High Prevalence of Vitamin D Deficiency in Patients With Basal Cell Nevus Syndrome

Jean Y. Tang, MD, PhD; Angela Wu, BA; Eleni Linos, MD, PhD; Neeta Parimi, MS; Wayne Lee, BS; Michelle Aszterbaum, MD; Maryam M. Asgari, MD; David R. Bickers, MD; Ervin H. Epstein Jr, MD

Objectives: To evaluate vitamin D status in patients with basal cell nevus syndrome (BCNS) who practice photoprotection because of their genetic predisposition to skin cancer and to determine risk factors for deficiency.

Design: Retrospective cohort study.

Setting: Academic medical centers.

Patients: Forty-one ambulatory patients with BCNS who participated in a 2-year chemoprevention clinical trial. Population-based controls (n=360) were selected and matched by age, sex, Fitzpatrick skin type, and season/ geography.

Main Outcome Measures: Levels of 25-hydroxyvitamin D (25[OH]D) and vitamin D deficiency (defined as a 25[OH]D level of ≤20 ng/mL).

Results: Twenty-three patients with BCNS (56%) were vitamin D deficient. Patients with BCNS had mean 25(OH)D levels below those of the general population (−3 ng/mL; P=.02) and were 3 times more likely to be vitamin D deficient (56% vs 18%; P < .001). Levels of 25(OH)D were lower in patients who were overweight (−3.0 ng/mL; P=.04) and who had blood collected in the winter compared with the summer (−7.1 ng/mL; P<.001).

Conclusion: Patients with BCNS may be at increased risk for vitamin D deficiency, depending on their adherence to photoprotection practices.

Trial Registration: clinicaltrials.gov Identifier: NCT00023621

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Vitamin D deficiency has been associated with an increased risk of autoimmune disease,1 fractures,2 cancer,3 cardiovascular disease,4 and all-cause mortality.5 Results from the National Health and Nutrition Examination Survey (NHANES), which is representative of the US population, suggest that vitamin D deficiency is common, with approximately 20% of white participants considered deficient on the basis of serum levels of 25-hydroxyvitamin D (25[OH]D) 20 ng/mL or less (to convert to nanomoles per liter, multiply by 2.496). Vitamin D deficiency is more frequent in certain subgroups, including elderly, dark-skinned, or overweight individuals; nursing home residents; and people residing in areas of low UV exposure (≥35° North [N]).7 There is increasing concern that sun protection, recommended by dermatologists to prevent further UV damage in populations susceptible to skin cancer, may result in abnormally low levels of 25(OH)D, which may have subsequent detrimental effects on health.8,9

To address this issue, the American Academy of Dermatology recently issued a position statement on vitamin D deficiency and the potential need for dermatologists to recommend oral supplementation, especially for patients who adhere to strict photoprotection.10 Patients with a history of skin cancer are regularly advised to avoid sun exposure, but there are insufficient data on the prevalence and severity of vitamin D deficiency among patients with skin cancer and scarce information to identify those at highest risk for deficiency.11 Previous studies have reported increased vitamin D deficiency in patients with skin cancer, but these results have not been compared with those in individuals without skin cancer, and those studies did not adjust for known variables that affect 25(OH)D levels such as age, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), and Fitzpatrick skin types.11-13
Our primary aims were to evaluate the vitamin D status of patients with basal cell nevus syndrome (BCNS) (Gorlin syndrome; Mendelian Inheritance in Man 109400) and to identify predictors of deficiency, which may be useful in clinical practice. We measured levels of 25(OH)D in patients with BCNS who are genetically predisposed to developing basal cell carcinomas (BCCs). In contrast to individuals with sporadic BCCs, which are few in number and generally acquired by patients in their sixth to seventh decades of life, patients with BCNS develop multiple BCCs in young adulthood.14,15 Individuals with BCNS inherit a mutated copy of the PTH1R tumor suppressor gene (OMIM 601309)19 and display wide phenotypic variability. Some patients with BCNS develop a few BCCs in their lifetime, whereas others develop thousands.14,15 Similar to other UV-sensitive patients, such as those with xeroderma pigmentosum, patients with BCNS generally try self-photoprotection by using sunscreen and by avoiding the sun during peak hours in an attempt to prevent these skin cancers that can be locally destructive and can cause significant morbidity.12,15 Our goals were to identify predictors of low 25(OH)D levels and to assess the prevalence of vitamin D deficiency among patients with BCNS.

STUDY PARTICIPANTS

We surveyed 41 ambulatory patients with BCNS undergoing a chemoprevention clinical trial with celecoxib, a type of oral non-steroidal anti-inflammatory drug.17 Sixty patients were initially enrolled in the clinical trial, 43 were enrolled for at least 1 year, and 41 had evaluable blood samples for 25(OH)D measurements. We obtained written consent for all subjects, and all aspects of the study were reviewed and approved by the institutional review board of the University of California, San Francisco, and Columbia University Medical Center. Patients who were at least 18 years of age were recruited from all parts of the United States. Enrollment began on May 11, 2001, and was completed on June 12, 2004. Study participants were seen at the following 4 study centers: Newport Beach, California; New York, New York; San Francisco, California; and South Euclid, Ohio. A diagnosis of BCNS was established if a subject had 2 of the following major criteria: multiple BCCs or a single BCC before age 20 years, jaw cysts, and palmoplantar pits.14 Study dermatologists recorded subject age, BMI, geographic residence, and self-reported race/ethnicity. Race/ethnicity was assessed because BCCs are more likely to occur in white patients, such as those with xeroderma pigmentosum, patients with BCNS generally try self-photoprotection by using sunscreen and by avoiding the sun during peak hours in an attempt to prevent these skin cancers that can be locally destructive and can cause significant morbidity.12,15 Our goals were to identify predictors of low 25(OH)D levels and to assess the prevalence of vitamin D deficiency among patients with BCNS.

STATISTICAL ANALYSIS

We used univariate and multivariate (adjusting for BMI) regression techniques to determine the association between baseline characteristics and 25(OH)D levels in patients with BCNS.

METHODS

DEMOGRAPHIC VARIABLES AND 25(OH)D LEVELS FROM NHANES

Comparisons were made with 25(OH)D levels in the general population based on data collected for the 2003-2004 NHANES. The NHANES data included demographic characteristics (age, BMI, and self-reported race) for 10,122 participants in the household interviews, with a high response rate of 79%.12 Standardized digital photographs were taken of a random subset of these participants (n = 2,996) during physical examination at nationally stationed mobile examination centers. Two independent dermatologists reviewed the photographs to assign a Fitzpatrick skin type23 on a scale of I to VI.14 Levels of total 25(OH)D were measured using a radioimmunoassay kit (DiaSorin, Inc, by the National Center for Environmental Health, Centers for Disease Control and Prevention. Levels of 25(OH)D measured in the NHANES control subjects using the radioimmunoassay or the chemiluminescent immunoassay are comparable because both assays use the same antibody.24 Because physical and laboratory examinations occurred in mobile examination centers, NHANES preferentially scheduled data collection in southern latitudes (<35°N) during November to March and in northern latitudes during April to October to avoid inclement weather problems and to improve data collection. This procedure created a season-latitude study design in which at least 73% of the data collected from November through March came from latitudes of less than 35°N, and at least 86% of the data collected from April through October came from latitudes of 35°N or greater. For each patient with BCNS, we selected approximately 9 controls (for a total of 360) who were matched by age, sex, race, Fitzpatrick skin type, and season/geography. To compare the prevalence of vitamin D deficiency between patients with BCNS and NHANES controls, we used 25(OH)D values from blood collected in the summer in patients with BCNS from northern latitudes and 25(OH)D values from blood collected in the winter in the patients with BCNS from southern latitudes to match the inherent season-latitude design of NHANES. If a patient with BCNS had multiple 25(OH)D measurements, we took the average 25(OH)D value for each season (summer vs winter) to compare with NHANES data.
Table 1. Baseline Characteristics of Patients With BCNS and NHANES Control Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients With BCNS (n=41)</th>
<th>NHANES Controls (n=368)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>40.2 (11.0)</td>
<td>39.7 (8.0)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>30.1 (6.9)</td>
<td>28.3 (6.4)</td>
</tr>
<tr>
<td>Male sex</td>
<td>22 (54)</td>
<td>173 (48)</td>
</tr>
<tr>
<td>Fitzpatrick skin type &lt;=III</td>
<td>41 (100)</td>
<td>360 (100)</td>
</tr>
<tr>
<td>No. of BCCs per subject</td>
<td>22 (18)</td>
<td>NA</td>
</tr>
<tr>
<td>at baseline, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residence in latitude &gt;35°N</td>
<td>21 (51)</td>
<td>241 (67)</td>
</tr>
<tr>
<td>Frequent daily sunscreen useb</td>
<td>33 (80)</td>
<td>NA</td>
</tr>
<tr>
<td>Avoidance of midday sunlight</td>
<td>37 (90)</td>
<td>NA</td>
</tr>
<tr>
<td>Daily multivitamin usec</td>
<td>14 (34)</td>
<td>184 (51)</td>
</tr>
<tr>
<td>Mean No. of measurements</td>
<td>3 (range, 1-6)</td>
<td>1</td>
</tr>
<tr>
<td>25(OH)D level, mean (SD), ng/mL</td>
<td>24.5 (12.4)</td>
<td>27.5 (10.0)</td>
</tr>
</tbody>
</table>

Abbreviations: BCC, basal cell carcinoma; BCNS, basal cell nevus syndrome; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); N, north; NA, not applicable; NHANES, National Health and Nutrition Examination Survey; 25(OH)D, 25-hydroxyvitamin D.

SI conversion factor: To convert 25(OH)D to nanomoles per liter, multiply by 2.496.

a Patients and controls were matched by age, race, sex, Fitzpatrick skin type, and season/geograhic residence. Unless otherwise indicated, data are expressed as number (percentage) of subjects.

b Defined as almost always or always use of daily sunscreen.

c Data were available from 35 patients with BCNS.

Multivariate regression analysis using mixed-effects models with a random subject effect were used to account for the correlation of different 25(OH)D measurements from the same person. We checked for model fit by plotting residuals. Fisher exact test was used for comparisons of proportions. All P values were 2 sided. Statistical analyses were performed using commercially available software (SAS [SAS Institute Inc, Cary, North Carolina] and STATA [StataCorp, College Station, Texas]). Unless otherwise indicated, data are expressed as mean (SD).

RESULTS

Forty-one patients with a diagnosis of BCNS were included in this study. Table 1 shows the baseline characteristics of our study population. The mean age of our cohort was 40.2 (11.0) years (range, 21-67 years) and 22 (54%) were men. All subjects were non-Hispanic white with Fitzpatrick skin types of I, II, or III as classified by a study dermatologist (MA, DRB, or EHE). Most subjects were overweight (BMI, >25.0) with a mean BMI of 30.1 (6.9), consistent with previous reports of the large body habitus in patients with BCNS.14 The average number of BCCs among our patients with BCNS was 22 at the start of the clinical trial. In our chemoprevention clinical trial, patients were stratified into a high (≥15 tumors at baseline) or low (<15 tumors) burden of disease.17 Patients in this study were balanced in terms of their burden of disease (20 of 41 patients with a high burden and 21 with a low burden), and there was no difference in 25(OH)D levels in patients with BCNS who had a low vs high burden of disease. In general, patients with BCNS practiced photoprotection by avoiding sunlight during peak hours (10 AM to 2 PM) and by using sunscreen daily. Twenty-eight of the 35 patients with BCNS surveyed (80%) reported almost always using sunscreen daily (sun protection factor of ≥15), and only 4 (11%) reported rarely or never using sunscreen daily. Subjects were equally distributed by geographic residence in the United States, with 22 (54%) of the participants living in low UV-exposure areas (latitude, ≥35°N). On average, each subject had 3 plasma measurements (range, 1-6) throughout the 2-year study, and we calculated a mean 25(OH)D level per patient. The mean 25(OH)D level of all 41 subjects was 24.5 (12.4) ng/mL, which is in the insufficient range (≤30 ng/mL).

We sought to determine whether known risk factors for vitamin D deficiency such as age, BMI, sex, geographic residence, and season of blood collection could predict 25(OH)D levels in individuals with BCNS.25 Table 2 shows the results from multivariate regression analysis examining independent predictors of 25(OH)D levels. Season of blood collection and BMI were the only significant predictors. Comparing across subjects, every 5-U increase in BMI was associated with a −3-ng/mL decrease in 25(OH)D level (95% confidence interval [CI], −5.5 to −0.2; P = .04). Levels of 25(OH)D were 7.1 ng/mL higher in a summer compared with a winter season of blood collection (95% CI, 3.5-11.0; P < .001). After multivariate adjustment, subjects who reported using a daily vitamin supplement had 6.8-ng/mL-higher 25(OH)D levels (95% CI, −1.0 to 15.0; P = .09), which approached but did not reach statistical significance. Age, sex, and geographic residence were not associated with significant changes in 25(OH)D levels.

We compared 25(OH)D levels in 22 patients with BCNS who had serial blood collections in the summer and winter seasons of the same year (Figure 1). Patients with BCNS have significantly higher levels of 25(OH)D in the summer compared with the winter, in contrast to patients with xeroderma pigmentosum, who showed no seasonal variation.11 Levels of 25(OH)D were 7 ng/mL higher in the summer compared with winter (27.4 vs 20.3 ng/mL, P = .04) in patients with BCNS, simi-
ular to the seasonal variation seen in a previous study of 25 patients with sporadic skin cancers (patients with BCNS) from Sydney, Australia.13

Studies on the vitamin D status in NHANES6,7 demonstrated that a large proportion of the US population is deficient (25(OH)D levels ≤20 ng/mL). To determine whether there was a difference in mean 25(OH)D values and prevalence of vitamin D deficiency, we compared 25(OH)D levels in patients with BCNS with those of population-based controls from NHANES 2003-2004 who had information on important baseline risk factors for vitamin D deficiency such as age, race, BMI, and dermatologist-assessed Fitzpatrick skin types.21,23,26,27 We matched 9 NHANES controls from each patient with BCNS by age, sex, race, skin type, and season/geography and identified a total of 360 controls. Table 1 shows that NHANES controls were closely matched to patients with BCNS; however, we did not have information on the number of tumors or photoprotective habits in NHANES controls. Use of a daily multivitamin supplement was higher in controls compared with patients with BCNS (184 [51%] vs 4 [34%]). Overall, patients with BCNS had −3 ng/mL lower mean 25(OH)D levels compared with NHANES controls (24.5 vs 27.5 ng/mL; P = .02) in univariate analysis. Adjustment for BMI did not attenuate this difference.

Figure 1. Levels of 25-hydroxyvitamin D (25(OH)D) in 22 patients with basal cell nevus syndrome (BCNS) who had serial blood collections in the summer and winter season of 1 year. Patients with BCNS have higher 25(OH)D levels in the summer (mean [SD], 27.4 [11.7] ng/mL compared with the winter [20.3 [10.4] ng/mL; P = .04). Horizontal lines indicate mean levels. To convert 25(OH)D to nanomoles per liter, multiply by 2.496.

Figure 2. Percentage of patients with basal cell nevus syndrome (BCNS) (n=41) and National Health and Nutrition Examination Survey (NHANES) control subjects (n=360) who had vitamin D deficiency (25-hydroxyvitamin D levels ≤20 ng/mL) or severe deficiency (≤10 ng/mL). The NHANES controls were matched by age, sex, race, Fitzpatrick skin type, and season/geography. To convert 25(OH)D to nanomoles per liter, multiply by 2.496.

Our key findings are that patients with BCNS have mean 25(OH)D levels below those of the general population and are 3 times more likely to be vitamin D deficient. Most of the patients with BCNS in this study (56%) were vitamin D deficient. Among the patients with BCNS, high BMI and blood collection during the winter were significant risk factors for lower 25(OH)D levels. Age, sex, and geographic residence were not associated with significant changes in 25(OH)D levels in this study, likely because of the limited sample size.

To our knowledge, this is the largest study of vitamin D status in patients with a genetic predisposition for skin cancer. Our findings are consistent with previous reports of vitamin D deficiency in patients with sporadic skin cancer13 and confirm the findings of Querings and Reichrath,11 who first showed low 25(OH)D levels in BCNS. In contrast to patients with xeroderma pigmentosum, who have no seasonal variation in their 25(OH)D levels presumably owing to extremely rigorous photoprotection,12 patients with BCNS in this study had higher levels of 25(OH)D in the summer compared with winter. It seems likely that patients with BCNS may be more similar to patients with sporadic skin cancers whose photoprotective practices do not completely block UV-induced cutaneous vitamin D synthesis, especially in the summer. One previous study of Australian patients with skin cancer showed a similar 5-ng/mL increase in summer 25(OH)D levels compared with winter levels.13 Among patients with BCNS, those with a high BMI had lower 25(OH)D levels, consistent with the previous findings that obesity contributes to lower 25(OH)D levels owing to sequestration of vitamin D in body fat compartments.26,28 Our results support the hypothesis that obesity and increased photoprotection practices may contribute to the increasing trend of vitamin D deficiency in the United States.21

Our study had several limitations. First, we had a relatively small number of patients because of the rarity of BCNS, which has a prevalence of 1 per 50,000 to 1 per 164,000.14 Second, controls were drawn from the population and were not individual subjects because this was a retrospective study of stored plasma samples from a completed multicenter clinical trial of celecoxib for BCC prevention. Celecoxib is not known to affect the synthesis
or absorption of vitamin D. We did not survey for detailed UV exposure history or specific photoprotective habits and could not measure the impact of frequency of sunscreen use on 25(OH)D levels given the uniformly high use among patients with BCNS. We had information on daily multivitamin use only and did not have detailed information on actual cholecalciferol supplements or dosages or on vitamin D intake from dietary sources such as milk or fish. However, most vitamin D is generally obtained from cutaneous synthesis of vitamin D via UV exposure of the skin rather than through dietary sources because few foods are naturally fortified. We did not assay levels of 1,25-dihydroxycholecalciferol, calcium, or parathyroid hormone or perform bone density scans in patients with BCNS. Abnormal findings in these measurements could have reflected more severe forms of vitamin D deficiency. Although patients with BCNS may be a fair proxy for photoprotecting patients with skin cancer, other factors may contribute to vitamin D deficiency in this disease; however, mice with mutations in Ptch1 are not known to have any defects in the vitamin D synthesis pathway. We did not detect a difference in 25(OH)D levels in patients with BCNS who had a low vs high burden of disease, which could be because of the high phenotypic variability in patients with BCNS (range, 1-1000 BCCs per patient) or factors other than 25(OH)D levels that may influence the number of BCCs in these patients.Strengths of this study include the multiple measurements of 25(OH)D levels at different seasons and detailed information on covariates, such as Fitzpatrick skin type and BMI, that can affect cutaneous vitamin D synthesis or storage, respectively.

It may not be surprising that patients with a genetic predisposition to sun-induced cancers report a high frequency of photoprotection and may be vitamin D deficiency. However, the magnitude of this deficiency and the possible additive effect of obesity, which is common in these patients, make individuals with BCNS optimal candidates for cholecalciferol supplementation. Furthermore, if the mechanism for the association between low 25(OH)D levels in patients with BCNS is indeed photoprotection, these results may be applicable to patients without BCNS who have sporadic BCCs and for whom photoprotection is currently recommended. Given that sporadic BCC is the most common cancer worldwide with more than 1 million cases reported annually in the United States and that most patients with BCC survive for many years after their diagnosis, screening for vitamin D deficiency may become an important part of the care of this population.

The optimal amount of serum vitamin D levels for health maintenance and disease prevention is still being defined. The intake level currently recommended to be adequate for adults younger than 70 years is 200 to 400 IU. Taking into account multiple health outcomes such as autoimmune disease, cancer prevention, and bone health, optimal concentrations of 25(OH)D of greater than 30 ng/mL have been suggested. A cholecalciferol supplement of 1000 IU increases 25(OH)D levels by an average of 10 ng/mL. Thus, patients with BCNS may require 1000 IU to increase their winter 25(OH)D level from 20.3 ng/mL to the sufficient range (≥30 ng/mL). Use of a daily multivitamin supplement led to a statistically nonsignificant increase in 25(OH)D levels in patients with BCNS; however, overall use was low. Our findings may be relevant for the Institute of Medicine review of vitamin D requirements to be conducted in November 2010. Further studies are needed to determine the optimal amount of cholecalciferol supplementation required for preventing deficiency in individuals using photoprotection at the population level.

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Correspondence: Jean Y. Tang, MD, PhD, Department of Dermatology, Stanford University Medical Center, 450 Broadway St, Pavilion C, Redwood City, CA 94063 (tangy@stanford.edu).

Author Contributions: Drs Tang and Epstein had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Tang, Bickers, and Epstein. Acquisition of data: Tang, Wu, Lee, Aszterbaum, Bickers, and Epstein. Analysis and interpretation of data: Tang, Wu, Linos, Parimi, Asgari, and Epstein. Drafting of the manuscript: Tang, Wu, Linos, Lee, and Epstein. Critical revision of the manuscript for important intellectual content: Tang, Linos, Parimi, Aszterbaum, Asgari, and Epstein. Statistical analysis: Tang, Linos, and Parimi. Obtained funding: Tang, Bickers, and Epstein. Administrative, technical, and material support: Tang, Wu, Aszterbaum, Asgari, and Bickers. Study supervision: Tang and Epstein.

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