Trusts, giving rise to the question whether these tests should be requested directly in patients where there is clinical suspicion of vitamin D insufficiency, or whether they should be reserved for those cases where the (often cheaper) routine bone turnover markers show an abnormality. We applied receiver operating characteristic (ROC) analysis[22] to assess the discriminatory ability of serum ALP, calcium, phosphate, and PTH to detect hypovitaminosis D in a total of 1186 serum requests for vitamin D analysis.

## MATERIALS AND METHODS

*Laboratory tests.* All requests received by the department of Chemical Pathology at St. George's Healthcare NHS Trust for serum vitamin D analysis, where there were also matched data for ALP, calcium and phosphate, were reviewed over 2 separate periods, January 1998 to June 2000 (Cohort 1) and July 2001 to June 2003 (Cohort 2). From 2001, serum PTH was routinely measured within the Trust, and data for PTH was available in all samples forming Cohort 2.

All routine biochemical measurements were made using a Bayer Dax 72 (Bayer Diagnostics, Basingstoke, UK) (Cohort 1) and with a Beckman LX20 (Cohort 2) by the manufacturers' recommended methods. Vitamin D was measured by radioimmunoassay (Diasorin Ltd, Wokingham, UK) with a lower assay limit of 5 nmol/l (Cohort 1). Vitamin D and PTH were measured in Cohort 2 using an automated immunoassay system, the Nichols Advantage (Nichols Institute, San Clemente, CA, USA) with a detection limit of 20 nmol/l and 1.1 pmol/l, respectively. Both vitamin D methods showed excellent agreement, as did the routine chemistry methods. In all samples the serum creatinine was less than 150 µmol/l.

*ROC curve analysis.* The value of routine biochemical testing in the detection of hypovitaminosis D was assessed by ROC curve analysis. This is a well established methodology for assessing test accuracy, originally developed for evaluating radar signals and subsequently applied to a range of diagnostic techniques[22]. Subjects are divided into those with or without the feature under test (in this case Vitamin D above or below 20 nmol/l) and the sensitivity and specificity of the discriminator under consideration (in this case ALP, calcium, and phosphate) calculated at different cut-off values from the lowest to the highest value in the data set. The sensitivity is then plotted against 1 – specificity for each cut-off value. The area under the curve (AUC) reflects the clinical efficiency of the discriminator (in this case the ability of ALP, calcium, and phosphate to distinguish subjects with vitamin D above or below 20 nmol/l). Tests with an AUC of 0.5-0.7 have low accuracy, 0.7-0.9 moderate accuracy, and > 0.9 high accuracy. Separate ROC curves were constructed (Analyse-It® statistical add-in for Excel®) for ALP, calcium, and phosphate, dividing patients into those with a vitamin D > 20 nmol/l and those ≤ 20 nmol/l (Figure 1). In Cohort 2 similar ROC curves were constructed for ALP, calcium, phosphate, and PTH for the whole group, and for ALP, calcium, and phosphate in the subset with a serum PTH greater than 7 pmol/l (the upper limit of the reference range for the assay).

*Demographic features and risk factors for vitamin D insufficiency.* A representative 6-month period was selected from January to June 1999. During this time there were 129 cases of hypovitaminosis D (< 20 nmol/l). Demographic features, prevalence of risk factors for vitamin D insufficiency, symptoms at presentation, and referral patterns were ascertained by notes examination and telephone consultation in early 2000 in the 50 patients of this group with the lowest vitamin D concentration (range 7-12 nmol/l).

## RESULTS

*ROC curve analysis.* In Cohort 1 there were 467 requests for vitamin D analysis with full supporting biochemical bone profiles, comprising 144 males, 315 females (8 unspecified gender), age range 1.6 - 97.4 years, median 53 years. The areas under the ROC curves (95% confidence intervals, CI, in parentheses) were ALP 0.583 (0.532-0.635), calcium 0.648 (0.599-0.698), and phosphate 0.522 (0.469-0.574) (Figure 1).

In Cohort 2 there were 719 requests for vitamin D analy-

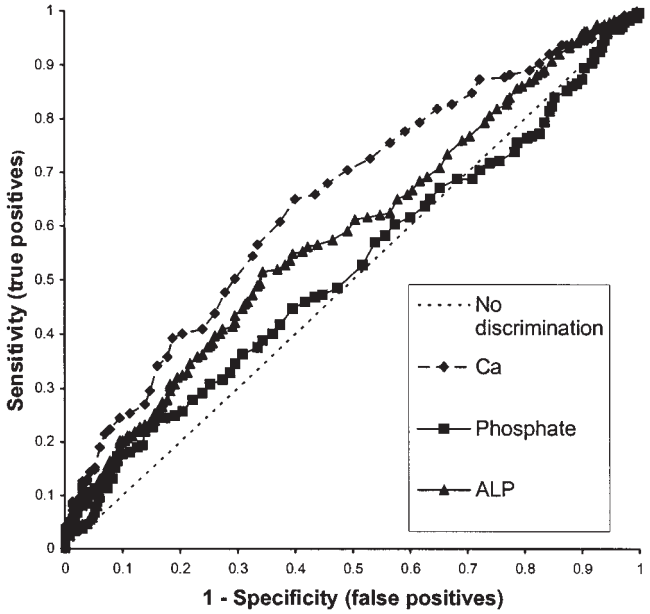


*Figure 1.* Cohort 1. ROC curve analysis for routine biochemical tests for the detection of vitamin D ≤ 20 nmol/l.

sis with full supporting biochemistry bone profiles including serum PTH, comprising 197 males and 522 females, median age 58 years. The areas (95% CI) under the ROC curves were ALP 0.621 (0.575-0.668), calcium 0.665 (0.617-0.713), phosphate 0.585 (0.532-0.637), and PTH 0.699 (0.652-0.747) (Figure 2). The sensitivity and specificity of calcium, phosphate, ALP, and PTH set at the upper (ALP, PTH) or lower (calcium, phosphate) limits of the reference range for detecting subjects with a vitamin D < 20 nmol/l are shown in Table 1.

In Cohort 2 there were 337 vitamin D analyses where serum PTH was greater than 7 pmol/l (46.9% of all vitamin D assays), median age 61.5 years. The area under the ROC curves in this subset with raised PTH (95% CI) were ALP 0.616 (0.554-0.678), calcium 0.701 (0.643-0.758), and phosphate 0.582 (0.515-0.649) (Figure 3). The sensitivity and specificity of calcium, phosphate, and ALP set at the upper (ALP) or lower (calcium, phosphate) limits of the reference range for detecting subjects with a vitamin D < 20 nmol/l in this subgroup with PTH > 7 pmol/l is shown in Table 1.

*Demographic features, risk factors, and clinical presentation.* In the subset of 50 patients from Cohort 1 with severe vitamin D insufficiency (range 7-12 nmol/l), 84% were female, 56% were over 50 years old, 16% between 41 and 50 years, and 28% below 40 years. Ninety-two percent were originally from the Indian subcontinent or Africa and 88% had been living in the UK for over 10 years (see Table 2). Dietary assessment revealed that 50% were vegetarian and a further 16% were vegan (Table 3). Sunlight exposure was assessed on the basis of (1) the extent of usual body coverage by clothing when outdoors, and (2) the average number of times the individual usually went outdoors per week (see Table 3). Body coverage by clothing was recorded as being normal in 28% of cases, partially occlusive of sunlight in 40% of cases, and totally occlusive of sunlight in 32% of cases. The number of times each individual in this group went outdoors per week was low, with 60% of patients usually going out less than 5 times per week.

Symptoms were generally non-specific and musculoskeletal in nature, including 68% with either a history of pain (50%) or weakness (18%). In 24% the symptoms specifically did not include pain. In 8% of cases a lack of understanding of English precluded an accurate assessment of symptoms. Referral to the hospital was made in all cases to a total of 7 different departments including 34% to rheumatology, 18% to respiratory medicine, 18% to general

*Table 1.* Sensitivity and specificity of calcium and phosphate at the lower limit of the reference range and of ALP and PTH at the upper limit of the reference range in the detection of samples with vitamin D < 20 nmol/l from Cohort 2 (n = 719) [A] and from the subgroup of Cohort 2 with PTH > 7 pmol/l (n = 337) [B].

| | Sensitivity | Specificity |
|---|---|---|
| A | | |
| ALP > 100 U/l | 39.9 | 78.1 |
| Calcium < 2.1 mmol/l | 15.0 | 97.3 |
| Phosphate < 0.75 mmol/l | 93.3 | 3.4 |
| PTH > 7 pmol/l | 67.4 | 61.4 |
| B | | |
| ALP > 100 U/l | 46.2 | 72.7 |
| Calcium < 2.1 mmol/l | 17.4 | 97.6 |
| Phosphate < 0.75 mmol/l | 90.2 | 3.4 |

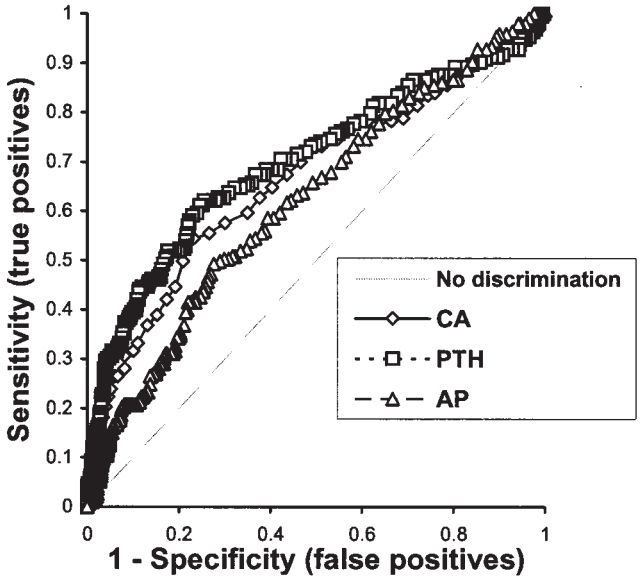


*Figure 2.* Cohort 2. ROC curve analysis for routine biochemical tests for the detection of vitamin D ≤ 20 nmol/l.

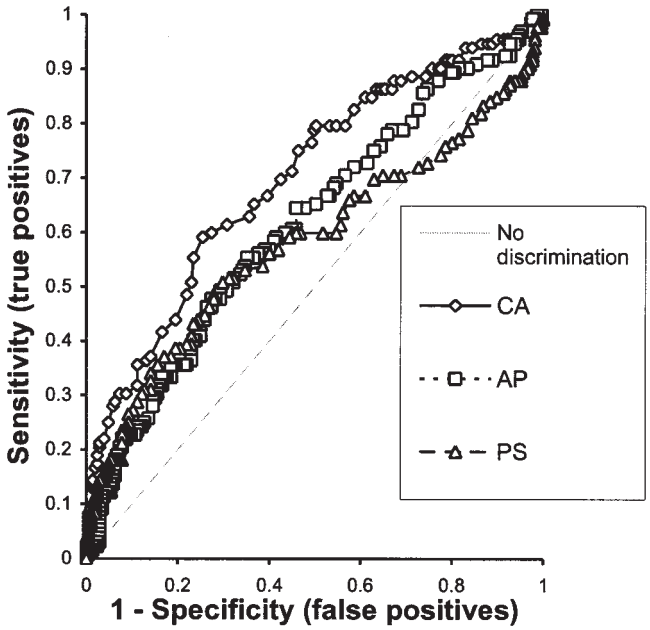


*Figure 3.* Cohort 2. Subgroup with elevated serum parathyroid levels (> 7 nmol/l). ROC curve analysis for routine biochemical tests for the detection of vitamin D ≤ 20 nmol/l.

*Table 2.* Demographic features of 50 patients with the lowest vitamin D concentration in a cohort of 129 patients with vitamin D deficiency.

| Ethnic Origin (%) | | | | | |
|---|---|---|---|---|---|
| Indian H | Indian M | Pakistan M | Africa M | Caucasian | Other* |
| 42 | 6 | 26 | 12 | 6 | 8 |
| Duration of residence in UK, yrs (%) | | | | | |
| 0–5 | 6–10 | 11–15 | 16–20 | 21–25 | > 25 |
| 4 | 8 | 12 | 6 | 16 | 54 |

H: Hindu; M: Moslem. * 1 Pakistan Christian, 2 Sri Lankan Hindu, 1 Moslem from Yemen.

*Table 3.* Risk factors for vitamin D deficiency in 50 patients with the lowest vitamin D concentration in a cohort of 129 patients with vitamin D deficiency. Sunlight occlusive clothing was defined as: normal: head and parts of the limbs exposed; partial occlusion: head exposed but limbs always completely covered; complete occlusion: head and limbs both always completely covered.

| Sunlight Occlusive Clothing (%) | | | |
|---|---|---|---|
| Normal | Partial Occlusion | Complete Occlusion | |
| 28 | 40 | 32 | |
| Number of Outdoor Excursions Per Week (%) | | | |
| 0 | 1–2 | 3–4 | > 5 |
| 18 | 22 | 20 | 40 |
| Diet (%) | | | |
| Non-Vegetarian | Vegetarian | Vegan | |
| 34 | 50 | 16 | |

internal medicine, 12% to endocrinology, 10% to gastroenterology, and the remainder to orthopedics and care of the elderly.

## DISCUSSION

We have shown that neither an elevated serum ALP, nor a low calcium or phosphate are able to reliably detect hypovitaminosis D (vitamin D < 20 nmol/l) in 2 separate large cohorts totaling 1186 patients (n = 467 + 719) over a 4.5 year period. In both cohorts the areas under the ROC curves for ALP, calcium, and phosphate were below 0.7, the criterion for a useful or discriminatory test.

As persistent vitamin D insufficiency leads to secondary hyperparathyroidism, it has been suggested that an elevation in PTH is a sensitive pointer to significant hypovitaminosis D[23,24]. The availability of PTH data in Cohort 2 (n = 719) allowed an assessment of the effects of PTH in the laboratory diagnosis of hypovitaminosis D. The ROC analysis in this cohort revealed that PTH was unable to discriminate samples with a low vitamin D, nor were ALP or phosphate any more likely to do the same in the subgroup of Cohort 2 (n = 337) with hyperparathyroidism. Serum calcium became more discriminatory in the presence of a high PTH, as the area under the curve for calcium rose from 0.665 in all samples in Cohort 2 to 0.701 in the subgroup with hyperparathyroidism, but even so the values remained poorly discriminatory.

The inability of PTH to discriminate hypovitaminosis D may be explained by the concept of functional hypoparathyroidism. Sahota[25] has reported that 50% of patients with hypovitaminosis D (< 30 nmol/l) fail to develop hyperparathyroidism, and as a result have lower 1,25 dihydroxyvitamin D, and hence a lower serum calcium as a result of less calcium absorption. In practical terms, however, the absolute values of calcium in patients with and without secondary hyperparathyroidism in this study remained within the reference range, supporting our conclusions that calcium abnormalities are unlikely to lead to detection of hypovitaminosis D in the clinical setting.

A clinician is only likely to be prompted to review a case, or consider a diagnosis not apparent from history or examination, by laboratory results outside the reference range. Our data show that the sensitivity and specificity of each of ALP (> 100 U/l), calcium (< 2.1 mmol/l), phosphate (< 0.75 mmol/l), and PTH (> 7 pmol/l) at specific cut-off values that represent the upper or lower limits of the quoted reference range of the laboratory are very poor with respect to detecting vitamin D < 20 nmol/l. Although it has been shown that different degrees of hypovitaminosis D are associated with a rise in ALP and PTH, the absolute values still remain within the reference ranges[24], and it is unlikely that these subtle changes would alert a clinician to the diagnosis.

We reported the ROC values using a vitamin D threshold of 20 nmol/l because this represents the lower detection limit of the assay used in Cohort 2. Furthermore as this is a relatively low vitamin D concentration, it is more likely to be associated with changes in routine biochemistry, which might be detected in routine clinical practice. We have also performed the same ROC analyses dividing samples into those with a vitamin D greater or lower than 30 nmol/l, 35 nmol/l, and 40 nmol/l. At each threshold the same negative findings are found with serum ALP, calcium, and PTH being unable to discriminate between high or low vitamin D. Thus our findings indicate that abnormalities of routine biochemistry are unable to discriminate hypovitaminosis D defined by the lower limit of the laboratory threshold (20 nmol/l) or by biologically relevant higher thresholds such as 30 or 40 nmol/l where changes in muscle strength and sway have been reported[9,10].

Detection of vitamin D insufficiency is of clinical importance given high prevalence rates in many populations[8,12-17,24,26], and significant biological longterm seque-

lae, particularly with respect to muscle weakness increasing the likelihood of falls and an increased fracture risk due to bone fragility and ultimately osteomalacia[1-5]. The gold standard diagnostic test for osteomalacia is a bone biopsy, but this is hard to advocate as it is invasive, painful, and not widely available. The finding of a low bone mineral density, or malabsorptive states such as Crohn's and celiac disease should prompt further investigations, including assessment of vitamin D status. Nevertheless many patients with hypovitaminosis D may remain undetected, with bone biochemistry values within the reference ranges, unless clinical suspicion is raised. In our subgroup of 50 patients with the most severe hypovitaminosis D, symptoms were unhelpful, being non-specific in the majority of patients, suggesting that there is little in the history to alert a clinician to the condition. This is of general relevance to physicians, as shown by the wide range of medical departments to which these patients were referred within the hospital.

Clinical suspicion of hypovitaminosis D should be based on an awareness and assessment of risk factors. While sunlight is the most important source of vitamin D, it is intriguing that a large multinational study found no relation between vitamin D and latitude within Europe, with unexpectedly lower levels in Southern compared to Northern European countries[24]. This suggests that the contribution of sunlight may be overcome by the effects of other factors, such as occlusive clothing and dietary vitamin D fortification or restriction. An assessment of risk should therefore include both sunlight exposure and diet. Indeed Thomas, *et al*[16] found that in addition to insufficient sun exposure and being housebound, inadequate dietary vitamin D intake was an independent predictor of vitamin D insufficiency in a study of 164 patients in a general medical ward in Massachusetts, USA. Furthermore occlusive dressing or veiling also poses a significant risk for vitamin D deficiency, irrespective of latitude or average hours of daily sunshine, as illustrated in a study from Lebanon where clothing is completely occlusive and 60% of women had serum vitamin D levels less than 10 ng/ml[27].

In our study we found the majority of the subgroup (n = 50) of patients with severe insufficiency (vitamin D < 12 nmol/l) to have at least one such risk factor, in that 72% wore occlusive or partially occlusive clothing, 60% went outdoors less than 5 times a week, 66% had a restricted diet, 92% were from the Indian subcontinent or Africa, and 88% had resided in the UK for at least 10 years. This high prevalence suggests that an awareness of risk factors is likely to facilitate the detection of hypovitaminosis D.

In summary we have shown that abnormalities of routine markers of bone profile, beyond laboratory reference ranges, are unable to discriminate patients with vitamin D insufficiency, even in those where serum PTH is elevated. Therefore the finding of normal ALP, calcium, phosphate, or PTH should not be interpreted as implying normal vitamin D status. The diagnosis of hypovitaminosis D should be made on the basis of clinical suspicion, arising from an awareness of risk factors, leading to direct measurement of serum vitamin D.

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