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INVESTIGATIVE REPORT

Association of 25-hydroxyvitamin D with Metabolic Syndrome in Patients with Psoriasis: A Case-control Study

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Vitamin D deficiency is associated with higher cardiovascular risk and metabolic syndrome (MeS) criteria. The main objective of this study was to analyse the association of 25-hydroxyvitamin D (25-OHD) serum levels with MeS (National Cholesterol Education Program–Adult Treatment Panel-III criteria) in 46 Spanish patients with psoriasis, but without arthritis and systemic treatment, and 46 control subjects, matched by sex and age. The patients with psoriasis showed significantly lower level of 25-OHD than controls (30.5 vs. 38.3 ng/ml; $p = 0.0001$). Patients with MeS had significantly lower serum levels of 25-OHD than those without MeS (24.1 ± 7.5 vs. 32.8 ± 8.9, $p = 0.007$), and a negative correlation was found between 25-OHD and waist circumference, diastolic blood pressure, fasting glucose, and triglyceridaemia. In the control group no significant correlation between 25-OHD and MeS was found. Although the sample was small, our results suggest a potential protective role for 25-OHD in the metabolic profile of patients with psoriasis without arthritis. ***Key words: psoriasis; vitamin D; metabolic syndrome; cardiovascular risk.***

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Vitamin D has classically been associated with phosphorus-calcium metabolism and bone physiology. However, the finding of vitamin D receptors at different sites (1) suggests that vitamin D also has important extraskeletal functions. Thus, low levels of vitamin D have been associated with adverse cardiovascular outcomes (2, 3) and metabolic syndrome (MeS). Individuals meeting Adult Treatment Panel (ATP-III) criteria for MeS have been found to have a greater likelihood of a cardiovascular event over the following 10 years (4).

Psoriasis has been associated with a higher prevalence of MeS and an increase in cardiovascular events (5–7), as also observed for other inflammatory dermatological diseases (8).

Several studies have reported vitamin D deficiency in patients with autoimmune diseases (9) as well as in psoriatic patients (10, 11).

Given the scarcity of published data relating vitamin D status and MeS in psoriasis, we conducted a case-control study in order to evaluate the association of serum 25-hydroxyvitamin D (25-OHD) levels with the presence of MeS and metabolic parameters in patients with psoriasis.

METHODS

Psoriatic patients

Patients with active psoriasis were systematically recruited from the outpatient clinic of the Dermatology Department of San Cecilio University Hospital (Granada, Spain). Inclusion criteria were: a clinical diagnosis of psoriasis, age ≥ 18 years, and residence in the metropolitan area of Granada. Exclusion criteria were: "sunny" holidays in the previous month, intake of calcium or vitamin D supplements in the previous 3 months, psoriatic arthritis (Classification Criteria for Psoriatic Arthritis criteria), psoriasis systemic treatment in the previous 6 months, antihypertensive, lipid-lowering, or antidiabetic therapy in the previous 3 months, or medical history of rheumatoid arthritis, type 1 diabetes mellitus, inflammatory bowel disease, multiple sclerosis, or renal function impairment.

Control individuals

Control individuals from the same geographical area were recruited from the dermatology outpatient clinic (mainly naevi, seborrhoeic keratosis, or verruca) matched with psoriasis patients by sex and age (± 2 years). Individuals were recruited with a time difference less than 7 days since their matched psoriatic patient was evaluated. Exclusion criteria were the same as established for the psoriatic patients group. All patients or controls were recruited between 18 July and 30 August 2011 to avoid bias due to seasonal variations in vitamin D.

The study was approved by the ethics committee of San Cecilio University Hospital, and written informed consent was obtained from all patients in accordance with the Helsinki Declaration.

Clinical and laboratory parameters

Data were gathered on: age, sex, family history of psoriasis and age at diagnosis. We also recorded current tobacco habit (pack-years), alcohol intake (g/week), and an estimation of the time spent in the open air over the previous 4 weeks. Patients were asked about their consumption of vitamin D-rich and fortified foods in their usual diet, including: salmon, sardine, tuna, egg-yolk, and vitamin-D fortified butter, margarine, milk, yoghurt, cheese, and breakfast cereals (12). These data were

used to calculate their daily vitamin D intake (in international units; IU). Physical activity was assessed as the usual level of exercise over the previous year by means of the Tromsø physical activity questionnaire, which has proven to be a good predictor of heart rate at rest and physical condition, comparable to the objective assessment of activity by accelerometry (13).

Participants' waist circumference, weight and height were recorded and their body mass index (BMI; kg/m^2) calculated. Fitzpatrick phototype was also evaluated. Systolic (SBP) and diastolic (DBP) blood pressures were measured after a 5-min rest, and again after a 10-min interval, and the mean values were recorded. Moreover, in psoriatic patients Psoriasis Area and Severity Index (PASI), and body surface area (BSA) were also registered.

Blood samples were drawn between 08.00 h and 09.00 h for laboratory analysis of biochemical parameters (triglycerides (TG), total cholesterol (TC), low density lipoprotein (LDL), high density lipoprotein (HDL), and fasting glucose), intact parathyroid hormone (iPTH), serum calcium, serum phosphorus, serum creatinine, and determination of serum 25-(OH)D levels by radioimmunoassay. Prevalence of the MeS was calculated according to National Cholesterol Education Program-Adult Treatment Panel (NCEP-ATP-III) criteria (14).

Statistical analysis

After descriptive statistical analysis of the general characteristics of the study participants, the Kolmogorov–Smirnov test was used to examine the distribution of variables, and the Levene test to study the variance. Student's *t*-test was applied to compare mean values of quantitative variables when the distribution was normal and the Mann–Whitney *U* test when it was not. Qualitative variables were analysed with the χ^2 test or with Fisher's exact test if at least one cell had an expected count <5. For paired samples the Student's *t*-test for paired samples and McNemar test were used. Pearson's coefficient was used to test the correlation between quantitative variables and serum 25-(OH)D level. Binary logistic regression models (Wald method) were used to measure the association between the presence of MeS and vitamin D levels in a multivariate analysis. $p \leq 0.05$ was considered significant. SPSS 17.0 was used for data analyses (SPSS Inc., Chicago, IL, USA).

RESULTS

This study includes 92 individuals, 46 psoriatic patients without arthritis who were receiving no systemic treatment for psoriasis or any anti-diabetic, anti-hypertensive, or lipid-lowering therapy, and 46 healthy controls.

Table I summarizes data on the MeS parameters and the confounding factors associated with vitamin D status. Patients with psoriasis presented lower significant

Table I. *General data for the study population*

Variable	Psoriasis *n* = 46	Control *n* = 46	*p*-value
Age, years, mean ± SD	45.57 ± 9.96	45.89 ± 10.06	0.876
Sex, male, %	26 (56.5)	26 (56.5)	1.000
PASI, mean ± SD	4.28 ± 4.38	–	–
Body surface area, %, mean ± SD	5.10 ± 7.08	–	–
Time with psoriasis, years, mean ± SD	18.58 ± 11.81	–	–
Family history of psoriasis, *n* (%)	20 (43.5)	–	–
Fitzpatrick skin phototype			0.532
I–III, %	22 (47.8)	25 (54.4)	
IV–VI, %	24 (52.2)	21 (45.6)	
Waist circumference, cm, mean ± SD	97.57 ± 10.74	94.58 ± 11.75	0.207
Body mass index, kg/m^2, mean ± SD	28.50 ± 5.44	26.84 ± 3.80	0.093
Smoking, pack-years, mean ± SD	11.97 ± 12	9.85 ± 12.28	0.405
Alcoholism, g/week, mean ± SD	89.83 ± 135.41	71.54 ± 92.56	0.452
Physical activity, level 1 (%)	17 (37.0)	19 (41.3)	0.669
Vitamin D intake, IU/day, mean ± SD	188.72 ± 136.83	172.92 ± 102.18	0.532
Sun exposure h/week, mean ± SD	25.98 ± 16.42	23.87 ± 17.14	0.548
Systolic blood pressures, mmHg, mean ± SD	132.52 ± 16.76	126.07 ± 25.95	0.288
Diastolic blood pressures, mmHg, mean ± SD	81.76 ± 10.28	76.30 ± 16.07	0.095
Fasting glucose, mg/dl, mean ± SD	102.09 ± 45.21	86.46 ± 9.36	0.026
Total-C, mg/dl, mean ± SD	207.57 ± 37.05	201.54 ± 38.85	0.452
LDL-C, mg/dl, mean ± SD	129.57 ± 31.04	125.85 ± 35.22	0.593
HDL-C; mg/dl, mean ± SD	52.52 ± 14.38	54.54 ± 13.36	0.487
TG, mg/dl, mean ± SD	140.74 ± 91.64	103.61 ± 47.46	0.017
Metabolic syndrome, *n* (%)	14 (30.4)	8 (17.4)	0.143
Calcium, mg/dl, mean ± SD	9.34 ± 0.40	9.34 ± 0.44	0.964
Phosphorus, mg/dl mean ± SD	3.25 ± 0.54	3.11 ± 0.55	0.184
Intact parathyroid hormone, pg/ml, mean ± SD	41.90 ± 14.70	39.80 ± 14.05	0.402
Creatinine, mg/dl, mean ± SD	0.75 ± 0.13	0.76 ± 0.13	0.783
25-hydroxyvitamin D, ng/ml, mean ± SD	30.52 ± 9.29	38.31 ± 9.56	0.000
<20 ng/ml (%)	9 (19.6)	0 (0)	
20–<25 ng/ml (%)	7 (15.2)	0 (0)	
25–<30 ng/ml (%)	9 (19.6)	8 (17.4)	
30–<40 ng/ml (%)	14 (30.4)	23 (50.0)	
>40 ng/ml (%)	7 (15.2)	15 (32.6)	

SD: standard deviation; PASI: Psoriasis Area and Severity Index; IU: International Units; Total-C: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglycerides.

25-OHD levels than controls (30.5 ± 9.3 vs. 38.3 ± 9.6 ng/ml; $p = 0.0001$); 54.4% vs. 22.6% in the control group ($p < 0.0001$) evidenced vitamin D insufficiency (< 30 ng/ml). A higher proportion of individuals met MeS criteria in the psoriatic group (30.4% vs. 17.4% in control group) ($p = 0.143$), and the patients had increased fasting glucose (102.1 vs. 86.5 mg/dl, $p = 0.026$) and TG (140.7 vs. 103.6 mg/dl, $p = 0.017$) levels.

In psoriatic patients, 25-OHD serum levels were negatively associated with age ($r = –0.477$, $p = 0.001$), BMI ($r = –0.410$, $p = 0.005$), waist circumference ($r = –0.454$, $p = 0.002$), alcohol intake ($r = –0.305$, $p = 0.039$), DBP ($r = –0.320$, $p = 0.030$), fasting glucose ($r = –0.329$, $p = 0.026$), and serum TG ($r = –0.368$, $p = 0.012$) (Fig. S1[1]). A trend to signification correlation was found between 25-OHD level and SBP ($r = –0.287$; $p = 0.053$), sun exposure ($r = 0.266$; $p = 0.074$), and daily vitamin D intake ($r = 0.257$; $p = 0.085$). No significant correlation was found between psoriasis-related variables (PASI, BSA, family history of psoriasis and "time with psoriasis") and 25-OHD levels[2].

In the control group, a positive correlation was found between 25-OHD levels and sun exposure (r = 0.427, $p = 0.003$) and between 25-OHD levels and HDL-c levels (r = 0.286, $p = 0.054$).

Both groups were divided regarding the presence of MeS (Table SI[1]). In the psoriasis group, the mean serum 25-OHD level was significantly lower in patients with MeS (24.1 ± 7.5 vs. 32.8 ± 8.9, $p = 0.007$). In the control group no significant differences were found in 25-OHD levels among individuals with and without MeS. Patients with psoriasis and MeS presented nearly significant higher values of PASI (3.61 vs. 6.18, $p = 0.08$). Also, patients and controls with MeS showed higher significant BMI than patients or controls without MeS. No significant differences were found in age, sex, smoking status, alcohol intake, physical activity, sun exposure, or daily vitamin D intake in patients or controls regarding the presence of metabolic syndrome.

The binary logistic regression model for MeS in psoriatic patients showed a positive significant association with 25-OHD insufficiency ($p = 0.038$) after controlling for age, BMI, alcohol intake, sun exposure, vitamin D intake and physical activity (Table II).

Table II. *Binary logistic regression model for metabolic syndrome (MeS) (NCEP-ATP III) in psoriatic patients. 25-hydroxyvitamin D (25-OHD) shows an independent association with MeS after adjusting for potential confounding factors*

Variable	Odds ratio	95% confidence interval	*p*-value
Age	0.948	0.853–1.053	0.317
Body mass index	1.080	0.926–1.259	0.328
Alcohol intake	0.999	0.993–1.005	0.825
Sun exposure	1.000	0.960–1.042	1.000
Vitamin D intake	1.003	0.996–1.010	0.429
Physical activity	1.260	0.243–6.534	0.783
25-OHD insufficiency	0.844	0.720–0.990	0.038

DISCUSSION

In this study serum 25-OHD levels were significantly lower in patients with psoriasis than in controls. Moreover, in the psoriatic group serum 25-OHD levels were significantly and inversely correlated with some MeS criteria, i.e. waist circumference, DBP, fasting glucose and TG levels. Thus, psoriatic patients with MeS showed a significantly lower level of 25-OHD than patients without MeS. Low levels of 25-OHD in psoriatic patients have been described previously (10, 11).

Waist circumference and BMI (proxies for adiposity) were previously reported to be negatively associated with vitamin D in general and psoriatic populations (10, 15). This relationship can be partially explained by the liposolubility of vitamin D and its reduced bioavailability in bodies with a high fat content (15), although a significant negative association between MeS and vitamin D independent of adiposity was observed in a study of morbidly obese patients (16). In our study the association between 25-OHD and MeS persisted after binary logistic regression that included the BMI. Regarding the lower level of vitamin D in obese subjects, a lower level of exposure to the sun has been suggested due to poor mobility or cosmetic concerns[3]. In addition to the possible reduction in vitamin D biodisponibility in obese subjects, it has been suggested that vitamin D could regulate adipogenesis, and that pre-adipocyte differentiation inhibition is mediated via the vitamin D receptor-dependent inhibition of C/EBPα and peroxisome proliferator-activated receptor γ expression (17).

Regarding other MeS criteria, all have shown an inverse correlation with 25-OHD levels in epidemiological or experimental studies supporting these associations. Vitamin D receptors are present in human

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[2]In the psoriasis group, serum 25-OHD levels were calculated according to the presence of NCEP-ATP III criteria and were significantly lower in patients with higher waist circumference (≤ 102 cm vs. > 102 cm: 34.30 ± 8.71 vs. 26.39 ± 8.22 ng/ml, $p = 0.004$), higher fasting glucose (< 100 mg/dl vs. ≥ 100 mg/dl: 32.55 ± 9.10 vs. 24.05 ± 6.80 ng/ml, $p = 0.007$), and higher TG (< 150 mg/dl vs. ≥ 150 mg/dl: 32.49 ± 8.69 vs. 26.45 ± 9.44 ng/ml, $p = 0.024$), and a trend to signification was found for DBP (< 85 mmHg vs. ≥ 85 mmHg: 32.91 ± 9.29 vs. 27.67 ± 8.66, $p = 0.085$). No significant differences in 25-OHD serum levels were found as a function of the presence of systolic hypertension or low HDL-C levels.

[3]However, we controlled this potential confounding factor in the present study by various means: exclusively enrolling residents of the same locality (Granada metropolitan area, Southern Spain); excluding patients who had been on a sunny holiday in the previous month; performing the study within a narrow time-interval; and obtaining a self-estimate of sun exposure during the previous month. Moreover, no significant differences in sun exposure were found between obese and non-obese patients (data not shown).

cells that can contribute to modifying blood pressure (e.g. cardiomyocytes, vascular smooth muscle cells, endothelial cells, and renin-producing juxtaglomerular cells) (18, 19). Experimental studies have reported a regulative role for vitamin D in the renin system (19, 20). Moreover, vitamin D supplementation has been reported to have a beneficial effect on blood pressure in humans (21) and rats (22). A role for vitamin D in glucose metabolism is supported by the presence of vitamin D receptors (23) and the 1α-hydroxylase enzyme (24) in β pancreatic cells, and by experimental findings of increased glucose-mediated insulin secretion in animals after vitamin D administration (25). The present finding of an inverse association between serum 25-OHD and TG values is also in agreement with cross-sectional or longitudinal studies (26, 27). Moreover, pro-inflammatory cytokines related with lipolysis (increase in free fatty acids) and insulin-resistance can be regulated by vitamin D (28, 29). Although in our sample significant correlation between vitamin D and HDL-c has not been found, a significant direct correlation has been found in other studies. It could be explained by the direct relationship found between vitamin D and apolipoprotein A-I, the main component of HDL-c. However, intrinsic mechanism is unknown (30). See Fig. S2[1]) for an integrated view of potential interrelations between different components of MeS and 25-OHD.

Currently, the intrinsic mechanisms that regulate the extraskeletal functions of vitamin D are not well known. In the study by Oh et al. (31), macrophages from a group of patients (obese, diabetic, hypertensive patients with vitamin D deficiency) showed a significant suppression of foam cell formation by reducing acetylated or oxidized low-density lipoprotein cholesterol uptake when were cultured in a media with 1,25-$(OH)_2$D vs. macrophages cultured in a vitamin D-deficient media. However, this significant effect was not observed in a control group (obese, non-diabetic, hypertensive patients with vitamin D deficiency). In this sense, differences in correlation between MeS parameters and vitamin D have been found in our study in psoriasis group vs. control group.

There are few studies evaluating the benefit of vitamin D supplementation on metabolic parameters. In the study of Al-Daghri et al. (32) a small benefit in terms of the cholesterol profile was found after one year of vitamin D supplementation in a general population. Moreover, different benefits of vitamin D supplementation have been reported, depending on population features; a greater benefit seems to exist in patients receiving dialysis than in the general population (33). Thus, based on differences found in correlation of 25-OHD-metabolic parameters among the psoriasis group and the control group in the present study, it might be hypothesized that a greater benefit could result from vitamin D supplementation in a psoriasis population.

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