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 (I²) 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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Low vitamin D levels have been associated with several autoimmune diseases, including rheumatoid arthritis, Crohn’s disease, systemic lupus erythematosus, and multiple sclerosis. In addition, there have been reports on the association between hypovitaminosis D and autoimmune skin conditions such as psoriasis, bullous pemphigus, alopecia areata, and vitiligo. A potential link between vitamin D deficiency and psoriasis has also been reported. 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. 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.

RESULTS

Systematic Review of the Literature. Ten studies were identified for inclusion in this review. The initial search yielded 107 articles. Eighty-five 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 level (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 was 96%, p = 0.0001.

DISCUSSION

Figure 1. Flow diagram of search results and screening process.
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.15,32 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.32 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/control 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 monocytes/macrophages.15,40-41 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.6

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.42 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.43 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                | Representativeness of the sample | Justified sample size | Ascertainment of exposure | Comparable non-residents rate between two groups | Study controls for the most important factor | Study controls for any additional factor | Ascertainment of exposure (max of 2 stars) | Independent blind assessment (two stars) | Self-report | Total |
|----------------------|---------------------------------|-----------------------|---------------------------|-----------------------------------------------|---------------------------------------------|------------------------------------------|-----------------------------------------|-----------------------------------------|------------|-------|
| Wilson et al.26       | Truly representative            |                      |                           |                                               |                                             |                                          |                                         |                                         |            | 8     |

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

| Study                | 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 | Total |
|----------------------|--------------------------|---------------------------------|-----------------------|------------------------|---------------------------------------------|------------------------------------------|-----------------------------------------|-----------------------------------------------|------------------|-------|
| Solak et al.28        |                         |                                  |                       |                        |                                             |                                          |                                         |                                                |                  | 7     |
| Maleki et al.21       |                         |                                  |                       |                        |                                             |                                          |                                         |                                                |                  | 7     |
| Petho et al.22        |                         |                                  |                       |                        |                                             |                                          |                                         |                                                |                  | 9     |
| Zuchi et al.25        |                         |                                  |                       |                        |                                             |                                          |                                         |                                                |                  | 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.26 |                         |                                  |                       |                        |                                             |                                          |                                         |                                                |                  | 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) |
|---------------|--------------|----------|----------------|-------------|-----------------------------|-------------------------------------|-----------------------------------------------|------------------------|
| Solak et al.  | Case-control | Turkey   | 43 41          | 36.72 ± 8.00 | 0 - 5 years: 8 (18.6%)      | Psoriasis without arthritis          | Matched with age                               | NA                     |
| Maleki et al. | Case-control | Iran     | 50 43          | 43.80 ± 13.68| 10.37 ± 9.87                | Chronic plaque psoriasis            | Age- and sex-matched controls from northeastern Iran | Deficiency (< 20 ng/mL) |
| Petho et al.  | 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.  | Case-control | Brazil   | 20 20          | 46.40 ± 14.90| 3.5 ± 9                     | 25% palmoplantar psoriasis; 75% psoriasis vulgaris | Healthy individuals                            | NA                     |
| Chandrashekar et al. | 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. | Case-control | Egypt   | 48 40          | 43.88 ± 15.17| NA                          | Histopathologically proven psoriasis | Age- sex- skin prototype and socioeconomic- match individuals | NA                     |
| Al-Mutairi et al. | 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. | 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. | Case-control | Spain   | 43 43          | 44.33 ± 8.71 | 1991                        | Fitzpatrick skin phototype II, III, or IV | Randomly selected age- and sex-matched controls with non-photosensitive dermatologic diseases other than psoriasis | Deficiency (< 10 ng/mL) |
| Wilson et al.  | Cross-sectional | USA  | 148 5,693     | 20 - 59      | NA                          | Participants without psoriasis      | NA                                            | Deficiency (< 20 and < 30 ng/mL) |

Table 4. The outcomes of the included studies.

| Study         | Vitamin D Deficiency | Control | 25(OH)D (ng/mL) | P value |
|---------------|-----------------------|---------|-----------------|---------|
| Solak et al.  | Deficiency NA; Insufficiency NA | Deficiency NA; Insufficiency NA | 21.2 ± 8.7 | 25.2 ± 14.1 | 0.12 |
| Maleki et al. | Deficiency 84%; Insufficiency NA | Deficiency 93%; Insufficiency NA | 14.92 ± 6.31 | 12.52 ± 4.54 | 0.21 |
| Petho et al.  | Hypovitaminosis D 81% | Hypovitaminosis D 57% | 21.4 ± 9.23 | 28.3 ± 14.43 | 0.0001 |
| Zuchi et al.  | Deficiency 25%; Insufficiency 65% | Deficiency 20%; Insufficiency 60% | 23.55 ± 7.60 | 22.35 ± 3.10 | 0.7536 |
| Chandrashekar et al. | Deficiency NA; Insufficiency NA | Deficiency NA; Insufficiency NA | 13.3 ± 6.9 | 22.4 ± 18.4 | 0.004 |
| El-Moaty Zaher et al. | Deficiency NA; Insufficiency NA | Deficiency NA; Insufficiency NA | 21.05 ± 3.66 | 37.02 ± 5.06 | < 0.005 |
| Al-Mutairi et al. | Deficiency 12%; Insufficiency NA | Deficiency 9%; Insufficiency NA | 12.8 ± 5.6 | 21.6 ± 8 | < 0.005 |
| Gisondi et al. | Deficiency 57.8% | Deficiency 297% | 207 ± 11.3 | 37.1 ± 27.6 | 0.0001 |
| Orgaz-Molina et al. | Deficiency 25.6%; Insufficiency 79.1% | Deficiency 9.3%; Insufficiency 58.1% | 24.41 ± 7.89 | 29.53 ± 9.38 | 0.007 |
| Wilson et al.  | < 20.33%; < 30.72.5% | < 20.34.9%; < 30.764% | 24.2 ± 1.5 | 23.6 ± 0.9 | 0.37 |
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Figure 2. Pooled mean differences in serum 25-hydroxyvitamin D level between patients with psoriasis and control participants.

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.\textsuperscript{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\textsuperscript{18} 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.\textsuperscript{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.
