Normal vitamin D levels can be maintained despite rigorous photoprotection: Six years' experience with xeroderma pigmentosum

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Background: Although sun protection is advocated for skin cancer prevention, sunlight is also important in generation of vitamin D in the skin. There is concern that sun protection may result in an abnormally low level of vitamin D.
Objective: To assess the risk of vitamin D deficiency in a sunlight-deprived population, we studied eight ambulatory patients with xeroderma pigmentosum (XP) who practiced intensive sun protection during a chemoprevention study of oral isotretinoin.
Methods: We surveyed the patients to determine the extent of sun protection and vitamin D intake and measured the serum levels of two vitamin D metabolites (25-hydroxyvitamin D [25-OHD] and 1,25-dihydroxyvitamin D [1,25-$(OH)_2$D]), calcium, and parathyroid hormone during 6 years.
Results: The patients all wore protective clothing and sunscreens when outdoors. Estimated mean vitamin D intake was normal. The mean values of serum 25-OHD were low normal, but 1,25-$(OH)_2$D, calcium, ionized calcium and parathyroid hormone levels were normal. Lack of seasonal variation in serum 25-OHD indicated rigorous photoprotection.
Conclusion: Despite rigorous sun protection normal vitamin D levels can be maintained in ambulatory patients with XP.
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Vitamin D is an essential hormone required for bone integrity and calcium homeostasis.[1-3] In human beings, vitamin D is obtained by two routes: by sunlight exposure of the skin and by eating foods containing vitamin D. Some investigators believe that the daily vitamin D requirement is mostly provided by casual exposure to sunlight.[2] Therefore there has been increasing concern regarding possible vitamin D deficiency in persons practicing daily photoprotection by use of sunscreens and UV-protective clothing.[2]

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Xeroderma pigmentosum (XP) is an inherited disease characterized by sun sensitivity, photophobia, early-onset freckling, and subsequent tumors on sun-exposed surfaces.[4,5] Patients with XP have a more than 1000-fold risk of sunlight-induced cutaneous basal cell carcinoma, squamous cell carcinoma, or melanoma, with a median age of first skin cancer of less than 10 years.[6] Patients with XP are advised to take extreme photoprotective measures by minimizing daylight time outdoors, wearing sun-protective clothing including UV radiation–absorbing eyewear, and constant use of sunscreens. These patients would, therefore, be expected to be at high risk for vitamin D deficiency. We examined serum vitamin D metabolites, calcium, and parathyroid hormone (PTH) levels over time in a group of photoprotected patients with XP.[7]

METHODS

Eight patients with XP were studied (four males and four females; mean age at beginning of the study, 27 years [range, 14-49 years]). They were all the partici-

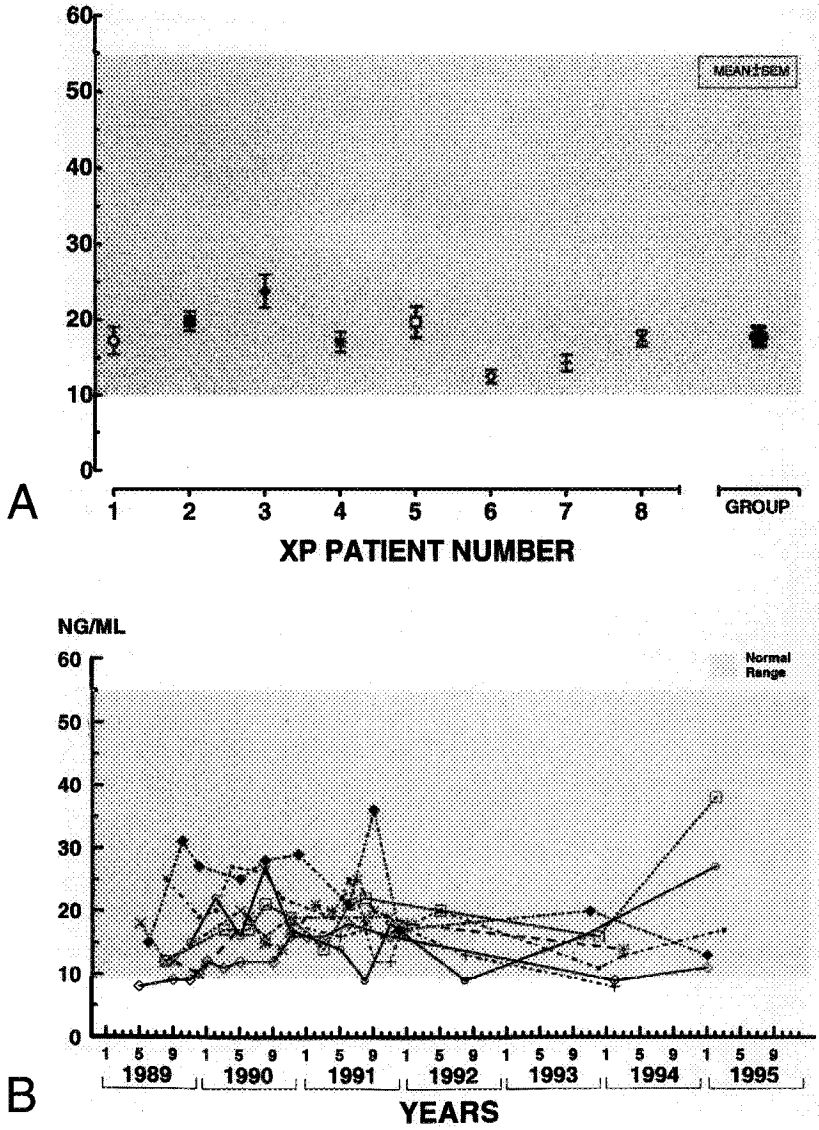

Fig. 1. 25-Hydroxyvitamin D serum levels. **A,** Mean serum 25-OHD values over 6 years for each patient with XP (represented by individual symbols). Group mean (mean of the means) represented as final bold symbol. **B,** Multiple serum 25-OHD values plotted over 6 years for each XP patient (represented by individual lines). Almost all values are in low- to mid-normal range.

pants in a study of the use of oral isotretinoin for skin cancer prevention.[7] They did not receive supplemental vitamin D or calcium and did not use oral contraceptives. Values of serum calcium, ionized calcium, 25-hydroxyvitamin D (25-OHD), and 1,25-dihydroxyvitamin D (1,25-$[OH]_2D$) and PTH (intact) were assessed from 1989 through 1995. The patients lived throughout the United States from as far south as California to as far north as Wisconsin. Serum 25-OHD levels were determined by either competitive protein binding assay after C-18 chromatography (Smith-Kline-Beecham) or by high-pressure liquid chromatography done after a cartridge (solid-phase) extraction (Mayo Labs). Serum 1,25-$(OH)_2D$ levels were determined by cartridge extraction with subsequent radioreceptor assay. The interassay coefficient of variance was 15%. Serum calcium values were determined by means of the Synchron CX3 clinical system (within-run precision of 2%). Serum ionized calcium values were determined with the NOVA 8 Calcium/pH Analyzer. Accuracy was within 2%. PTH values were determined by immunochemiluminescent assay with an average interassay coefficient of variance of 8%. Vitamin D dietary intake was assessed by means of a 1-week dietary survey prepared by the National Institutes of Health Clinical Center Nutrition Department based on the current recommended dietary allowance.[7] Photoprotection was

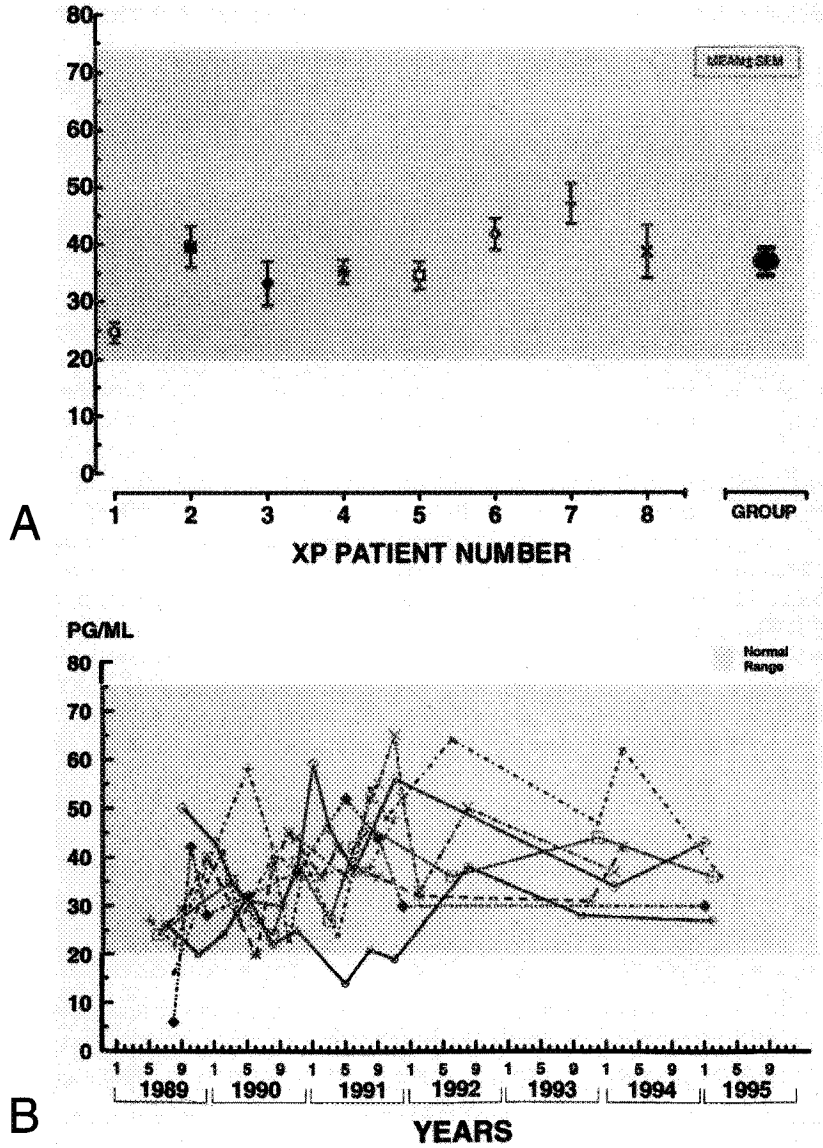

Fig. 2. 1,25-Dihydroxyvitamin D serum levels. **A,** Mean 1,25-$(OH)_2D$ values over 6 years for each patient with XP. Values were in normal range for all. Group mean (mean of the means) represented as final bold symbol. **B,** Multiple 1,25-$(OH)_2D$ values over 6 years for each patient with XP. Almost all are in normal range.

assessed with a survey of usual clothing, sunscreen application, and outdoor exposure.

RESULTS

Sun protection

All eight patients with XP utilized extreme sun protection measures by staying indoors during daylight hours, wearing sun-protective clothing, and applying sunscreens of at least sun protection factor (SPF) 15 each day. They reported daily sunlight exposure averaging 5 minutes or less. Several of the patients had a history of marked sun burning on minimal sun exposure before diagnosis of XP. During the course of this study none experienced sunburning.

Vitamin D values

The serum 25-OHD values determined from 1989 through 1995 are shown in Fig. 1. The mean value for the 88 determinations (range, 7 to 14 determinations per patient) in all eight patients with XP was 17.8 ± 1.5 ng/ml (normal range, 10

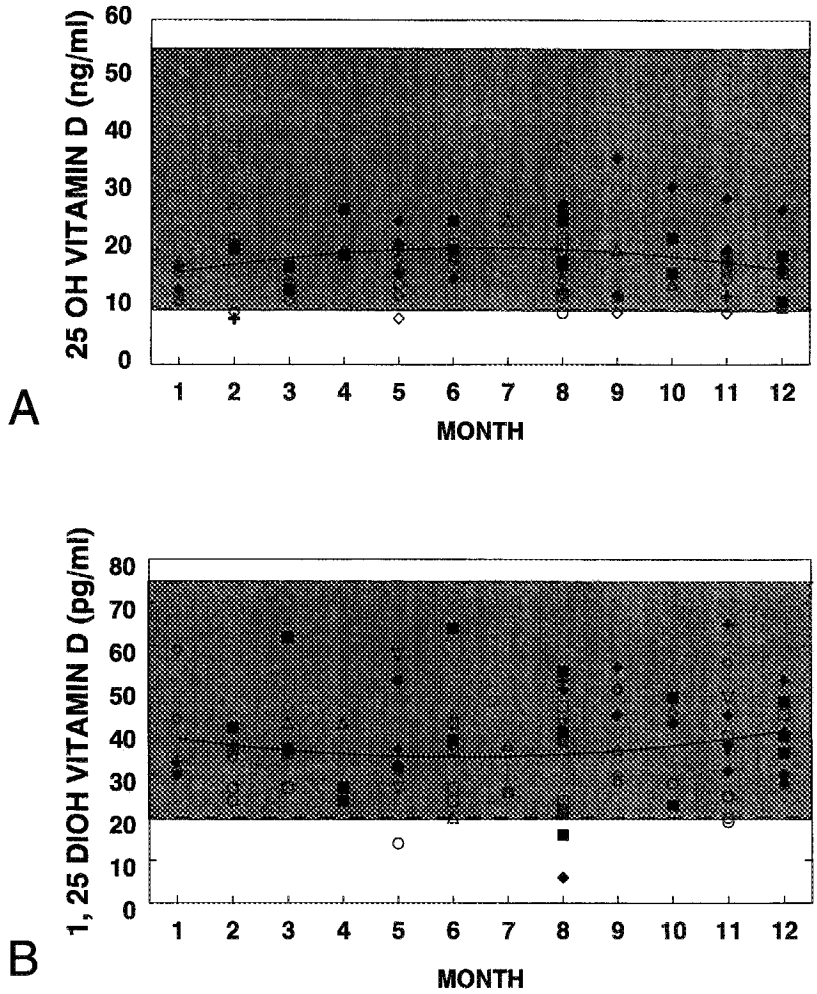

Fig. 3. Monthly changes in serum vitamin D levels. **A,** Monthly levels of serum 25-OHD for each patient with XP. *Solid line,* Mean value for each month. **B,** Monthly levels of serum 1,25-$(OH)_2$D for each patient with XP. *Solid line,* Mean value for each month.

to 55 ng/ml) (Fig. 1, *A*). The mean values for each patient were also in the low-normal range (Fig. 1, *A*). The values for serum 25-OHD are plotted over the course of observation for each patient in Fig. 1, *B*. Although the values vary considerably over time, almost all are in the low- to mid-normal range.

The serum 1,25-$(OH)_2$D values determined from 1989 through 1995 are shown in Fig. 2. The mean value for the 88 determinations (range, 7 to 15 determinations per patient) was 36.9 ± 3.1 pg/ml (normal range, 20 to 76 pg/ml) (Fig. 2, *A*). The mean values for each patient were also in the normal range (Fig. 2, *A*). The values for serum 1,25-$(OH)_2$D are plotted during the course of observation for each patient in Fig. 2, *B*. Although the values vary over time, almost all are in the normal range. In addition, as with serum 25-OHD, the 1,25-$(OH)_2$D values do not show a trend toward increasing or decreasing during the period of observation.

Because vitamin D is produced in the skin after sun exposure, values of serum vitamin D may be expected to be higher during the summer months if the skin is not protected from sunlight.[2,8,9] The monthly values of serum vitamin D are shown in Fig. 3. There was a small increase in mean serum 25-OHD levels in the summer months that was not statistically significant (Fig. 3, *A*). The mean value for August (20 ± 1.9 ng/ml, n = 16) was only slightly greater than that for January (15 ± 1.2 ng/ml, n = 6) and was much less than the upper limit of normal of 55 ng/ml. The mean values of

serum 1,25-$(OH)_2D$ also showed no increase during the summer months (Fig. 3, *B*).

Serum calcium and PTH

Serum calcium levels reflect both ionized calcium and calcium bound to protein. The mean value for the 196 serum calcium determinations for all eight patients (range, 10 to 32 determinations per patient) from 1989 through 1995 was 2.32 ± 0.02 mmol/L (normal range, 2.05 to 2.5 mmol/L). The means of all eight patients were also within the normal range. Ionized calcium levels are not affected by serum protein alterations.[10] The mean of 14 serum ionized calcium values was 1.23 ± 0.04 mmol/L for the seven patients tested. This is within the normal range of 1.17 to 1.31 mmol/L.

Low vitamin D levels may be compensated by increasing the levels of PTH. However, the mean intact PTH levels in the seven patients with XP tested was 36.1 ± 3.4 pg/ml (normal range, 10 to 65 pg/ml).

Vitamin D and diet

Seven of the patients with XP were surveyed for dietary intake of vitamin D near the end of the study. The current recommended daily allowance of vitamin D for adults is 200 IU.[11] The patients reported adequate dietary vitamin D with an estimated mean daily intake of 307 IU (range, 136 to 543 IU). The main source of dietary vitamin D was milk. Two patients reported vitamin D–deficient diets averaging 136 IU/day (patient 3) and 142 IU/day (patient 1). Patient 1 had the lowest mean value of serum 1,25-$(OH)_2D$ and had sporadic values at or below the lower limit of normal for both serum 25-OHD and 1,25-$(OH)_2D$ (Figs. 2 and 3). Patient 3 had serum vitamin D levels that were similar to other patients who reported a higher vitamin D intake.

DISCUSSION

Vitamin D is an essential hormone required for bone integrity and calcium homeostasis.[1-3,9,12] The active form of vitamin D increases intestinal absorption of calcium and phosphorus.[10] It also induces the maturation of osteoclastic stem cells that causes resorption of calcium and phosphorus from bone. In human beings, vitamin D is obtained from two separate sources. Sunlight exposure converts epidermal and dermal stores of 7-dehydrocholesterol (provitamin D_3) to previtamin D_3 (precholecalciferol) and then to vitamin D_3 (cholecalciferol). Vitamin D_3 is also ingested in foods. Major sources include milk fortified with vitamin D, fish liver oils, and egg yolks. Once vitamin D_3 is obtained by sun exposure or ingestion, it undergoes two sequential hydroxylations. The major circulating form, 25-OHD, is produced by the liver. The level of serum 25-OHD is a measure of the body stores of vitamin D. A small fraction of 25-OHD is converted in the kidney to its active form (1,25-$[OH]_2D$, calciferol). Serum calcium levels are maintained by an interplay involving 1,25-$(OH)_2D$ and PTH.

Some investigators believe that the daily vitamin D requirement is mostly provided by casual exposure to sunlight.[2,13] In addition, exercise is associated with elevated serum levels of 25-OHD.[14] There has been increasing concern about vitamin D deficiency in persons practicing daily photoprotection by use of sunscreens and UV-protective clothing.[2] Homebound elderly persons appear to be subject to osteoporosis and increased bone fractures.[8,15-17] This concern has been supported by studies showing the negative effects of long-term sunscreen use, clothing, and particular seasons on vitamin D synthesis. Clothing prevents cutaneous production of vitamin D.[18] Sunscreen with an SPF of 8 suppresses cutaneous synthesis of vitamin D_3.[19] Long-term use of *para*-aminobenzoic acid containing sunscreens is associated with lower levels of serum 25-OHD.[9,20] A randomized, double-blind, Australian study of broad-spectrum sunscreen (SPF 17) versus placebo demonstrated an decrease in the mean level of serum 1,25-$(OH)_2D$ in the sunscreen group.[21] However, no person in either group had a vitamin D level outside the normal range during the 7-month study.

Use of oral isotretinoin (0.5 to 1.0 mg/kg per day) for treatment of acne for 4 months[22] or for 20 weeks[23] resulted in no change in the level of serum 25-OHD but produced a 13% to 15% drop in the mean serum 1,25-$(OH)_2D$, a level that nevertheless remained in the normal range. Our patients received oral isotretinoin (0.5 to 2.0 mg/kg per day) for up to 6 years but had a low normal level of serum 25-OHD and a normal level of serum 1,25-$(OH)_2D$. In four of these patients the mean value for bone mineral density of the femur and radius was normal and that of the lumbar spine was elevated.[24]

The present study shows maximally photoprotected, nearly non-sun-exposed, active, ambulatory patients are capable of maintaining a normal vitamin D level through a normal diet. Although the vitamin D stores were low normal, as indicated by a low normal level of serum 25-OHD, the active metabolite, 1,25-$(OH)_2$D, was in the normal range. Similar results were found in sun-protected young Japanese patients with XP.[25] The absence of a significant seasonal change in the level of serum 25-OHD and the lack of seasonal variation in serum 1,25-$(OH)_2$D indicates that the sun protection was rigorous in our patients. Moreover, a normal level of both serum calcium and ionized calcium was maintained in the patients with XP without compensatory elevation of PTH. Therefore normal serum vitamin D levels and calcium-PTH axis function can be maintained by an adequate diet despite intensive sun protection. Concerns about vitamin D deficiency should not preclude routine sunscreen use in the normal, active population.

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