THE ASSOCIATION BETWEEN VITAMIN D VALUES AND PSORIASIS: A LITERATURE REVIEW

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ABSTRACT

The Vitamin D deficiency could be involved in the development of psoriasis, Vitamin D deficiency being considered to be involved in the development of disorders related to cellular immune system. The aim of this study is to review the literature in order to find if there is an association between the Vitamin D level in the serum and psoriasis. A search for relevant articles was performed using PubMed, Web of Science and Springer databases. A total of 19 articles fulfilled the criteria for inclusion in this review. 14 studies revealed statistically significant lower levels of Vitamin D in psoriatic patients when compared to healthy controls. The other 5 studies did not find a statistically significant difference between 25-hydroxycholecalciferol levels in psoriasis group and in control group.

Keywords: vitamin D, psoriasis, 25-hydroxy vitamin D level, 25-hydroxycholecalciferol

Introduction

Psoriasis represents a complex, immune-mediated systemic disease, which is influenced by environmental factors and genetic ones. These factors contribute to its development and phenotypic expression. Although, historically was considered as a skin-limited disease, psoriasis is now known to be a disorder of systemic inflammation, associated with inflammatory arthritis, and increasingly understood to be associated with cardiovascular diseases and metabolic syndrome (1) supplementary and total vitamin D intake and incident psoriasis in women. A prospective study was performed of 70,437 US female nurses aged

47-74 enrolled in the Nurses' Health Study who did not have psoriasis at baseline in 1994 and who completed semi-quantitative food frequency questionnaires in 1994, 1998, 2002 and 2006. The incidence of clinician-diagnosed psoriasis was ascertained and validated by self-reported questionnaires. 502 confirmed incident psoriasis cases were documented during 973.057 person-years of follow-up from 1994 June to 2008 June. Association between vitamin D intake and incident psoriasis was assessed using multivariable-adjusted cox regression analysis. After adjusting for age, smoking, body mass index, calorie intake, UV flux, exercise and alcohol use, there was no significant association between vitamin D intake

(dietary, supplementary and total vitamin D. The pathogenesis of psoriasis is not completely known (2). In psoriasis, all therapeutic strategies aim to reduce the symptoms and the burden of the disease.

Topical corticosteroids are used generally for controlling mild symptoms. Also, other interventions are vitamin D and their analogs supplementation, or other local anti-inflammatory ointments. Phototherapy and systemic immunosuppressants are generally used for severe cases (3) however, requires several hospital visits weekly, interfering with (school.

Vitamin D is an oil-soluble vitamin implicated in calcium absorption, bone metabolism, calcium and phosphorus homeostasis, skeletal mineralization and it also has numerous other metabolic and physiological functions. UVB exposure helps keratinocytes from the epidermis to synthesize previtamin D₃ which is later converted to the active form of vitamin D, known as 1,25 dihydroxycholecalciferol. The levels of vitamin D from the serum are changing with the season. Maximum values are reached in the seasons with high sun exposure, while in the seasons with low sun exposure, the levels reach minimum values (2). The reference values for vitamin D (25-hydroxycholecalciferol) are considered to be 30–50 ng/ml (75–125 nmol/l). Values less than 20 ng/ml (50 nmol/l) indicate Vitamin D deficiency (4) and vitamin D analogs are widely used in its treatment. It is evident that ultraviolet radiation enables vitamin D-3 (cholecalciferol. Low serum levels of 25-OH vitamin D have been reported in numerous diseases such as cardiovascular diseases (5), autoimmune diseases, malignancies, multiple sclerosis, metabolic disorders, inflammatory bowel disease or psoriasis (6).

Vitamin D has many roles, evidence suggesting that vitamin D can modulate the activity in dendritic cells and keratinocytes and the proliferation in T-cells. All metabolites of vitamin D act via the vitamin D receptors. One of the metabolites, 25-hydroxycholecalciferol, has double activity in keratinocytes: inhibition of their proliferation and enhancement of the maturity. Taking this influence on the keratinocytes into consideration, a deficiency in 25-hydroxycholecalciferol might be a risk factor

in the development of psoriasis, with possible implications in disorders related to cellular immune system and angiogenesis. Some theories consider that psoriasis could activate a vicious circle with severe deterioration of cutaneous functions and, furthermore, a progressive decline of vitamin D derivatives levels in the whole body (4) and vitamin D analogs are widely used in its treatment. It is evident that ultraviolet radiation enables vitamin D-3 (cholecalciferol.

The aim of this study was to review the literature for studies comparing the 25 OH vitamin levels in patients with psoriasis compared to healthy controls.

Material and methods

We searched for relevant articles on PubMed, Web of Science and Springer, by using „Vitamin D” and „Psoriasis” as keywords. For inclusion in our study, the following criterion was set: comparison between the vitamin D serum level in psoriatic patients and in healthy controls. It were taken into consideration either retrospective studies, or prospective studies. The studies that were lacking healthy human controls were excluded.

After searching PubMed, Web of Science, and Scopus for the keywords, after the screening, over one thousand unique, eligible articles were identified (Figure 1). After applying the inclusion and the exclusion criteria, 19 articles were considered eligible for this review.

Figure 1 Flow diagram of study selection

Table 1 Studies with statistically significant difference

Authors	Sample	Main Results
Chandrashekar, L., 2015 (7)	43 psoriatic patients 43 healthy controls	Vitamin D level was significantly lower in the psoriasis patients group (13.3 ± 6.9 vs 22.4 ± 18.4 , $p=0.004$), concluding that psoriasis is associated with lower vitamin D levels and high levels of inflammation markers such as hs-CRP and ischemia-modified albumin.
Myśliwiec, H., 2016 (8)	115 patients with exacerbated plaque type psoriasis, 38 healthy persons	The study revealed that serum 25-OH vitamin D levels were decreased in both groups, but a higher prevalence of deficiency was observed in the psoriasis group (66% vs 24% during the summer and 66% vs 71% during the winter) ($p=0.0003$). 25-OH vitamin D serum concentrations of psoriatic patients were significantly lower compared to the control group ($p=0.0003$). Exposure to UVB, serum 25-OH vitamin D levels increased and the PASI score improved.
Filoni, A., 2018 (9)	170 psoriatic patients 51 patients with autoimmune bullous disease, 340 healthy controls	25-OH Vitamin D serum level differ ($p=0.0001$) among the three groups. In patients with psoriasis the levels were significantly lower compared to healthy controls (18.2 ± 11.1 ng/mL vs 34.3 ± 13.3 ng/mL) ($p=0.0007$).
Orgaz-Molina, J., 2014 (10)	46 patients with psoriasis, without arthritis and systemic treatment 46 control subjects	Significantly lower 25-OH Vitamin D levels in psoriatic patients compared to control subjects (30.5 ± 9.3 vs. 38.3 ± 9.6 ng/mL; $p = 0.0001$); Lower than 30ng/mL values were observed in 54.4% of psoriasis group vs. 22.6% in the control group ($p < 0.001$).
Mattozzi, C., 2018 (11)	141 caucasian subjects with moderate to severe psoriasis, 62 healthy controls	Patients with psoriasis presented lower values of 25-OH vitamin D compared to healthy controls.
Ricceri, F., 2013 (12)	68 patients with chronic plaque psoriasis 60 healthy controls	Psoriasis patients group presented significantly lower levels of 25-OH vitamin D ($p<0.05$). Most of them had Vitamin D levels lower than normal, 97% with deficiency and 68% with insufficiency.
Orgaz-Molina, J., 2012 (13)	43 patients with psoriasis 43 control subjects	25-OH vitamin D serum concentration was significantly lower in the psoriasis patients group (24.41 ± 7.80 vs 29.53 ± 9.38 ; $P=0.007$). One quarter of the patients within psoriasis group were Vitamin D deficient (25,6%) compare to 9.3% in the comparison group ($p=0.043$); 79.1% of the patients retested Vitamin D insufficiency, versus 58,1% in the control group ($p=0.037$).
Al-Mutairi, N., 2014 (14)	93 psoriasis patients 50 controls	25-OH vitamin D was 31.5 ± 14.41 nmol/L in the patient group and 53.5 ± 19.6 nmol/L in controls ($p=0.015$).
Al-Mutairi, N., 2013 (15)	100 patients with stable plaque psoriasis (psoriasis area and severity index ≥ 10) with no systemic treatment in the past 3 months 100 healthy volunteers	25-OH vitamin D concentration was 29.53 nmol/L ± 9.38 nmol/L in patients, and 53.5 nmol/L ± 19.6 nmol/L in healthy controls ($p<0.0001$).
Amon, U., 2018 (16)	Subgroup a (1461 patients with clear diagnoses of skin diseases or allergies, among which 180 with psoriasis vulgaris) Subgroup b (71 healthy controls)	The mean value for 25-OH Vitamin D level in psoriasis patients was 22,6 ng/ml, with SD of 10,7 ng/ml; 43.8% presented Vitamin D deficiency. The healthy group had a mean value of 44,1 ng/ml with SD of 10.7 ng/ml, with 1.4% being Vitamin D deficient. Significance level for the difference, $p<0.001$.
Bergler-Czop, B., 2016 (4)	40 adults with psoriasis 40 healthy subjects	Average 25-OH Vitamin D values for study group was 32,25nmol/l, with sd 6,79nmol/l while in the control group, the mean value was 57,62 nmol/l with sd of 6,82 nmol/l ($p=0.048$). For both groups, most of the subjects were vitamin D deficient.
Orgaz-Molina, J., 2014 (17)	44 psoriatic patients without arthritis 44 controls	25-OH vitamin D level for study group was 29.92 ng/mL, significantly lower compared to control group, 38.00 ng/mL, $p<0.0001$.
Gisondi, P., 2012 (18)	145 patients with chronic plaque psoriasis 112 patients with rheumatoid arthritis (RA) 141 healthy controls	The levels of 25-OH Vitamin D differ significantly among the three groups ($p=0.001$), with mean values of 20.7 ± 11.3 (psoriasis group), 24.0 ± 11.4 (rheumatoid arthritis groups) and 37.1 ± 27.6 in control group. The vitamin D levels were significantly lower in psoriatic patients group compared to control group ($p=0.01$).
Atwa, M. A., 2013 (19)	43 patients with plaque psoriasis 55 rheumatoid arthritis patients 40 healthy controls matched for age	Values for 25-OH Vitamin D were statistically different among the three groups ($p<0.001$). (11.74 ± 3.60 ng/ml in psoriasis group, 15.45 ± 6.42 ng/ml in rheumatoid arthritis group, and 24.55 ± 11.21 ng/ml in control group).

Total number of people assessed was 10068, stratified as follows: 1593 patients with psoriasis, 1499 patients with other diseases and 6976 healthy controls.

Results

From the studies included in the review, 14 of them revealed a statistically significant difference between the vitamin D serum level in psoriatic patients and in healthy controls. These studies are presented in Table 1. In the remaining 5 studies, the difference between the vitamin D serum level from psoriatic patients and from healthy group was not statistically significant. These studies are described in Table 2.

Discussion

In all the 14 studies that revealed a statistically significant difference between the vitamin D serum level among the compared groups, the vitamin D levels were lower in the psoriatic patients group.

Chandrashekar et al. found that 25-hydroxy vitamin D serum levels were significantly lower in psoriasis cases. Psoriasis severity, assessed by using PASI score, correlated negatively with serum levels of 25-OH vitamin D (7). Myśliwiec et al. observed vitamin D deficiency both in psoriatic patients and in the control group with significantly lower values in the first group. The

prevalence of the deficiency among psoriatic patients was higher compared to the control group, especially during summer. Also, the 25-hydroxy vitamin D level increased after UVB phototherapy (8) in between psoriasis. Vitamin D regulates function of the dendritic cells, proliferation and maturation of the keratinocytes and lymphocytes T. The aim of the study was to evaluate serum vitamin D (25OHD).

Filoni et al. revealed the relationship of vitamin D serum level with the age of the patient, the season when measured and the time from the start of the disease. They also found that 45.8% of psoriasis patients had vitamin D deficiency (<20 ng/mL) and 38.9% had vitamin D insufficiency (20–30 ng/mL) (9).

Orgaz-Molina et al. compared in 2014 46 psoriatic patients, without arthritis and 46 control subjects. They found significantly lower levels of 25-OH vitamin D in the patients group. Furthermore, in the psoriatic group serum 25-OH vitamin D levels were significantly and negatively correlated with some metabolic syndrome criteria. Thus, psoriatic patients with metabolic syndrome showed a significantly lower level of 25-OH vitamin D than patients without metabolic syndrome (10). In 2012, Orgaz-Molina et al. compared 43 psoriatic patients and 43 control subjects and found that serum 25-OH vitamin D levels were lower in psoriatic patients, even after adjusting for confounding factors. They did not found a significant correlation between 25-OH

Table 2 Studies with non-statistically significant difference

Authors	Sample	Results
Solak, B., 2016 (20)	43 patients with psoriasis, without arthritis and 41 healthy controls, less than 50 years old.	No significant difference was observed for men, 26.6 ± 8.6 nmol/l (psoriasis group) vs 22.2 ± 10.1 nmol/l (control group), $p=0.272$. In females the vitamin D level was significantly lower 18 ± 7.3 nmol/l vs 27.1 ± 15.9 nmol/l ($p=0.012$). Overall, the difference was not statistically significant ($p=0.12$).
Nayak, P., 2018 (21)	Hospital-based case-control. 61 patients with psoriasis and 61 age and sex matched controls.	86.9% of patients with psoriasis and 83.6% of controls had lower levels of vitamin D. No statistically significant difference was observed ($p=0.1$). Both case group and control group had low levels of vitamin D.
Wilson, P., 2013 (22)	Population based study, 20-59 years old, self-reported with psoriasis	Mean 25-OH vitamin D was 24.2 ng/mL and 23.6 ng/mL for participants with and without psoriasis ($P = 0.37$). More than 70% of the participants, in both groups were vitamin D deficient, and 33% of psoriasis patients and 34.9% from control group were Vitamin D deficient.
Maleki, M., 2016 (23)	Cross-sectional study, dermatology clinic, 50 psoriatic patients and 43 healthy controls.	The mean serum vitamin D level, for participants with psoriasis was 14.92 ± 6.31 ng/mL while in the control group, it was 12.52 ± 4.54 ng/mL. The difference was not statistically significant ($P = 0.21$). The prevalence of Vitamin D deficiency was 84% in psoriatic patients group and 93% in control group.
Zuchi, M.F., 2015 (24)	20 psoriatic patients, aged 19 to 76 compared with 20 patients aged 1 to 84.	The median vitamin D serum level in the psoriasis cases was 23.55 ± 7.6 ng/ml and in the controls was 22.35 ± 3.10 ng/ml ($p = 0.73$). Percentage of patients with Vitamin D deficiency and insufficiency was almost equal (5/20 vs 4/20 and 13/20 vs 12/20). In the psoriasis patients group, males had higher levels of Vitamin D when compared to females (25.35 ± 2.9 vs 20.85 ± 6.7 , $p=0.0317$).

vitamin D levels and psoriasis manifestations evaluated through PASI score, mean time with psoriasis, or other chronic diseases (13) 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).

Mattozzi et al. obtained a similar results, with vitamin D levels lower in psoriatic patients and vitamin D levels with negative correlation with the clinical severity of the disease (11). Ricceri et al. found that serum 25-OH vitamin D had significant negative correlations with PASI score ($P < 0.001$) (12).

Al-Mutairi et al. concluded that serum levels of vitamin D were significantly lower in psoriatic patients than in healthy persons (15) a lot of co-morbidities (diabetes, obesity, heart disease, etc.). Furthermore, there was a highly significant elevation of serum 25-OH vitamin D and serum LL-37 among psoriasis patients after narrowband ultraviolet B treatment (14).

Amon et al. found that serum level of 25-OH vitamin D was significantly lower in psoriatic subgroup compared to the healthy subgroup ($p < 0.001$). They did not find a correlation between quality of life, as measured by the Dermatology Life Quality Index, and 25-OH vitamin D levels for patients with psoriasis. The percentage of psoriatic patients with vitamin D serum level lower than 20 ng/mL was 43.9% (16). Bergler-Czop et al. revealed a statistically significant difference in 25-hydroxycholecalciferol level between patients with psoriasis and healthy individuals. The level of 25-hydroxycholecalciferol was seriously deficient in both groups. Also, it was found a negative correlation of vitamin D serum level with both PASI ($r = -0.43$) and the duration of psoriasis ($r = -0.53$) (4) and vitamin D analogs are widely used in its treatment. It is evident that ultraviolet radiation enables vitamin D-3 (cholecalciferol).

Orgaz-Molina et al. analyzed the association between 25-hydroxy vitamin D serum levels and subclinical carotid atherosclerosis in psoriasis patients and found a significant negative correlation between serum 25-OH vitamin D levels and the Maximal Intima-Media Thickness ($rs = -0.678$, $p < 0.0001$). No correlation was found in healthy controls. Also, serum levels of vitamin

D were significantly lower ($p = 0.003$) in psoriatic patients with carotid atheromatous plaque than in those without it. Moreover, serum 25-OH vitamin D showed an inverse correlation with age ($rs = -0.499$, $p = 0.001$), Body Mass Index ($rs = -0.300$, $p = 0.048$), total cholesterol ($rs = -0.475$, $p = 0.001$), low density lipoprotein cholesterol ($rs = -0.465$, $p = 0.001$) and triglycerides ($rs = -0.396$, $p = 0.008$) levels (17).

Gisondi et al. established that the 25-OH vitamin D levels were lower in patients with psoriasis when compared with healthy controls, while no difference between patients with psoriasis and those with rheumatoid arthritis. Furthermore, 25-OH vitamin D serum levels showed high seasonal variability. Serum levels of vitamin D at patients with psoriasis (ng/mL) were 19.1 ± 7.6 in spring, 27 ± 14.5 in summer, 20.1 ± 12.6 in autumn and 16 ± 10.5 in winter ($P < 0.01$) (18). Atwa et al. found a significant difference in 25-OH vitamin D level among the psoriatic patients group and the healthy controls group. They also found that 25-OH vitamin D serum level was not correlated with PASI, DAS28 (Disease activity score index of a 28 joint count), TNF- α , CRP (C-reactive protein) or ESR (erythrocyte sedimentation rate) in psoriatic patients (19).

From all the 19 studies included in this review, 5 of them did not reveal a statistically significant difference between the vitamin D level in psoriatic patients and in healthy controls. Among these 5 studies, only one revealed lower levels of vitamin D in psoriatic patients compared with healthy controls, while in the other four studies the psoriatic patients had higher vitamin D levels than healthy persons. Also, we must acknowledge the fact that in all these five studies, the vitamin D levels were lower than normal, in high proportion of the subjects, from both study groups (case group and control group).

Solak et al. compared 43 psoriasis patients without arthritis and 41 healthy persons and found that the percentage of overall osteopenia and osteoporosis was significantly higher in patients with psoriasis when compared with the control group, but there was not a significant difference between the two groups regarding serum vitamin D levels (20). Nayak et al. revealed that vitamin D levels were significantly lower in females

when compared to males in both psoriasis cases ($P=0.02$) and controls ($P=0.006$). Also, there was not a significant correlation between the severity of the disease and serum levels of vitamin D, calcium and C-reactive protein (20).

Wilson found that Psoriasis Life Impairment was not associated with 25-OH vitamin D, but Body Mass Index had an inverse association with 25-OH vitamin D level (coefficient $= -0.40$, $P < 0.001$) (22). Maleki et al. concluded that serum 25-OH vitamin D did not correlate with family history ($P=0.92$) or with joint ($P=0.53$) or nail ($P=0.27$) involvement, but it did correlate with female gender ($P=0.04$) and higher PASI score ($P=0.03$) (23). Zuchi et al. did not find significant differences in vitamin D serum levels between psoriasis patients and healthy controls ($P = 0.735$), but they find vitamin D serum to be lower in women with psoriasis when compared to men with psoriasis ($P = 0.03$), difference that was not statistically significant among healthy controls ($p = 0.62$) (24).

Conclusions

From our review we conclude that the vitamin D levels in psoriatic patients tend to be lower when compared to non-psoriatic patients. Also, even in the case of the studies in which a difference was not observed, most of the participants had lower than normal levels for Vitamin D.

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