Original article

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Association between circulating 25-hydroxyvitamin D levels and psoriasis, and correlation with disease severity: a meta-analysis

Y. H. Lee[1] and G. G. Song[1]

[1]*Division of Rheumatology, Department of Internal Medicine, Korea University College of Medicine, Seoul, Korea*

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Summary

Background. Psoriasis is a chronic, autoimmune, inflammatory skin disorder. 25-hydroxy vitamin D [25(OH)D] deficiency may contribute to the pathogenesis of psoriasis through reduction in antiproliferative, anti-inflammatory and antiangiogenic activities.

Aim. To evaluate the relationship between circulating 25(OH)D levels and psoriasis, and to determine the correlation between serum/plasma 25(OH)D levels and psoriasis severity.

Methods. We performed a meta-analysis to compare serum/plasma 25(OH)D levels between patients with psoriasis and healthy controls (HCs), and to determine the correlation coefficients between circulating 25(OH)D levels and psoriasis severity as assessed by Psoriasis Area and Severity Index (PASI).

Results. Ten articles with a total of 571 patients with psoriasis and 496 HCs were included. The 25(OH)D level was significantly lower in the psoriasis group than in the HC group. Subgroup analysis by sample size revealed a significantly lower level of 25(OH)D in the psoriasis group for large ($N > 80$) but not for small ($N < 80$) sample sizes. Stratification by adjustment for age and/or sex or sample type revealed a significantly lower 25(OH)D level in the psoriasis group after adjustment for serum but not after nonadjustment for plasma. Meta-analysis of the correlation coefficients revealed a small but statistically significant positive correlation between circulating 25(OH)D levels and PASI.

Conclusions. This meta-analysis demonstrated that circulating 25(OH)D levels are lower in patients with psoriasis, and that a small but statistically significant negative correlation exists between 25(OH)D levels and psoriasis severity.

Introduction

Psoriasis is a chronic, autoimmune, inflammatory skin disorder characterized by keratinocyte hyperproliferation and increased blood flow induced by the stimulation of tissue-resident immune cells with markedly altered cutaneous cytokine profiles.[1] Psoriasis is considered to be a T-helper (Th)1/Th17/Th22 immunomediated inflammatory disease; it affects approximately 2% of the population and markedly influences quality of life.[2] Although its aetiology is not yet fully understood, environmental and immunological factors are thought to be associated with the pathogenesis of psoriasis.

The compound 25-hydroxy vitamin D [25(OH)D] exerts immunomodulatory actions by enhancing the innate immune system and modulating the adaptive immune system. It alters the expression of genes that affect cellular functions, such as proliferation, differentiation, apoptosis and angiogenesis.[3] It also ameliorates T-cell receptor-induced T-cell proliferation and promotes the generation of regulatory T cells, and it

Correspondence: Dr Young Ho Lee, Division of Rheumatology, Department of Internal Medicine, Korea University Anam Hospital, Korea University College of Medicine, 73, Inchon-ro, Seongbuk-gu, Seoul, 02841, Korea
E-mail: lyhcgh@korea.ac.kr

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promotes the differentiation of monocytes to macrophages and regulates macrophage response, preventing macrophages from releasing inflammatory cytokines.

25(OH)D deficiency may contribute to the pathogenesis of psoriasis through the reduction in antiproliferative, anti-inflammatory and anti-angiogenic activities.[4] However, studies that have compared circulating 25(OH)D levels between patients with psoriasis and healthy controls (HCs) and determined the relationship between 25(OH)D levels and psoriasis severity have reported inconsistent results.[5–16]

To overcome the limitations of individual studies and resolve inconsistencies, we performed a meta-analysis, comparing the serum/plasma 25(OH)D levels between patients with psoriasis and HCs, and evaluated the correlation of these levels with disease severity.

Methods

Identification of eligible studies and data extraction

The MEDLINE, EMBASE, and Cochrane databases were searched to identify all available research articles (up to December 2016). The following keywords and subject terms were used in the search: 'vitamin D', '25(OH)D', 'level OR serum OR plasma OR circulating' and 'psoriasis'. All references cited in the retrieved papers were also reviewed to identify additional studies that were not included in the aforementioned electronic databases.

Studies were considered eligible if they met one or more of the following criteria: (i) they were case–control, cohort or cross-sectional studies; (ii) they provided data on 25(OH)D levels in case and control groups; and/or (iii) they provided data on the relationship between psoriasis severity as assessed by the Psoriasis Area and Severity Index (PASI). Studies were excluded if they (i) contained overlapping or insufficient data or (ii) were reviews or case reports.

The following information was extracted from each study: primary author, year of publication, country, ethnicity, number of participants, assay method, mean and SD of the 25(OH)D level, and correlation coefficients between the 25(OH)D level and psoriasis disease severity. In cases where the data were provided as medians, interquartile ranges or ranges, we computed the mean and SD by using previously described formulae. The biologically active form of vitamin D is 1,25-dihydroxy vitamin D [1,25$(OH)_2$D]. However, serum levels of 1,25$(OH)_2$D bear little or no relationship to vitamin D stores. The major circulating form of vitamin D is 25(OH)D, and assessing this is the best test to determine vitamin D status. Thus we evaluated 25(OH)D levels in this meta-analysis. We scored the quality of each included study based on the Newcastle–Ottawa Scale.[17]

Evaluation of statistical associations

To ensure data continuity, results were presented as standardized mean differences (SMDs), correlation coefficients or 95% CIs. SMDs were calculated by dividing the mean difference between two groups by the pooled SD, and were used when different scales were integrated to measure the same concept. We also assessed within- and between-study variations and heterogeneities by using Cochran Q statistic.[18] The heterogeneity test was used to assess the null hypothesis that all studies were evaluating the same effect. When the significant Q statistic ($P < 0.10$) indicated heterogeneity across studies, the random effects model was used for the meta-analysis.[19] Otherwise, the fixed effects model was used, which assumed that all studies estimated the same under-lying effect, and we only considered within-study variation.[18] We quantified the effect of heterogeneity using the formula[20]

$$I^2 = 100\% \times (Q - df)/Q,$$

where I^2 measures the degree of inconsistency between studies and determines whether the percentage total variation across studies is due to heterogeneity rather than chance.

Statistical manipulations were performed using the Comprehensive Meta-Analysis software (Biostat Inc., Englewood, NJ, USA).

Sensitivity test and evaluation of heterogeneity and publication bias

To examine the potential sources of heterogeneity observed in the meta-analysis, a meta-regression analysis was performed using the following variables: study region, age and/or sex adjustment, data type, sample type, publication year and sample size. A sensitivity test was performed to assess the influence of each individual study on the pooled SMR by omitting each study individually. We evaluated publication bias by applying funnel plots and Egger linear regression test,[21] which measured funnel-plot asymmetry by using a natural logarithm scale of SMRs. When there

was indication of asymmetry, we used the 'trim and fill' method to adjust summary estimates for the observed bias.[22] This method excludes small studies until funnel plot symmetry is achieved, recalculating the centre of the funnel before the removed studies are replaced with their missing mirror-image counterparts; a revised summary estimate is then calculated by using all original studies, together with the hypothetical 'filled' studies.

Results

Studies included in the meta-analysis

We identified 302 relevant studies by electronic and manual search methods, of which 19 were selected for full-text review based on the title and abstract; 7 of these were later excluded because they had no data on 25(OH)D levels or contained duplicate data. Thus, 12 articles, comprising 571 patients with psoriasis and 496 HCs, met the inclusion criteria[5–16] (Table 1). The patients had not been exposed to any drug previously in the studies, there were no patient populations with psoriatic arthritis except in one study,[6] and none of the patients had taken oral corticosteroids that might induce osteopenia/osteoporosis. Except for one,[15] studies did not mention which type of psoriasis (chronic plaque, guttate, palmoplantar, scalp) was considered. The quality assessment score of each study ranged from 6 to 9. Selected characteristics of these studies relating to the association between 25(OH)D levels and psoriasis are summarized in Table 1.

Meta-analysis comparing circulating 25(OH)D levels in patients with psoriasis and HCss

The 25(OH)D level was significantly lower in the psoriasis group than in the HC group (SMD = −0.64, 95% CI = −1.22 to −0.05, $P = 0.03$) (Table 2, Fig. 1). Stratification by study region revealed a significantly decreased 25(OH)D level in the psoriasis group in Western countries (SMD = −0.92, 95% CI = −1.60 to −0.22, $P = 0.01$) but not in the Middle East, South America or Asia (Table 2). Stratification by adjustment for age and/or sex revealed a trend towards lower 25(OH)D level in the psoriasis group after adjustment (Table 2). Subgroup analysis by sample size revealed a significantly lower 25(OH)D level in the psoriasis group when the sample numbers were large ($N > 80$) (SMD = −0.84, 95% CI = −1.58 to −0.09, $P = 0.03$) but not when they were small ($N < 80$) (SMD = −0.07, 95% CI = −0.45 to −0.31, $P = 0.72$) (Table 2, Fig. 2). The computed mean and SD data were classified as calculated data, while the mean and SD data presented in the studies were regarded as original data. Stratification by data type revealed a significantly lower 25(OH)D level in the psoriasis group when the original data were used, but not when the calculated data were used. Stratification by sample type revealed a significantly lower 25(OH)D level in the psoriasis group for serum but not for plasma (Table 2).

Table 1 Characteristics of the individual studies included in the meta-analysis.

			Number					Results		
Authors	Country	Region	Patients	HCs	Data	Matched	Study quality	SMD*	Magnitude†	*P*
Bergler, 2016[5]	Poland	West	40	40	Original	Age, sex	9	−3.51	Large	< 0.05
Maleki, 2016[6]	Iran	Middle East	50	43	Original	Age, sex	9	0.43	Small	0.04
Cubillos, 2016[7]	France	West	8	14	Calculated	Age	7	−0.10	No effect	0.83
Zuchi, 2015[8]	Brazil	South America	20	20	Calculated	Age, sex	6	0.28	Small	0.38
Chandrasherkar, 2015[16]	India	Asia	43	43	Original	Age, sex	9	−0.61	Moderate	< 0.05
Orgaz, 2014[9]	Spain	West	44	44	Original	Age, sex	9	−0.91	Large	< 0.05
Vural, 2014[10]	Turkey	West	57	41	Original	Age	7	−0.06	- No effect	0.79
Al-Mutairi, 2014[15]	Kuwait	Middle East	93	50	Original	None	7	−1.70	Large	< 0.05
Atwa, 2013[11]	Saudi Arabia	Middle East	43	40	Original	Age	7	−1.56	Large	< 0.05
Gisondi, 2012[12]	Italy	West	145	141	Original	Age, sex	7	−0.78	Moderate	< 0.05
Guilhou, 1990[13]	France	West	20	15	Original	None	7	−0.19	No effect	0.58
Mawer, 1984[14]	UK	West	8	5	Calculated	Age	8	−0.88	Large	0.14

HC, healthy control; SMD, standardized mean difference. *'+ or −' means, respectively, a high or low 25(OH)D level in psoriasis compared with HCs, †magnitude of Cohen *d* effect size: 0.2–0.5 = small effect; 0.5–0.8 = medium effect; ≥ 0.8 = large effect.

Table 2 Meta-analysis of the association between 25(OH)D levels and psoriasis.

			Test of association			Test of heterogeneity		
Groups	Population	Studies, *n*	SMD*	95% CI	*P*	Model†	*P*	I^2
All	Overall	12	−0.64	−1.22 to 0.05	0.03	Random	0.00	94.5
Study region	West	7	−0.92	−1.60 to 0.22	0.01	Random	0.00	92.1
	Middle East	3	−0.94	−2.34 to 0.45	0.19	Random	0.00	96.8
	Asia	1	−0.61	−1.04 to 0.18	0.01	NA	NA	NA
	South America	1	0.28	−0.34 to 0.90	0.38	NA	NA	NA
Matched for age, sex	Yes	10	−0.57	−1.21 to 0.07	0.08	Random	0.00	94.5
	No	2	−0.97	−2.45 to 0.51	0.20	Random	0.00	93.6
Sample size	$N > 80$	8	−0.84	−1.58 to 0.09	0.03	Random	0.00	96.2
	$N < 80$	4	−0.07	−0.45 to 0.31	0.72	Fixed	0.36	6.31
Data type	Original	9	−0.77	−1.45 to 0.06	0.03	Random	0.00	95.8
	Calculated	3	−0.01	−0.48 to 0.45	0.96	Random	0.22	33.6
Sample	Serum	11	−0.68	−1.30 to 0.06	0.03	Random	0.00	94.9
	Plasma	1	−0.19	−0.86 to 0.48	0.58	NA	NA	NA

NA, not available; SMD, standardized mean difference. *Magnitude of Cohen *d* effect size: 0.2–0.5 = small effect; 0.5–0.8 = medium effect; ≥ 0.8 = large effect; †fixed or random effects model.

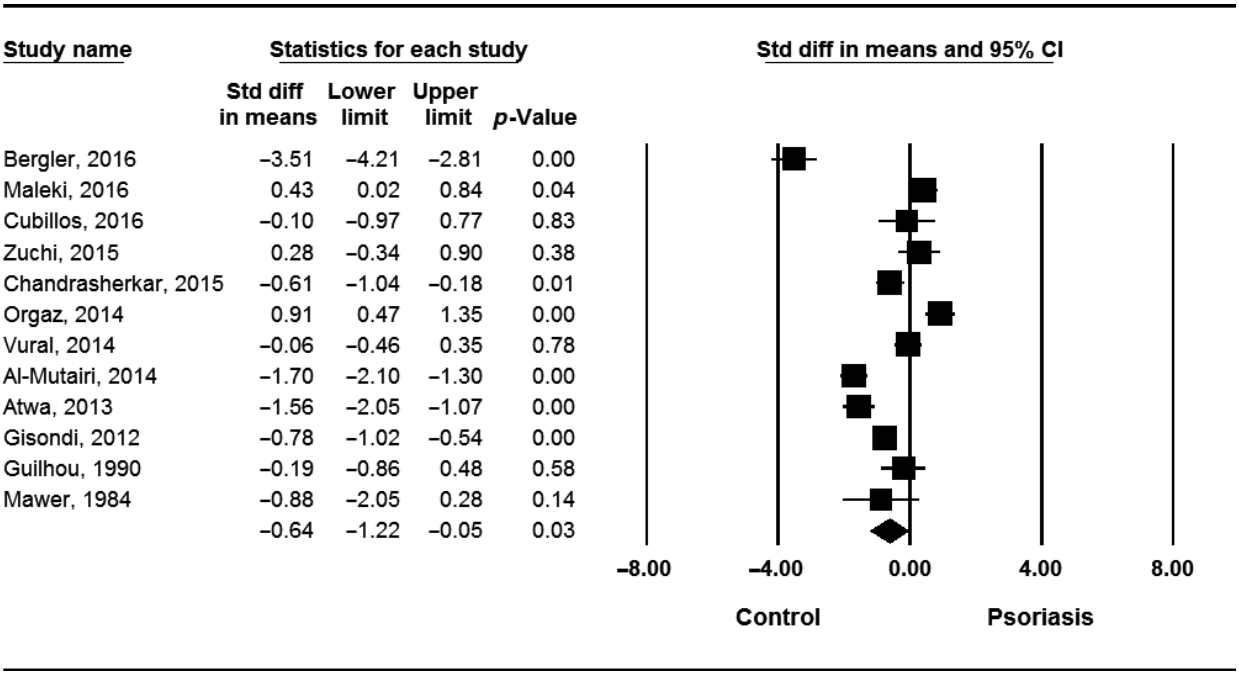

Figure 1 Meta-analysis of the relationship between 25(OH)D levels and psoriasis.

Meta-analysis of the correlation coefficient between circulating 25(OH)D levels and psoriasis severity

The meta-analysis revealed that circulating 25(OH)D levels were negatively associated with psoriasis severity as assessed by PASI (Table 3). Meta-analysis of the correlation coefficients showed a small but statistically significant positive correlation between circulating 25(OH)D levels and PASI (SMD = −0.39, 95% CI = −0.76 to −0.01, $P = 0.04$) (Table 3, Fig. 2). Stratification by study region revealed a statistically significant negative correlation between circulating 25(OH)D levels and PASI in Western countries (SMD = −0.64, 95% CI = −1.12 to −0.71, $P < 0.05$) but not in the Middle East (Table 3).

Sensitivity test and the evaluation of heterogeneity and publication bias

Between-study heterogeneity was identified during the meta-analysis of 25(OH)D status in patients with

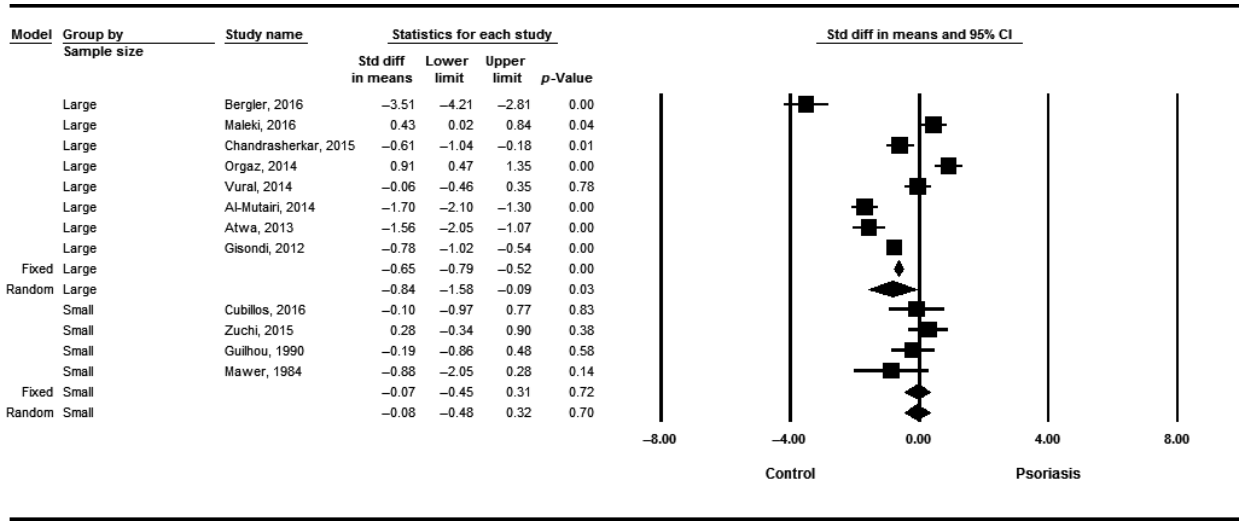

Figure 2 Meta-analysis of the relationship between 25(OH)D levels and psoriasis by sample size.

Table 3 Meta-analysis of the correlation coefficients between 25(OH)D levels and psoriasis severity.

			Test of association			Test of heterogeneity		
Groups	Population	Studies, *n*	CC	95% CI	*P*	Model	*P*	I^2
All	Overall	3	−0.39	−0.76 to 0.01	0.04	Fixed*	0.11	54.6
Study region	West	2	−0.64	−1.12 to 0.17	0.01	Fixed	0.26	20.9
	Middle East	1	0.06	−0.56 to 0.68	0.85	NA	NA	NA

CC, correlation coefficient; NA, not available. *Fixed effects model.

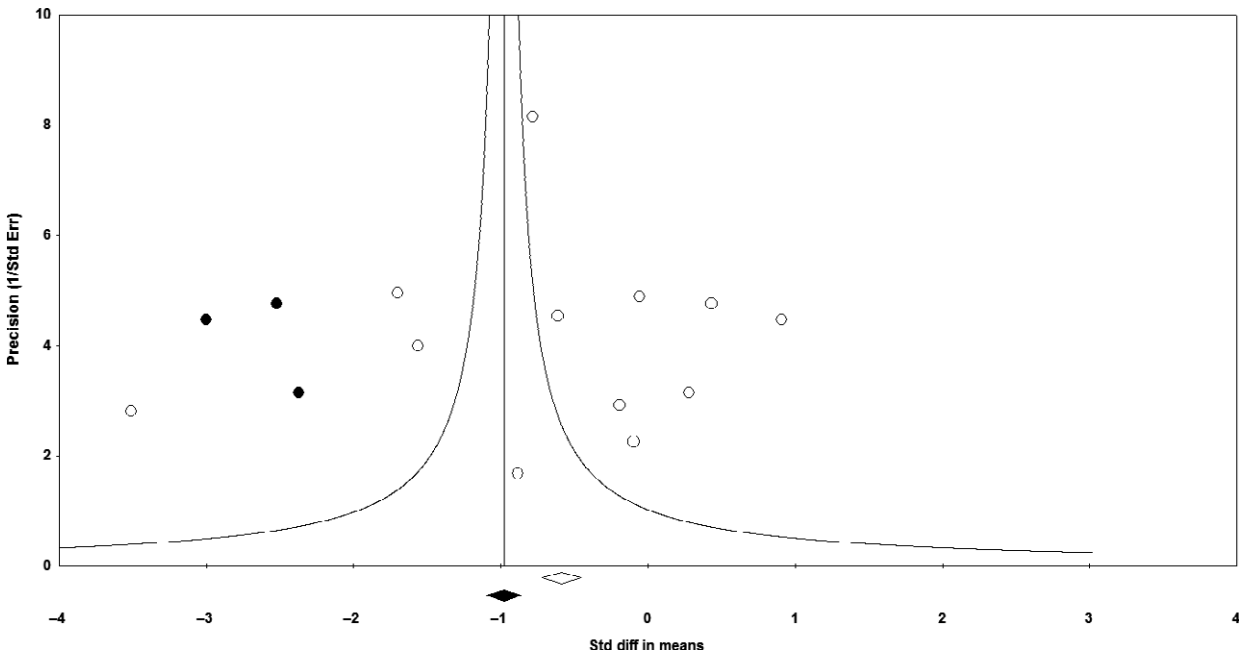

Figure 3 Funnel plot of studies that examined the association between 25(OH)D levels and psoriasis (Egger regression test, $P = 0.91$). The filled circles represent studies that had publication bias. The diamonds at the bottom of the figure indicate the summary effect estimates before (open symbols) and after (filled symbols) adjustment for publication bias.

psoriasis (Table 2). Meta-regression analysis showed that study region ($P = 0.01$), sample size ($P < 0.05$) and data type ($P < 0.05$), but not adjustment ($P = 0.19$), publication year ($P = 0.83$) or sample type ($P = 0.19$), had a significant impact on heterogeneity in the meta-analysis of 25(OH)D levels. Sensitivity analysis showed that only five individual studies significantly affected the pooled OR. Egger regression test showed no evidence of publication bias ($P = 0.91$), but the funnel plot revealed asymmetry, therefore the 'trim and fill' method was used to adjust for publication bias. However, SMD values that were significant before this adjustment remained significant even after this adjustment (SMD = −1.05, 95% CI = −1.68 to −0.41) (Fig. 3).

Discussion

This meta-analysis of 12 articles involving 571 patients with psoriasis and 496 HCs showed that circulating 25(OH)D levels were significantly lower among patients with psoriasis than among HCs. Our meta-analysis also revealed that low 25(OH)D levels negatively correlated with psoriasis severity. The decreased 25(OH)D levels in patients with psoriasis and the negative correlation between 25(OH)D levels and psoriasis severity indicate that 25(OH)D may influence the pathogenesis of psoriasis.

Psoriasis is considered to be a Th1/Th17/Th22-driven autoimmune inflammatory disease that involves the innate and acquired immune systems.[2] A low 25(OH)D status is reportedly associated with an increased risk of developing Th1-mediated autoimmune diseases, including rheumatoid arthritis, Type 1 diabetes, inflammatory bowel disease and multiple sclerosis. Low 25(OH)D levels can either be the cause or consequence of psoriasis. Low 25(OH)D levels in psoriasis may be attributable to lack of sun exposure, to sun avoidance, to frequent use of drugs that interfere with 25(OH)D metabolism (such as gluco-corticoids and immunosuppressive agents) or to low 25(OH)D intake.

Limitations

It is important to note the methodological limitations of the studies involved in this meta-analysis. First, most of the studies had a small sample size, and only a small number of studies evaluated the correlation coefficients between 25(OH)D levels and psoriasis severity. Thus, the meta-analysis may be under-powered. Second, the studies included in the meta-analysis were heterogeneous in terms of patient demographic characteristics and clinical features. Heterogeneity and confounding factors such as disease activity and the drugs used may have affected our results, which in turn may have been influenced by the limited information provided on the clinical status and disease activity. Third, the cross-sectional or observational study design does not allow identification of a causal relationship between low vitamin D and psoriasis. Fourth, several environmental conditions may contribute to low serum levels of vitamin D in patients with psoriasis, including poor dietary intake of vitamin D or practising sun avoidance. Inability to control the environment was another limitation of this study.

Nevertheless, this meta-analysis also has its strengths. To our knowledge, our meta-analysis is the first to provide combined evidence of 25(OH)D status in patients with psoriasis. Our data on the relationship between 25(OH)D levels and psoriasis achieved greater accuracy because of the increased statistical power and resolution enabled by pooling the results of the independent analyses.

Conclusion

Our meta-analysis demonstrated that circulating 25(OH)D levels are significantly lower in patients with psoriasis than in HCs, and that a small but statistically significant negative correlation exists between 25(OH)D levels and psoriasis severity. Thus, our meta-analysis suggests that 25(OH)D plays an important role in the pathogenesis of psoriasis. Further studies are necessary to elucidate whether decreased 25(OH)D levels contribute directly to the pathogenesis of psoriasis.

What's already known about this topic?

- Published data suggest that 25(OH)D deficiency may contribute to the pathogenesis of psoriasis, but the results are controversial.

What does this study add?

- We performed a meta-analysis of the published studies to investigate the relationship between psoriasis and 25(OH)D.
- We found a significant association between psoriasis and low circulating 25(OH)D levels.
- We found that a significant negative correlation exists between 25(OH)D levels and psoriasis severity.

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