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Hypovitaminosis D is Associated with Psoriasis: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction. Psoriasis is a chronic inflammatory and immune-mediated skin disease that affects over 7.2 million U.S. adults. Current treatment has improved clinical outcomes. Vitamin D is believed to affect the proliferation and regeneration of keratinocytes; therefore, its deficiency is a possible risk factor; however, there is still no definite evidence. The objective of this study was to synthesize existing data on the relationship between hypovitaminosis D and psoriasis.

Methods. A meta-analysis of relevant studies was conducted by doing a comprehensive search in the MEDLINE, EMBASE, and the Cochrane Central Register through July 2018 to identify relevant cohort studies and to assess serum 25-hydroxyvitamin D (25(OH) D) levels in adults with psoriasis. The primary outcome was the mean difference in serum 25(OH)D level between psoriatic patients and controls.

Results. The initial search identified 107 articles. Only ten studies met the criteria for full-paper review. Meta-analysis was conducted from ten prospective cohort studies involving 6,217 controls and 693 cases. The pooled mean difference in serum 25(OH)D level between psoriatic patients and controls was -6.13 ng/ml (95% CI, -10.93 to -1.32, p-value = 0.01). The between-study heterogeneity (I^2) was 98%, $p < 0.00001$.

Conclusion. Our meta-analysis was the first study to establish the relation between vitamin D and psoriasis. The result found a significant relationship between low 25(OH) D levels and psoriasis, but did not establish a causal relationship. Further studies will be required to establish whether vitamin D supplementation benefits patients with psoriasis.

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INTRODUCTION

Hypovitaminosis D is common in the United States and European countries, especially in the winter.[1,2] Vitamin D deficiency is considered one of the risk factors for osteoporosis. In addition, hypovitaminosis D has been associated with a variety of autoimmune diseases such as rheumatoid arthritis, Crohn's disease, systemic lupus erythematosus, and multiple sclerosis.[3-5] There are also several reports on the association between hypovitaminosis D and autoimmune skin conditions, such as pemphigus vulgaris, bullous pemphigus, alopecia areata, and vitiligo.[6-8] Vitamin D may have an essential role in modulating dendritic cell function, and regulating keratinocytes and T-cell proliferation that can lead to skin pathology.[9] This may be one of the explanations for the association between hypovitaminosis D and autoimmune diseases.

Psoriasis is considered a chronic inflammatory and immune-mediated skin disease that affects 3.2% of the U.S. population, or over 7.2 million adults over the age of 20.[10] There is increasing evidence that psoriasis is a systemic disorder, like other inflammatory diseases, such as rheumatoid arthritis and systemic lupus erythematosus, that can affect every ethnicity.[11] Clinical improvement of psoriasis following sun exposure, which may be due to a decrease in cutaneous lymphocyte-associated antigen (CLA)+ T cells, has been reported.[12] This clinical improvement also might be due to increased vitamin D production in the skin following sun exposure.[4,13,14] Moreover, some studies have identified an association between polymorphisms of vitamin D receptor (VDR) and the severity of psoriasis disease, believing it affects the alteration of the cutaneous barrier.[15-16] The hypotheses about Vitamin D and its properties as an inflammation modulator[16] may link to the pathogenesis and disease activity of psoriasis. From multiple literature reviews, we acknowledge an important relationship between vitamin D and psoriasis; however, there are no clear-cut data or evidence that hypovitaminosis D definitely is related to psoriasis. We conducted the first systematic review and meta-analysis to determine whether there was an association between hypovitaminosis D and psoriasis.

METHODS

A systematic review and meta-analysis were conducted and reported according to the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) guidelines.[17]

Eligibility Criteria. In this meta-analysis, studies were included that assessed serum vitamin D concentration (25-hydroxyvitamin D; 25(OH)D) or vitamin D deficiency in patients with psoriasis. Studies that met the following criteria were included:

(1) Human studies that included adult participants ≥ 18 years of age who had been diagnosed with psoriasis and normal controls and had serum 25(OH)D level measured.

(2) Prospective cohort, retrospective cohort, case-control, and cross-sectional studies in English.

(3) Reported outcomes including serum 25(OH)D levels in both cases and controls.

Literature Search and Selection. The search was conducted independently by two reviewers (SP and SP). Published studies

indexed in the MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) up to July 2018 were used as a database. One hundred seven relevant studies were selected. Differences in literature inclusion/exclusion were decided by consensus. Search keywords included: psoriasis, vitamin D, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, 25(OH)D, ergocalciferol, and cholecalciferol. No restrictions on languages were included in the search strategies. References of selected studies were reviewed carefully as well. After the search, two authors (SP, SP) independently reviewed abstracts and all relevant references. The full-text evaluation was undertaken when abstracts did not provide adequate information regarding eligibility criteria. Any disagreements on selected studies were resolved by a discussion between the two reviewers for final selection.

Risk of Bias and Quality Assessment. Two authors (SP, SP) independently assessed the quality of each study using the Newcastle-Ottawa Scale for assessing the quality of nonrandomized studies in meta-analyses.[18] A study that received seven or more stars was considered a high-quality study, four to six stars a moderate quality study, and zero to three stars a poor-quality study. The minimum score of included studies was six and the maximum was nine. Seven studies were considered high-quality and three studies were considered moderate-quality. Quality assessment scores using the Newcastle-Ottawa Scale tool for observational studies are reported in Tables 1 and 2.

Statistical Methods. Meta-analysis was performed using Review Manager 5.3 software from the Cochrane Collaboration (London, UK). The studies were reported as the standardized mean differences (SMD) with 95% confidence intervals (CI) comparing between two groups. Parameter estimates from studies were plotted using forest plots to evaluate the difference of vitamin D level between psoriatic patients and normal controls. Publication bias was evaluated using Egger's test. Heterogeneity of effect size was interpreted through I^2 and Q Statistic. Random effects models were used. Subgroup analysis was not performed due to the insufficient number of eligible studies.

RESULTS

Systematic Review of the Literature. Ten studies were identified for inclusion in this review.[19-28] The initial search yielded 107 articles (Figure 1); 85 were discarded because the abstracts did not meet the criteria. The full text of 22 articles was examined in more detail. Twelve studies did not meet the inclusion criteria as described. Ten studies met the inclusion criteria and were included in the review. The references of the ten studies also were reviewed. No relevant studies were obtained from these references. Data were extracted from ten studies, and a total of 6,217 controls and 693 cases from these studies were included in the meta-analysis. The characteristics of extracted studies included in this review are reported in Table 3.

Outcome. The extracted data regarding serum 25(OH)D level in psoriasis and control groups are presented in Table 4.

Meta-analysis. Ten studies were included in the meta-analysis of serum 25(OH) D (Figure 2). The pooled mean difference in serum 25(OH) D level was -6.13 ng/ml (95% confidence interval, -10.93 to -1.32, p = 0.01), lower in patients with psoriasis than in the control participants; the between-study heterogeneity (I^2) was 98%, p = value < 0.00001.

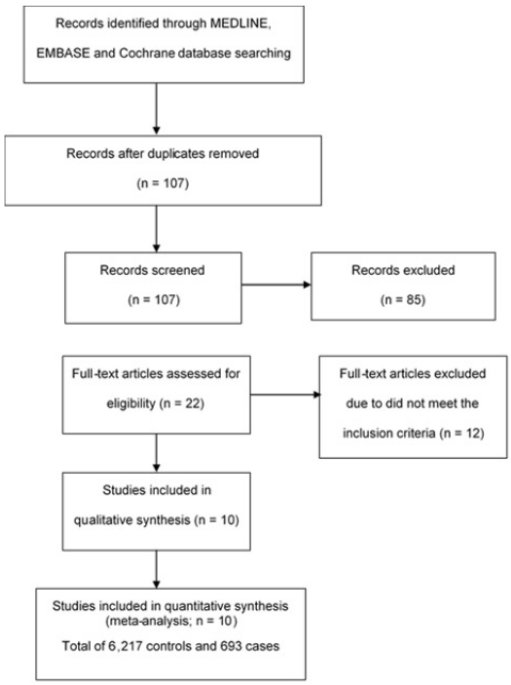


Figure 1. Flow diagram of search results and screening process.

Publication Bias. To investigate potential publication bias, we used Egger's test instead of funnel plot due to more accurate mean difference data. The Egger's test did not show a significant bias with p = 0.051 for the pooled mean difference in serum 25(OH) D (Figure 3).

DISCUSSION

Low vitamin D levels have been associated with several autoimmune diseases, including rheumatoid arthritis, Crohn's disease, systemic lupus erythematosus, and multiple sclerosis.[3-5] In addition, there have been reports on the association between hypovitaminosis D and autoimmune skin conditions such as pemphigus vulgaris, bullous pemphigus, alopecia areata, and vitiligo.[6-8] A potential link between vitamin D deficiency and psoriasis also has been reported.[15] The major finding of our systematic review and meta-analysis was that there is a significant relationship between low 25(OH) D levels and psoriasis. Our meta-analysis revealed that the serum vitamin D level was significantly lower in psoriatic patients compared to control patients. To the best of our knowledge, there is no previous systematic review and meta-analysis of the relationship between vitamin D levels and psoriasis.

Vitamin D is generally classified into two types, vitamin D2 (ergocalciferol) and D3 (cholecalciferol). Vitamin D2 (ergocalciferol) is not produced in the human body; whereas vitamin D3 (cholecalciferol) is synthesized in the skin from 7-dehydrocholesterol by ultraviolet light and is the primary source of vitamin D3 in humans. The other source of vitamin D3 is exogenous intake from food and supplements.[29] Vitamin D is essential for the maintenance of health. Vitamin D is necessary for the absorption of calcium in the small intestine, and it increases bone resorption and the release of calcium into the

blood by stimulating osteoclast maturation. Apart from calcium homeostasis, there has been evidence that vitamin D may have an essential role in cell maturation and immunity.[30] Also, vitamin D receptor (VDR) expression has been found in various human tissues including immune cells.[31]

The role of vitamin D in the skin has been studied widely within the past decades.[15,32] The active form of vitamin D regulates keratinocyte proliferation, differentiation, and apoptosis. Several reports in vitro and vivo studies found a dose-dependent relation between these effects.[33,34] The pathogenesis of psoriasis involves an abnormal function of an innate and adaptive segment of the immune system which T- lymphocyte cell is the central primary controller for these immune processes.[12] Subtypes of T-cell, including T-helper (Th)1, Th17 and Th22, interact with numerous cells through cytokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL) -6 and IL-17.[35] The defect of the T-cell function can cause abnormal skin regeneration.[36-37] Vitamin D also acts as a pluripotent immunomodulator that can inhibit proliferation of T-cell lymphocyte and induce regeneration of CD25+/CD4+ regulatory T-cell that preserves/controls immunological homeostasis and prevents autoimmune response against self-antigens.[38-39] In addition to T-cell regulation, vitamin D has a vital role in inflammatory function. Its metabolite is responsible for down-regulating the production and expression of TNF-α, IL-1β, IL-6, IL-8, and inflammatory profile of human monocytes/macrophages.[35,40] Finally, vitamin D also helps to protect skin from opportunistic infections by inducing autophagy in macrophages and normalize innate response of skin barrier integrity and permeability.[16]

The treatment of psoriasis by exposure to UV rays and sunlight has been known for decades, and the mechanism may be a vitamin D effect related to an increase in endogenous vitamin D synthesis in the skin.[41] Also in the standard treatment of psoriasis, topical vitamin D has been used as a first-line, single or combination medication with topical corticosteroid on localized plaque lesion.[42] However, the effect of vitamin D supplements in treating psoriasis is unclear, but positive outcomes after the treatment for psoriasis-related comorbidities have been reported including hypertension and metabolic syndrome.[43-45] Another association between low vitamin D level and psoriasis might be explained by the hypothesis that vitamin D modulates immune responses in certain conditions.[46] Low vitamin D levels possibly increase the risk of various autoimmune diseases, including psoriasis. Also, a high daily dose of vitamin D supplement improved Psoriasis Area and Severity Index (PASI) scores significantly in patients with psoriasis.[47] Our study with a large number of patients found a significant association between low vitamin D levels and psoriasis that support previous studies.

Table 1. Newcastle-Ottawa Scales adapted for cross-sectional studies.

Study	Selection						Comparability		Exposure				Total
	Representativeness of the sample		Justified sample size	Ascertainment of exposure		Comparable non-respondents rate between two groups	Comparability of different samples on the basis of the design or analysis		Assessment of outcome			Appropriate statistical test	
	Truly representative	Somewhat representative		Validated measurement tool (two stars)	Non-validated tool		Study controls for the most important factor	Study controls for any additional factor	Independent blind assessment (two stars)	Record linkage (two stars)	Self-report		
Wilson et al.[19]	*		*	**			*	*			*	*	8

Table 2. Newcastle-Ottawa Scales adapted for case-control studies.

Study	Selection				Comparability			Exposure		Total
	Adequate case definition	Representativeness of the cases	Selection of controls	Definition of controls	Study controls for the most important factor	Study controls for any additional factor	Ascertainment of exposure (max of 2 stars)	Same method of ascertainment for cases and controls	Non-response rate	
Solak et al.[20]	*	*		*	*	*	*	*		7
Maleki et al.[21]	*	*		*	*	*	*	*		7
Petho et al.[22]	*	*	*	*	*		**	*	*	9
Zuchi et al.[23]	*	*			*	*	*	*		6
Chandrashekar et al.[24]	*	*		*	*	*	*	*		7
El-Moaty Zaher et al.[25]	*	*			*	*	*	*		6
Al-Mutairi et al.[26]	*	*		*	*	*	*	*		7
Gisondi et al.[27]	*	*	*	*			*	*		6
Orgaz-Molina et al.[28]	*	*		*	*	*	*	*	*	8

Table 3. Characteristics of the included studies.

Study	Study design	Location	Sample Size (n)		Age (years)	Duration of disease (years)	Type of psoriasis	Controls	25(OH)D cutoff (ng/mL)
			Psoriasis	Controls					
Solak et al.[20]	Case-control	Turkey	43	41	36.72 ± 8.00	0 - 5 years: 8 (18.6%) 6 - 10 years: 16 (37.21%) > 10 years: 19 (44.19%)	Psoriasis without arthritis	Matched with age	NA
Maleki et al.[21]	Case-control	Iran	50	43	42.80 ± 13.68	10.37 ± 9.87	Chronic plaque psoriasis	Age- and sex-matched controls from northeastern Iran	Deficiency (< 20 ng/mL)
Petho et al.[22]	Case-control	Hungary	53	53	54.7 (31 - 84)	10.8	Psoriatic arthritis	Age- and gender-matched healthy volunteers	Hypovitaminosis D (< 30 ng/mL)
Zuchi et al.[23]	Case-control	Brazil	20	20	46.40 ± 14.90	3.5 ± 9	25% palmoplantar psoriasis; 75% psoriasis vulgaris	Healthy individuals	Deficiency (< 20 ng/mL); insufficiency (20 to < 30 ng/mL); sufficiency (≥ 30 ng/mL)
Chandrashekar et al.[24]	Case-control	India	43	43	44.6 ± 12.0	4.1375 ± 4	Fitzpatrick skin type V	Age- and gender-matched healthy volunteer	NA
El-Moaty Zaher et al.[25]	Case-control	Egypt	48	40	43.88 ± 15.157	NA	Histopathologically proven psoriasis	Age-, sex-, skin prototype- and socioeconomic-match individuals	NA
Al-Mutairi et al.[26]	Case-control	Kuwait	100	100	42	12.2 (0.3 - 31.3)	Plaque psoriasis with Fitzpatrick skin types III to V	Age- and sex-matched healthy controls	Deficiency (< 10 ng/mL)
Gisondi et al.[27]	Case-control	Italy	145	141	51.9 ± 13.3	19.8 ± 13.1	Chronic plaque psoriasis	The partners or relatives of patients if not affected by psoriasis	Deficiency (< 20 ng/mL)
Orgaz-Molina et al.[28]	Case-control	Spain	43	43	44.33 ± 8.71	19.91	Fitzpatrick skin phototype II, III, or IV	Randomly selected age- and sex-matched controls with non-photosensitive dermatologic diseases other than psoriasis	Deficiency (< 10 and < 20 ng/mL); insufficiency (< 30 ng/mL)
Wilson et al.[19]	Cross-sectional	USA	148	5,693	20 - 59	NA	NA	Participants without psoriasis	Deficiency (< 20 and < 30 ng/mL)

Table 4. The outcomes of the included studies.

Study	Vitamin D Deficiency		25(OH)D (ng/mL)		P value
	Psoriasis	Control	Psoriasis	Control	
Solak et al.[20]	Deficiency NA; Insufficiency NA	Deficiency NA; Insufficiency NA	21.2 ± 8.7	25.2 ± 14.1	0.12
Maleki et al.[21]	Deficiency 84%; Insufficiency NA	Deficiency 93%; Insufficiency NA	14.92 ± 6.31	12.52 ± 4.54	0.21
Petho et al.[22]	Hypovitaminosis D 81%	Hypovitaminosis D 57%	21.4 ± 9.23	28.3 ± 14.43	0.001
Zuchi et al.[23]	Deficiency 25%; Insufficiency 65%	Deficiency 20%; Insufficiency 60%	23.55 ± 7.60	22.35 ± 3.10	0.7356
Chandrashekar et al.[24]	Deficiency NA; Insufficiency NA	Deficiency NA; Insufficiency NA	13.3 ± 6.9	22.4 ± 18.4	0.004
El-Moaty Zaher et al.[25]	Deficiency NA; Insufficiency NA	Deficiency NA; Insufficiency NA	21.05 ± 3.66	37.02 ± 5.06	< 0.05
Al-Mutairi et al.[26]	Deficiency 12%; Insufficiency NA	Deficiency 9%; Insufficiency NA	12.8 ± 5.6	21.6 ± 8	< 0.005
Gisondi et al.[27]	Deficiency 57.8%	Deficiency 29.7%	20.7 ± 11.3	37.1 ± 27.6	0.001
Orgaz-Molina et al.[28]	Deficiency 25.6%; Insufficiency 79.1%	Deficiency 9.3%; Insufficiency 58.1%	24.41 ± 7.80	29.53 ± 9.38	0.007
Wilson et al.[19]	< 20 33%; < 30 72.5%	< 20 34.9%; < 30 76.4%	24.2 ± 1.5	23.6 ± 0.9	0.37

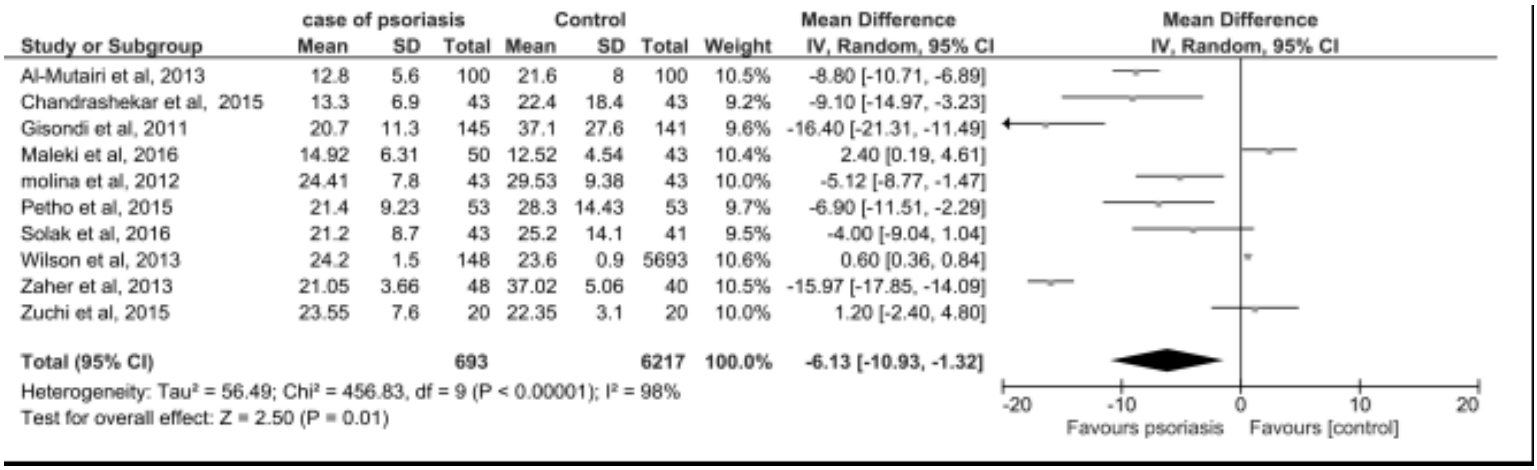
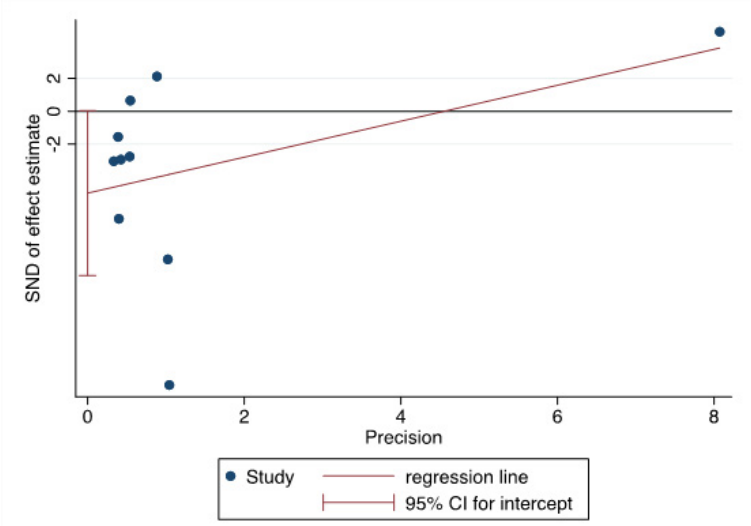


Figure 2. Pooled mean differences in serum 25-hydroxyvitamin D level between patients with psoriasis and control participants.



Number of studies = 10 Root MSE = 5.869

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	1.093919	.8247739	1.33	0.221	-.8080131	2.995851
bias	-4.980296	2.170842	-2.29	0.051	-9.986267	.0256751

Test of H0: no small-study effects P = 0.051

Figure 3. Egger's test results revealing no publication bias.

Regarding a positive relation between hypovitaminosis D and psoriasis, our study had several limitations. First, though all data from the international literature were included, the largest study was conducted by Wilson et al.[19] retrieving information from the National Health and Nutrition Examination Survey (NHANES). Therefore, all information was extracted from people who reside in the U.S. at only one point in time as is the nature of a cross-sectional study. Also, the data were collected through surveys on the severity of psoriasis without knowing the duration of disease, psoriasis type, and the majority of the patients reported having mild disease. Consequently, the study may have response bias and voluntary response bias. Even though the conclusion of this study favors the control group as shown in the forest plot (Figure 2) and serum vitamin D level (Table 4), there was no statistically significant difference which can be explained by a very small number of psoriasis patients (148 individuals) compared with the control group (5,693 individuals). Since this study[19] was discrepant and unclear regarding the association between psoriasis and vitamin D deficiency, our meta-analysis attempted to include all the available studies to analyze the result. Furthermore, the limitation of multiple unknown confounding variables inherent in a meta-analysis on studies involving different designs, differing follow-up periods, and differing patient demographic populations with diverse epidemiologic and clinical characteristics also should be determined.

CONCLUSION

In summary, this systematic review and meta-analysis indicated that there is a significant relationship between low 25(OH) D levels and psoriasis. However, it is unclear whether low vitamin D level is a pathophysiologic cause of psoriasis. The etiology of psoriasis remains unclear and is likely multifactorial.[15] Low vitamin D levels might be one of the causes of psoriasis. Based on our findings, it would be important to measure serum 25(OH) D levels in psoriatic patients not only to provide supplementation but also to prevent other complications associated with vitamin D deficiency.

Further research should investigate whether there is a causal relationship between vitamin D deficiency and psoriasis and whether therapeutic vitamin D supplementation in patients with psoriasis reduces the disease burden.

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