Deficiency of serum concentration of 25-hydroxyvitamin D in psoriatic patients: A case-control study

Jacinto Orgaz-Molina, MD,a Agustín Buendía-Eisman, MD, PhD,b Miguel A. Arrabal-Polo, MD, José Carlos Ruiz, MD,a and Salvador Arias-Santiago, MD, PhDab,cd
Granada, Spain

Background: Some autoimmune conditions have been associated with reduced vitamin D levels, including systemic lupus erythematosus, rheumatoid arthritis, diabetes mellitus, and multiple sclerosis.

Objective: The main objective of this study was to analyze the 25-hydroxyvitamin D (OHD) status of patients with psoriasis in comparison with control subjects without this disease.

Methods: This case-control study included 86 patients (43 with psoriasis and 43 age- and sex-matched control subjects) from the outpatient clinic of our hospital dermatology department in Granada, Spain. All patients and control subjects were studied during one 4-week period to avoid seasonal variations in vitamin D levels.

Results: Serum 25-OHD levels were significantly lower in psoriatic patients than in control subjects even after adjusting for confounding factors in a multivariate analysis (odds ratio 2.89, 95% confidence interval 1.02-7.64, \( P \leq 0.03 \) for vitamin D insufficiency). Low 25-OHD levels were negatively associated with C-reactive protein (inflammatory activation marker) and body mass index in multiple linear regression analysis. Psoriatic patients with body mass index greater than or equal to 27 kg/m² had a higher risk of 25-OHD insufficiency (sensitivity of 82.3% and specificity of 51.7%).

Limitations: Further studies with larger numbers of patients are required to analyze the pathogenic mechanisms underlying the relationship between 25-OHD deficiency and psoriasis.

Conclusions: The 25-OHD values are significantly lower in psoriatic patients than in control subjects. Low 25-OHD levels are negatively associated with C-reactive protein, an inflammatory activation marker, and with obesity. Psoriatic patients with a body mass index of 27 or more are likely to have vitamin D insufficiency. (J Am Acad Dermatol 10.1016/j.jaad.2012.01.040.)

Key words: autoimmunity; body mass index; C-reactive protein; psoriasis; Psoriasis Area and Severity Index; 25-hydroxyvitamin D.
the immune system is suggested by the presence of VDRs on activated T lymphocytes,7,8 the suppressive or inhibiting effect of 1,25-dihydroxyvitamin D in different autoimmune diseases, and in vitro and in vivo findings of vitamin D–induced changes in immune functions.9 Furthermore, dermatologists and other physicians have observed the effectiveness of vitamin D analogs to treat psoriasis plaques in daily clinical practice.10

Autoimmune conditions associated with reduced vitamin D levels include rheumatoid arthritis (RA), insulin-dependent diabetes mellitus (IDDM), and multiple sclerosis (MS),11-13 which share some immunologic features with psoriasis, such as Th1/Th2 dysregulation. With this background, we compared 25-OHD levels between patients with psoriasis and control subjects without psoriasis. All patients and control subjects were studied in one 4-week period to avoid seasonal variations in vitamin D levels.

METHODS

Patients and control subjects

This case-control study included 86 outpatients: 43 patients with psoriasis randomly selected from among patients of the psoriasis unit and 43 randomly selected age- and sex-matched control subjects (28 male and 15 female in each group) with nonphotosensitive dermatologic diseases other than psoriasis (mainly nevi, seborrheic keratosis, or verruca) from the Dermatology Department of San Cecilio University Hospital, Granada, Spain. Randomization was conducted using randomized number tables. All patients were studied during the same period (from May 16 to June 17, 2011) to avoid geographic differences in sun exposure and vitamin D levels. No patients or control subjects refused participation in the study.

Diagnosis of psoriasis was based on clinical findings (generalized psoriasis plaques). Inclusion criteria were: age between 18 and 65 years, the presence of plaque psoriasis not treated systemically or topically in the previous month, and the absence of vitamin D supplementation or current phototherapy treatment or the presence of chronic inflammatory disease such as MS, inflammatory bowel disease, RA, IDDM, lupus erythematosus, cutaneous lymphoma, nonmelanoma skin cancer, or any other cancer. Inclusion criteria for control subjects were the same as for cases except for the absence of psoriasis. The study was approved by the Ethics Committee of San Cecilio University Hospital, and written informed consent was obtained from all patients and control subjects in accordance with the Helsinki Declaration.

Clinical and laboratory parameters

The severity of psoriasis was assessed according to the Psoriasis Area and Severity Index (PASI) and body surface area. The weight, height, and abdominal circumference of subjects were measured, and their body mass index (BMI) (kg/m²) was calculated. Systolic and diastolic blood pressure (BP) was measured after a 5-minute rest and again after a 10-minute interval, and the mean values were recorded. Data were also gathered on: age, sex, mean time with psoriasis, personal history of psoriatic arthritis or nail psoriasis, family history of psoriasis, Fitzpatrick skin type, estimate of time spent outdoors (sum of estimated hours per weekday and weekend day), tobacco (cigarettes per day), and daily and weekend alcohol intake (grams per day). C-reactive protein (CRP), erythrocyte sedimentation rate, triglycerides, high-density lipoprotein cholesterol, and glycemia were analyzed in blood samples drawn between 8 and 9 AM. Serum 25-OHD levels were determined by commercially available radioimmunoassay in the biochemistry department of our hospital. Patients were interviewed to determine their usual dietary intake of vitamin D. The amount of vitamin D intake per day was similar (P > .05) between the psoriasis (140 IU) and control (115 IU) groups. Intake of vitamin D supplements was an exclusion criterion. Dietary vitamin D intake was not significantly correlated with serum 25-OHD concentration (P > .05).

Statistical analysis

The Kolmogorov-Smirnov test was used to examine the distribution of variables and the Levene test to
study the variance. When the distribution was normal, the Student t test was applied to compare mean values of quantitative variables, and when not normal, the Mann-Whitney U test was used. Qualitative variables were analyzed with $\chi^2$ test or with Fisher exact test if at least one cell had an expected count less than 5. Binary logistic regression models (Wald method) were used to measure the association between psoriasis and vitamin D insufficiency ($<30 \text{ ng/mL}$) in a multivariate analysis. Correlations among variables were studied by means of the Pearson coefficient, and multiple linear regression analysis was used to determine the independent predictors of vitamin D levels. The outcome variable was serum vitamin D concentration, and the model included the variables that proved significant in bivariate analyses (PASI, BMI, and CRP). The standardized coefficient of determination was calculated. $P$ less than or equal to .05 was considered significant. Software was used for the data analyses (SPSS 17.0, SPSS Inc, Chicago, IL).

RESULT

We studied 43 Caucasian patients (28 male and 15 female) with generalized psoriasis plaques. The mean time period with psoriasis was 19.91 years, the mean PASI value was 4.42, and the mean body surface area was 4.38. Of these 43 patients with psoriasis 14% had nail psoriatic arthritis and 7% had psoriatic arthritis. No gender differences were observed in any of the above parameters. A family history of psoriasis was reported by 46.8% of psoriatic patients versus 8.7% of the control subjects ($\chi^2 = 30.67, 95\% \text{ CI } 1.92-79.96$); vitamin D insufficiency ($<30 \text{ ng/mL}$) was found in 79.1% of patients with psoriasis versus 58.1% of control subjects ($\chi^2 = 30.77, OR 1.36, 95\% \text{ CI } 1.01-1.83$) (Table I). Multivariate studies with binary logistic regression showed a strong association between the presence of psoriasis and vitamin D insufficiency ($<30 \text{ ng/mL}$), even after adjustment for BMI, age, sex, dietary vitamin D intake, total sun exposure, and Fitzpatrick skin phototype as confounding factors (OR 2.89, 95% CI 1.02-7.64, $P < .05$) (Table III).

The mean serum 25-OHD concentration was significantly lower in patients than in control subjects (24.41 ± 7.80 vs 29.53 ± 9.38, $P = .007$) (Fig 1). Vitamin D deficiency ($<20 \text{ ng/mL}$) was observed in 25.6% of patients with psoriasis versus 9.3% of control subjects ($\chi^2 = 30.16, OR 2.75, 95\% \text{ CI } 1.02-7.96$); vitamin D insufficiency ($<30 \text{ ng/mL}$) was found in 79.1% of patients with psoriasis versus 58.1% of control subjects ($\chi^2 = 30.77, OR 1.36, 95\% \text{ CI } 1.01-1.83$) (Table II). Multivariate studies with binary logistic regression showed a strong association between the presence of psoriasis and vitamin D insufficiency ($<30 \text{ ng/mL}$), even after adjustment for BMI, age, sex, dietary vitamin D intake, total sun exposure, and Fitzpatrick skin phototype as confounding factors (OR 2.89, 95% CI 1.02-7.64, $P < .05$) (Table III).

No significant correlation was found between 25-OHD levels and PASI, body surface area, mean time with psoriasis, systolic BP, diastolic BP, high-density lipoprotein cholesterol, triglycerides, or glucose levels ($P > .05$). No differences in mean 25-OHD levels were found as a function of the presence/absence of psoriatic arthritis, nail psoriasis, or family history of psoriasis (data not shown).

A significant negative correlation was found between BMI and serum 25-OHD level ($r = -0.30, P = .005$). A receiver operating characteristic curve was performed, and an optimal cut-off BMI value of 27 (area under the curve = 0.65, $P = .024$) was obtained; above this value, psoriatic patients had a higher risk of vitamin D insufficiency (sensitivity of 82.3% and specificity of 51.7%) (Fig 2).

No significant differences in mean CRP or erythrocyte sedimentation rate values were found between patients and control subjects (0.251 vs 0.381 mg/dL for CRP, $P = .520$; 9.30 vs 7.77 mm/h for erythrocyte sedimentation rate, $P = .42$, respectively). High-sensitivity CRP was greater than 0.3 mg/dL in 25.6% of the psoriatic patients. In the psoriasis group, the CRP value was inversely correlated with the serum 25-OHD concentration ($r =$
e0.391; \( P = .009 \) (Fig 3) and positively correlated with the BMI (\( r = 0.528; \ P \leq .0001 \)).

The multivariate linear regression model showed that serum 25-OHD concentration was negatively associated with CRP level and BMI (\( R^2 \text{ of adjusted model} = 0.26; \ P = .009 \)) (Table IV).

**DISCUSSION**

In this study, multivariate analysis showed that serum 25-OHD levels were significantly lower in psoriatic patients than in control subjects after adjusting for confounding factors. The 25-OHD levels were negatively associated with CRP, a marker of inflammatory activation, and with BMI in multiple linear regression analysis. Psoriatic patients with BMI greater than or equal to 27 kg/m² were found to have a greater risk of 25-OHD insufficiency, with high sensitivity and specificity. A strength point of this study was that all patients were studied during the same 4-week period, thereby avoiding seasonal variations.

Vitamin D has long been regarded as essential for bone development, growth, mineralization, and the maintenance of skeletal integrity, and vitamin D status is increasingly considered important in various

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**Table I.** Demographics and possible confounding factors about serum 25-hydroxyvitamin D concentration and cardiovascular risk factors in patients with psoriasis and control subjects

<table>
<thead>
<tr>
<th>Variables</th>
<th>Psoriasis</th>
<th>Control</th>
<th>( P ) values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean ± SD</td>
<td>44.33 ± 8.71</td>
<td>43.95 ± 11.37</td>
<td>.865</td>
</tr>
<tr>
<td>Fitzpatrick skin phototype, n (%)</td>
<td>8 (18.6)</td>
<td>4 (9.3)</td>
<td>.458</td>
</tr>
<tr>
<td>III</td>
<td>22 (51.2)</td>
<td>25 (58.1)</td>
<td>.385</td>
</tr>
<tr>
<td>IV</td>
<td>13 (30.2)</td>
<td>14 (32.6)</td>
<td>.385</td>
</tr>
<tr>
<td>Estimated time spent outdoors, h/wk, mean ± SD</td>
<td>25.99 ± 18.78</td>
<td>28.22 ± 20.33</td>
<td>.598</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>Yes (&gt;5/d)</td>
<td>21 (48.8)</td>
<td>17 (39.5)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>22 (51.2)</td>
<td>26 (60.5)</td>
</tr>
<tr>
<td>Usual alcohol intake, n (%)</td>
<td>Yes (&gt;40 g/d)</td>
<td>18 (41.9)</td>
<td>18 (41.9)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>25 (58.1)</td>
<td>25 (58.1)</td>
</tr>
<tr>
<td>BMI, mean ± SD</td>
<td>29.68 ± 7.07</td>
<td>27.17 ± 4.45</td>
<td>.052</td>
</tr>
<tr>
<td>Systolic BP, mm Hg, mean ± SD</td>
<td>127.18 ± 13.97</td>
<td>125.53 ± 13.48</td>
<td>.57</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg, mean ± SD</td>
<td>80.79 ± 11.35</td>
<td>78.48 ± 9.50</td>
<td>.31</td>
</tr>
<tr>
<td>HDL-C, mg/dL, mean ± SD</td>
<td>50.88 ± 12.64</td>
<td>54.60 ± 13.69</td>
<td>.19</td>
</tr>
<tr>
<td>Triglycerides, mg/dL, mean ± SD</td>
<td>129.29 ± 67.45</td>
<td>94.48 ± 55.52</td>
<td>.01</td>
</tr>
<tr>
<td>Glycemia, mg/dL, mean ± SD</td>
<td>97.53 ± 24.92</td>
<td>94.13 ± 21.56</td>
<td>.51</td>
</tr>
</tbody>
</table>

*BMI,* Body mass index; *BP,* blood pressure; *HDL-C,* high-density lipoprotein cholesterol.

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**Table II.** Mean (SD), minimum, and maximum serum 25-hydroxyvitamin D concentration and percentages of deficiency (<20 ng/mL) and insufficiency (<30 ng/mL) 25-hydroxyvitamin D levels in patients and control subjects

<table>
<thead>
<tr>
<th>25-OHD</th>
<th>Psoriasis</th>
<th>Control</th>
<th>( P ) values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD, ng/mL</td>
<td>24.41 ± 7.80</td>
<td>29.53 ± 9.38</td>
<td>.007</td>
</tr>
<tr>
<td>Minimum</td>
<td>9.50</td>
<td>13.80</td>
<td>-</td>
</tr>
<tr>
<td>Maximum</td>
<td>44.30</td>
<td>51.10</td>
<td>-</td>
</tr>
<tr>
<td>&lt;10 ng/mL</td>
<td>2.3%</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>&lt;20 ng/mL</td>
<td>25.6%</td>
<td>9.3%</td>
<td>.043</td>
</tr>
<tr>
<td>&lt;30 ng/mL</td>
<td>79.1%</td>
<td>58.1%</td>
<td>.037</td>
</tr>
<tr>
<td>≥30 ng/mL</td>
<td>20.9%</td>
<td>41.9%</td>
<td>.037</td>
</tr>
</tbody>
</table>

*OHD,* Hydroxyvitamin D.
chronic diseases. In fact, the high prevalence of vitamin D insufficiency is defined as a global health problem, and most experts recommend a level greater than or equal to 30 ng/mL. More than 90% of vitamin D synthesis is dependent on ultraviolet (UV) exposure (cutaneous synthesis), and vitamin D deficiency was recently demonstrated in patients with lupus erythematosus, a photosensitive disorder that requires strict sun avoidance. However, vitamin D levels were not influenced by sun exposure in the current study, which found no significant differences in sun exposure (in hours/week) between patients and control subjects. Unlike patients with lupus erythematosus, patients with psoriasis know the clinical benefit of moderate doses of UV radiation and do not avoid sun exposure systematically.

We observed a significant negative correlation between BMI and serum 25-OHD concentration, as previously reported. One reason proposed for this relationship has been the lesser physical activity and therefore reduced sun exposure of heavier individuals. However, BMI proved to be an independent predictor of hypovitaminosis D in our multivariate linear regression analysis, even when the model included daily sun exposure. Moreover, we found no correlation between BMI and hours of daily sun exposure (data not shown). Other possible explanations include the reduced bioavailability of vitamin D as a result of its sequestration in fat and the activity of this vitamin as a body mass regulator. From a teleological and phylogenetic standpoint, the reduction in UV radiation during the autumn induces the organism of mammals to gain weight and prepare for the winter. In the current study, BMI proved to be an independent predictor of 25-OHD deficiency in patients with psoriasis, with a high sensitivity and specificity (receiver operating characteristic curve) for the optimal cutoff point of 27 kg/m².

Table III. Binary logistic regression model for vitamin D insufficiency (<30 ng/mL)

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriasis (vs control)</td>
<td>2.82</td>
<td>1.04-7.59</td>
<td>.04</td>
</tr>
<tr>
<td>Male sex (vs female)</td>
<td>0.68</td>
<td>0.22-2.06</td>
<td>.50</td>
</tr>
<tr>
<td>Age</td>
<td>0.99</td>
<td>0.95-1.04</td>
<td>.91</td>
</tr>
<tr>
<td>Food intake of vitamin D</td>
<td>1.29</td>
<td>0.72-2.32</td>
<td>.37</td>
</tr>
<tr>
<td>Total sun exposure</td>
<td>1.02</td>
<td>0.99-1.04</td>
<td>.13</td>
</tr>
<tr>
<td>Fitzpatrick skin phototype</td>
<td>0.89</td>
<td>0.41-1.92</td>
<td>.77</td>
</tr>
</tbody>
</table>

Presence of psoriasis was independent factor associated with vitamin D insufficiency after controlling for multiple confounding factors.

CI, Confidence interval; OR, odds ratio.

The relationship between age and vitamin D levels is controversial. Some authors have correlated age with vitamin D in a direct or indirect manner, whereas others have found no correlation, as in the current study (Table III). Our case-control study found significantly lower serum 25-OHD levels in psoriatic patients than in control subjects. Other autoimmune diseases have been associated with low vitamin D levels, such as RA, IDDM, and MS. Visscher et al reported fluctuations in MS consistent with seasonal changes in serum vitamin D levels, proposing that the development and behavior of this disease was influenced by latitude, an environmental factor. In the case of psoriasis, the prevalence varies among regions, although the prevalence is higher further toward the poles than between the tropics. Hence, there is some epidemiological-ecological evidence of a relationship between autoimmune disease and latitude in terms of radiation and vitamin D levels.

Evidence has gradually accumulated on the regulatory role of vitamin D in the immune system. The presence of VDRs has been reported in most immune cells, including activated CD4⁺ and CD8⁺ lymphocytes, and in antigen-presenting cells such as dendritic cells. In addition, many immune system cells express 1α-hydroxylase, which is regulated by immune signals and not by calcium.
Compromised vitamin D status has been associated with an increased risk for Th1 cytokine-mediated autoimmune diseases, including IDDM, MS, inflammatory bowel disease, and RA.9,39 Furthermore, animal studies demonstrated that 1,25-dihydroxyvitamin D prevents the development or ameliorates the symptoms of chronic inflammatory autoimmune reaction.40-45 Conversely, vitamin D deficiency has been shown to accelerate the development and increase the incidence of experimental MS and IDDM.46,47 Another instance of a relationship between vitamin D deficiency and autoimmunity was suggested by Silverberg et al,48 who reported very low 25-OHD levels (<15 ng/mL) in patients with vitiligo who had another autoimmune disease.

Systemic vitamin D administration has shown clinical benefits in psoriatic patients. Werner de Castro et al49 described the resolution of adalimumab-induced psoriasis after high doses of oral vitamin D, and Perez et al50 found a significant improvement in clinical parameters after oral calcitriol. Gaal et al51 reported that treatment with alfacalcidol significantly reduced the percentage of interferon-γ-producing CD8+ T lymphocytes and serum interferon-γ levels in patients with psoriatic arthritis in comparison with control subjects. In a pilot study, Huckins et al52 found a statistically significant improvement in tender joint count and physician global impression after treatment with 1,25-dihydroxivitamin D3 in patients with psoriatic arthritis. The effectiveness of vitamin D analogs for the topical treatment of psoriasis is very well documented.10

Deficient 25-OHD levels in patients with psoriasis may be associated with alterations in isoenzymes that affect the synthesis of vitamin D. Some studies have shown differences in VDR polymorphisms between patients with psoriasis and the general population.53 However, few data are available on the isoenzyme polymorphisms that influence serum 25-OHD levels, such as 7-dehydrocholesterol reductase (responsible for the availability of 7-dehydrocholesterol in the skin), liver 25-hydroxylase, CYP2R1 (involved in the conversion of vitamin D into 25-OHD), and CYP24A1 (a key degradation enzyme). In addition, polymorphisms in GC gene, which encodes vitamin D-binding protein, have a major effect on serum 25-OHD concentration.54

Deficient 25-OHD levels in psoriatic patients may also be secondary to an inflammatory environment, and CRP was negatively correlated with 25-OHD in the current study. Chodorowska et al55 reported that plasma acute-phase protein levels (CRP and

Table IV. Multiple linear regression analysis of independent predictors of serum 25-hydroxyvitamin D concentration in psoriatic patients

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Standardized β</th>
<th>t value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASI</td>
<td>0.35</td>
<td>2.31</td>
<td>.26</td>
</tr>
<tr>
<td>CRP</td>
<td>-0.34</td>
<td>-2.08</td>
<td>.024</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.16</td>
<td>-0.89</td>
<td>.037</td>
</tr>
<tr>
<td>Constant</td>
<td>29.2</td>
<td>5.83</td>
<td>.0001</td>
</tr>
</tbody>
</table>

Model adjusted $R^2 = 0.26; P = .009.$

CRP, C-reactive protein; PASI, Psoriasis Area and Severity Index.
fibrinogen) were significantly elevated in patients with psoriasis versus in healthy control subjects, and a recent study showed low 25-OHD levels to be associated with endothelial dysfunction and inflammatory activation markers (CRP and asymmetric dimethylarginine concentrations).56

Study participants were asked to estimate the hours that they spent outdoors on weekdays and at weekends. Although not an optimal method to evaluate sun exposure, the same method was used in both groups and no significant differences were found. Other confounding factors associated with UV radiation, such as changes in latitude or climate, were minimized by recruiting all patients from the same geographic area and studying them all in the same 4-week period. Finally, new studies with larger numbers of patients are required to analyze the pathogenic mechanisms underlying the relationship between 25-OHD deficiency and psoriasis.

In conclusion, serum 25-OHD levels are significantly lower in psoriatic patients than in healthy control subjects, as found in other autoimmune or inflammatory conditions. These data support the idea of intervention studies with vitamin D in patients with psoriasis. In psoriatic patients, low 25-OHD levels are associated with markers of inflammatory activation (CRP), which may explain this deficiency. These findings also suggest that vitamin D levels are associated with obesity and that psoriatic patients with a BMI greater than or equal to 27 are likely to have vitamin D insufficiency (sensitivity of 82.3% and specificity of 51.7%).

REFERENCES
