 DOI 10.1111/j.1365-2133.2008.08616.x

Serum 25-hydroxyvitamin D in erythropoietic protoporphyria

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Accepted for publication

4 February 2008

Key words

photodermatosis, photoprotection, porphyria, protoporphyria, sunscreen, vitamin D

Conflicts of interest

None declared.

Summary

Background Vitamin D, produced by the action of sunlight on skin, is an important hormone for calcium homeostasis and has been implicated as tumour-protective agent. Some previous studies of photosensitive patients who actively avoid sunlight have failed to show convincing evidence of vitamin D insufficiency.

Objectives The aim of this study was to characterize the vitamin D status of a large cohort of patients with erythropoietic protoporphyria (EPP).

Methods U.K. patients with EPP were recruited prospectively and seen locally by a single study investigator. A blood sample was taken for vitamin D assay. All blood analyses were performed in the same laboratory.

Results A cohort of 201 patients with known EPP was seen over a 7-month period between January and July. Thirty-four patients (17%) were deficient in vitamin D and 126 (63%) had insufficient vitamin D. Both insufficiency and deficiency were significantly associated with the total erythrocyte protoporphyrin concentration and inversely with the time in minutes to the onset of symptoms following sunlight exposure.

Conclusions This is the first report of significant levels of vitamin D deficiency and insufficiency in a large cohort of patients with a photodermatosis. Such individuals are at risk of associated adverse events. In future, clinicians should consider monitoring 25-hydroxyvitamin D levels and instigating oral supplementation or dietary advice if appropriate.

Vitamin D is an essential fat-soluble hormone required for bone integrity and calcium homeostasis.[1] It may also protect against the development of other conditions such as diabetes mellitus, hypertension, tuberculosis and some malignancies.[2–4] Approximately 90% of requisite vitamin D is formed within the skin as a result of sunlight photolysis of 7-dehydrocholesterol by ultraviolet (UV) B radiation, before a temperature-dependent isomerization to cholecalciferol.[5] Previous studies of photosensitive patients with xeroderma pigmentosum (XP) and Smith–Lemli–Opitz syndrome (SLOS) who actively avoid sunlight have failed to show convincing evidence of vitamin D insufficiency.[6,7]

Erythropoietic protoporphyria (EPP, MIM 177000) is a rare photodermatosis with systemic complications which results from an inherited partial deficiency of ferrochelatase, the terminal enzyme of haem biosynthesis. Excessive formation of its substrate, protoporphyrin IX, results in protoporphyrinaemia and accumulation in erythrocytes, plasma, skin and liver, prior to excretion in the bile.[8] Protoporphyrin can absorb light energy, damaging surrounding tissues through the generation of free radicals and clinically manifesting as painful photosensitivity within minutes of skin exposure to sunlight. The discomfort may last for several hours, cutaneous tolerance to sunlight may be reduced for several days afterwards and some individuals experience the symptoms even on cloudy days and in winter.[9] Management of EPP is based mainly on minimizing the acute adverse effects of sunlight by use of broad-spectrum sunscreens, occlusive clothing and behavioural measures to avoid direct sunlight.

Patients and methods

During a prospective study of U.K. patients with EPP,[9] we sought to characterize their vitamin D status. A cohort of 210 outpatients was seen over a 7-month period between January and July, representing a period with minimal and maximal vitamin D levels in normal populations,[10] at latitudes ranging from 51°N to 57·5°N. Each provided a blood sample for vitamin D assay and all analyses were performed in the same laboratory using a commercial radioimmunoassay (Diasorin Ltd,

Wokingham, U.K.). Serum 25-hydroxyvitamin D concentrations of < 10 and < 20 ng mL^{-1} (25 and 50 nmol L^{-1}) were used to identify those who were vitamin D deficient (VDD) or insufficient (VDI).[11] Nine patients were withdrawn from the analysis due to nonwhite skin coloration (n = 2: both VDI), systemic malignancy (n = 2), renal failure (n = 1), hepatic failure (n = 2), post-orthotic liver transplant (n = 1) and a patient taking ergocalciferol (n = 1). Statistical analysis was performed using the Mann–Whitney test.

Eighty per cent of the cohort regularly avoided sunlight, 87% wore long-sleeved occlusive clothing daily, 9% used a sunscreen at least once daily all year and 68% used sunscreen once daily or more frequently in sunny weather. No patients had ever had their vitamin D status checked by their physicians. Five patients reported coexistent osteoporosis, but other than analgesics, were not taking any other treatments for this. Three patients took fish liver oils daily as a health supplement, one of whom also took a calcium supplement. One further patient took calcium supplementation. Excepting a nonvegan vegetarian, all patients were omnivores; a more detailed dietary history was not taken.

Results

The mean serum hydroxyvitamin D was 18·32 ng mL^{-1} (range 4·9–51·4, quartiles 11·5, 23·5). One hundred and twenty-six patients (63%; 58 males, 68 females) were VDI, of whom 34 were VDD (17%; 15 males, 19 females). Of three patients taking dietary fish oil supplements, one was VDI. Of the twenty-one patients receiving UVB phototherapy to induce 'hardening' of their skin to sunlight sensitivity, only six (29%) were VDI and none was VDD.

The mean monthly serum 25-hydroxyvitamin D rose over the study period January to July from 15·5 to 21·3 ng mL^{-1} (Fig. 1). In the winter months of January and February 70% of patients (19 of 27) were VDI and 44% (seven of 27) were VDD: in the summer months of June and July 45% (34 of 75) were VDI and 37% (28 of 75) VDD. There appeared to be a slightly smaller proportion of children aged 16 years or under who were VDI or VDD compared with the overall population [three of 34 (11%) vs. 18 of 92 (20%)]. One hundred and eighty-one complete sample sets were available for analysis of calcium, phosphate and parathyroid hormone (PTH) biochemistry. Thirteen patients (7%) were deficient in adjusted serum calcium (11 VDI, of whom three were VDD) and 41 (23%) had an elevated serum phosphate (21 VDI, of whom three were VDD). Hyperparathyroidism was seen in 12 patients, of whom nine were VDI (two VDD) and the remaining three had serum 25-hydroxyvitamin D at the lower end of the normal range, at between 21 and 23 ng mL^{-1}.

Statistical analysis suggested that being VDI was associated with total erythrocyte protoporphyrin (TEP) ($P = 0·009$) and inversely associated with the time in minutes to the onset of symptoms following sunlight exposure ($P = 0·008$). Being VDD was associated with the age at symptom onset ($P < 0·0005$), TEP ($P = 0·02$) and inversely with minutes to symptom onset ($P = 0·03$). There was no association with calcium deficiency, raised phosphorus or elevated PTH, although elevated PTH approached significance with VDI status ($P = 0·57$).

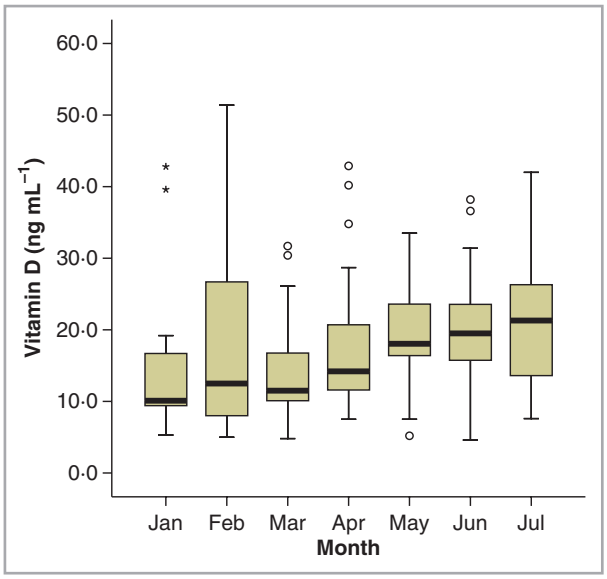

Fig 1. Boxplot of serum 25-hydroxyvitamin D by month of sampling (deficiency < 10 ng mL^{-1}, insufficiency < 20 ng mL^{-1}). The boxes contain results between the upper and lower quartiles and the dark bars within the boxes represent the median value. The whiskers represent smallest and largest values which are not outliers, while the circles are outliers (more than 1·5 box lengths above or below the box) and the stars extreme outliers (more than 3 box lengths above the box).

Discussion

We have shown a high prevalence of VDD and VDI status in a large cohort of patients with EPP, whose main risk factors were latitude of residence and their photodermatosis. In keeping with previous findings, we demonstrated an increase in median 25-hydroxyvitamin D between winter and summer.[7,10,12,13] However, a sizable proportion was VDI even in summer, implicating the photodermatosis and sun-avoidance measures as the most plausible explanation, and supporting the demonstrated association with sensitivity and TEP.

Although previously recognized in cases reports, studies of photosensitive populations with XP and SLOS, and normal populations using sunscreens, have not shown similar levels of vitamin D insufficiency.[6,7,12,13] Explanations include low study sensitivities due to smaller patient numbers, residency in sunnier environments, lack of skin discomfort in XP (an efficient prompt for rigorous sunlight avoidance in EPP), or the presence in SLOS of abnormally high concentrations of the vitamin D precursor, 7-dehydrocholesterol.

Since completion of this study, controversy over the correct values of the 25-hydroxyvitamin D normal range[5] has led to

our laboratory now using 30 ng mL^{-1} as the lower end of the normal range, increasing the proportion of VDI patients in our cohort to 91%. The findings of this study suggest that a sizeable proportion of an EPP cohort is VDI and at risk of important clinical outcomes. Treatment with oral calcium and vitamin D increases bone mass and reduces the risk of fractures,[14,15] so clinicians advising patients with EPP about sunlight avoidance should consider monitoring both serum 25-hydroxyvitamin D and PTH, and giving supplementation throughout the year. As the cutaneous synthesis of vitamin D is initiated by UVB-mediated photolysis of 7-dehydrocholesterol, use of UVB phototherapy to reduce symptoms appears to have additional therapeutic benefit.

Acknowledgments

This research was supported by the Royal College of Physicians (Lewis Thomas Gibbon Jenkins Memorial), the British Skin Foundation and the Dermatology Research Fund of the Royal Gwent Hospital.

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