

To what Extent does Vitamin D and its Serum Levels Influence the Severity of Hidradenitis Suppurativa: A Literature Review

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Vitamin D plays a role in inflammatory skin conditions and can improve them. Hidradenitis suppurativa (HS) is an autoinflammatory chronic skin disease in which most patients exhibit a hypovitaminosis D. However, it is uncertain whether vitamin D supplementation could relieve the severity of HS. A systematic literature search of PubMed and Web of Science was conducted on 4 September 2023. Studies that investigated vitamin D and its potential implications for the severity of HS were included. In contrast, studies that focused on the prevalence of vitamin D deficiency were excluded, as well as studies on syndromic HS. Seven studies with a total of 575 patients were included in the qualitative synthesis, of which 3 utilized a cross-sectional design, 2 were pilot studies, 1 a controlled cohort study, and 1 a prospective case-control study. In all included studies, HS patients were vitamin D deficient. There was evidence indicating that serum vitamin D levels negatively correlated with the severity of the disease, and at least suggestive evidence that vitamin D supplementation could have a positive impact on the course of HS. To better understand these correlations, conducting a randomized controlled trial study on vitamin D and its effects on HS severity is imperative.

Key words: hidradenitis suppurativa; acne inversa; diet therapy; vitamin D.

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Hidradenitis suppurativa (HS), also known as acne inversa or Verneuil's disease, is a multifactorial, polygenic, autoinflammatory chronic skin condition characterized by the presence of recurring or persistent painful, itchy, or purulent lesions in areas of the body that have apocrine sweat glands (1). Based on the definition, nodules, abscesses, and sinus tracts evolve primarily in areas with increased numbers of sebaceous glands such as the axilla, inguinal, gluteal, and perianal regions (2, 3). The primary focus of the pathogenesis is an autoinflammation of the pilosebaceous follicle (4), while bacterial colonization may exacerbate HS, but plays a minor role in the aetiology (5). Several studies suggest immune

SIGNIFICANCE

The deficiency of the steroid hormone vitamin D has been empirically demonstrated to be implicated in numerous dermatological diseases, and there are suggestions its deficiency might also play a role in the severity of the autoinflammatory skin disease hidradenitis suppurativa. In this review of 7 studies including 575 patients with hidradenitis suppurativa, all subjects were vitamin D deficient, and some studies indicated an inverse correlation between vitamin D status and disease severity. This review emphasises the relevance of vitamin D status in hidradenitis suppurativa and may help clinicians and patients with treatment decisions.

cells and interleukins like interleukin 17 (IL-17) as key players in the pathogenesis of HS (6–8), and a recently published study identified hypoxia-inducible factor-1 α (HIF-1 α) as a key facilitator in Th17 cell differentiation and keratinocyte hyperproliferation (9). Nevertheless, clarification of the pathogenesis of HS remains incompletely resolved and needs further investigation.

The steroid hormone vitamin D is suggested to regulate skin homeostasis by affecting the epidermis within its proliferation and differentiation and adnexal structures, in particular the hair follicle (13). 25-hydroxyvitamin D (25-OHD, calcidiol) is the marker of vitamin D status in patients and its levels should be at least 20 ng/mL (50 nmol/L) (14). To facilitate the comprehension of this work, we used vitamin D as a synonym for all variants of it. Because of its influence on the skin's homeostasis, it is not surprising that vitamin D status has been proven to be connected to a variety of dermatological conditions, such as psoriasis, atopic dermatitis, systemic lupus erythematosus (SLE), alopecia areata, and systemic sclerosis (13). Malfunction of vitamin D metabolism and vitamin D deficiency may also play a role in the pathogenesis of HS (15, 16). A few studies have shown that patients with HS tend to have low vitamin D levels; in most cases, they even have a significant deficiency (17–20). However, the origin of the deficiency remains speculative, as there are, on the one side, many factors that could influence the vitamin D level negatively, but, on the other side, vitamin D deficiency could be a crucial component in the pathogenesis of HS. Therefore, this review examines the existing data regarding the influence of vitamin D on HS.

METHODS

We carried out a literature search using PubMed and Web of Science following international standards with 2 independent raters. There were no limitations on the year of publication, the language, or the availability of full texts. Articles published up to September 2023 addressing how vitamin D and its serum levels can impact HS were identified. The following terms were implemented for the search: hidradenitis suppurativa OR Verneuil's disease OR acne inversa AND vitamin D OR hidradenitis suppurativa/diet therapy Medical Subject Headings (MeSH) OR diet therapy. By using the *all fields* section for our search via the databases, we were able to cover a large number of synonyms like diet, ergocalciferol, and in PubMed different MeSH Terms for the keywords. Cholecalciferol or 25-OHD as synonyms for vitamin D were not included in the search term because although it resulted in more hits, none of them provided any additional value to this specific topic. Pre-defined inclusion and exclusion criteria were applied to perform the screening of titles and abstracts. Studies that investigated vitamin D and its influence on the severity of HS were included. Reviews that included the same studies which our search term also yielded, studies that focused only on vitamin D levels in HS rather than its influence on the severity of HS, studies that investigated syndromic HS, and studies that focused on diet in HS generally without elaborating on vitamin D in detail were excluded. Ineligible articles were eliminated. After this first selection, the screening of eligible full-text articles and subsequently the selection of the finally included articles followed (**Fig. 1**). The selection process was carried out by 2 individuals and consecutively followed by a second rating. However, if a study could not be definitively in-

cluded or excluded, the authoring team, comprising 3 individuals, engaged in discussion and collectively decided on the procedure.

RESULTS

Study characteristics

Seven publications (published 2015–2022) were included for qualitative synthesis (**Table 1**) (20–26). Of these 7 studies, 3 were conducted in Italy (23, 24), 2 in Spain (21, 22), 1 in Jordan (20), and 1 in France (26). The sample sizes ranged from 22 patients (25) to 250 patients (23). Moreover, 3 studies used a cross-sectional design (20, 22, 23), 2 carried out a pilot study (25,26), 1 utilized a controlled cohort study (24), and 1 performed a prospective case-control study (21).

Seetan et al. (20) carried out a comparative cross-sectional study to evaluate vitamin D levels in HS patients in Jordan. They took blood samples from patients between April 2018 and March 2020 and analysed vitamin D levels by electrochemiluminescence binding assay. Sociodemographic characteristics like age, gender, and smoking status were raised by structured questionnaires; 110 patients with HS and a mean age of 43.1 ± 12.9 years

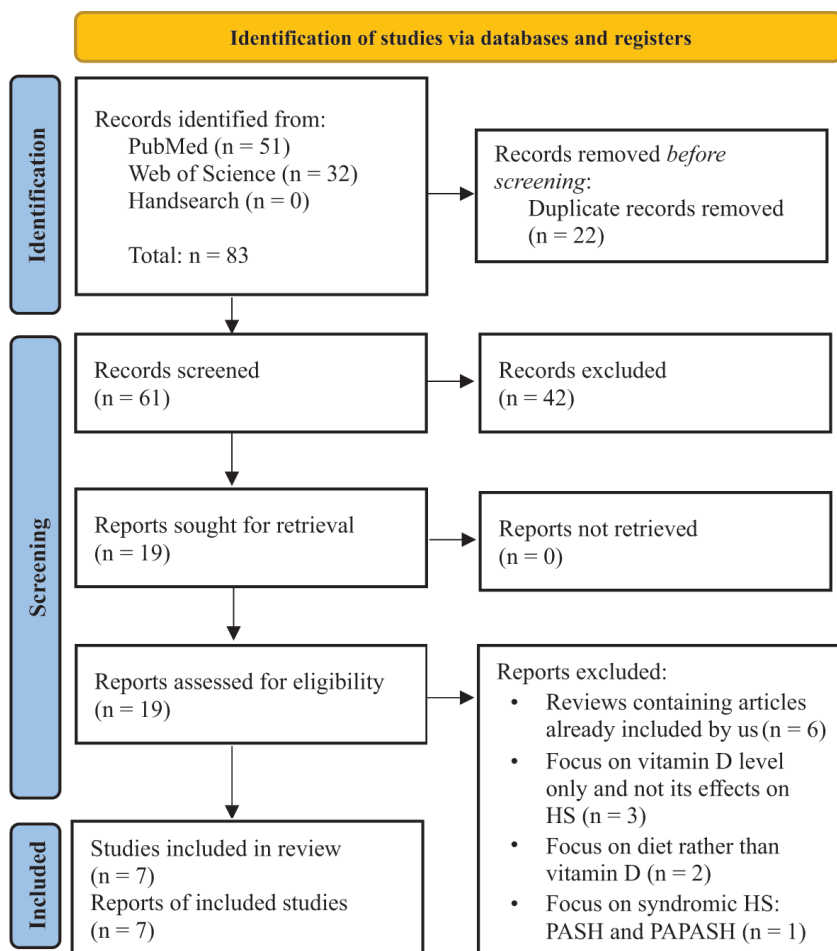


Fig. 1. PRISMA Flow Chart (39). Search date: 04.09.2023. HS: hidradenitis suppurativa; PASH: pyoderma gangrenosum, acne, and suppurative hidradenitis; PAPASH: pyogenic arthritis, acne, pyoderma gangrenosum, and suppurative hidradenitis.

Table I. Characteristics of 7 publications included

Authors (ref)	Population; country	Study design	Aim of the study	Results
Seetan K, et al. (20)	110 patients with HS (mean age 43.1±12.9 years) and 110 controls; Jordan	Comparative cross-sectional study	To analyse vitamin D levels in patients with hidradenitis suppurativa (HS)	Mean vitamin D level in patients was 8.4 ng/mL, and patients had significantly lower vitamin D levels than controls ($p < 0.001$). No significant correlation between vitamin D levels and disease severity in patients ($r = 0.08$, $p = 0.406$)
Navarro I, et al. (21)	81 patients (mean age 45.6±12.0 years) with HS and 79 controls (mean age 46.34±14.1 years); Spain	Prospective case-control study	To assess whether HS is associated with disturbances in trabecular bone score, bone mineral density, bone remodelling markers, and calciotropic hormones	High prevalence of vitamin D deficiency in patients with HS and slightly lower serum 25-hydroxyvitamin D (25OHD) levels in patients with severe HS than patients with mild-moderate HS (Hidradenitis Suppurativa-Physician's Global Assessment score [HS-PGA] <3 or >3). Same was found when International Hidradenitis Suppurativa Severity Score System (IHS4) was considered for measuring HS severity
Sánchez-Díaz M, et al. (22)	50 patients with severe HS (mean age 38.0±12.9 years); Spain	Cross-sectional study	To assess cardiovascular risk by means of intima-media thickness, metabolic syndrome, and analyse other potential biomarkers in patients with severe HS	IHS4 inversely correlated with vitamin D levels ($p = 0.04$). Inverse associations were found between vitamin D levels and the number of areas affected, and Hurley stage in univariate analysis. Number of areas affected and vitamin D also showed an inverse correlation in the multivariate analysis
Moltrasio C, et al. (23)	250 patients with HS (mean age 33.59±0.89 years); Italy	Retrospective cross-sectional study	To find possible correlations between 25OHD levels, IHS4 scores and CRP (C-reactive protein) serum levels on diagnosis of patients with HS	Significant inverse correlation between 25OHD levels and disease severity (IHS4) ($r = -0.76$, $p < 0.0001$). Patients with vitamin D deficiency had higher IHS4 scores than patients with vitamin D insufficiency
Fabbrocini G, et al. (24)	40 patients with resistant HS (mean age 27.3±2.6 years) and 40 healthy controls; Italy	Controlled cohort study	To assess a possible correlation between vitamin D hypovitaminosis and clinical severity of HS and to evaluate then effect of vitamin D supplementation on clinical responsiveness to prescribed therapy	27 patients had significant improvement in responsivity to prescribed therapies under vitamin D supplementation. Vitamin D levels were inversely related to SS (Sartorius score)
Ricceri F, et al. (25)	22 patients with HS, no mean age given; Italy	Pilot study	To find a possible association between vitamin D deficiency and specific demographic or clinical characteristics	All patients ($n = 22$) had a vitamin D deficiency whose severity had a mild correlation with disease severity of HS ($r = -0.6$)
Guillet A, et al. (26)	22 patients with HS (mean age 35 years), 14 out of 22 took part in second phase of the study; France	Pilot study	To evaluate a possible connection between HS and vitamin D deficiency and to ascertain if vitamin D supplementation possibly improves inflammatory lesions	All patients ($n = 22$) had vitamin D deficiency (<30 ng/mL). Vitamin D supplementation decreased number of nodules significantly in 14 patients (100%) of the second phase with a median decrease of -75%

HS: hidradenitis suppurativa; 25OHD: 25-hydroxyvitamin D; HS-PGA: Hidradenitis Suppurativa-Physician's Global Assessment; IHS4: International Hidradenitis Suppurativa Severity Score System; CRP: C-reactive protein; SS: Sartorius score.

were recruited at the Department of Dermatology at Jerash Hospital, Jordan. The mean disease duration was 19.4 ± 11 months, and 54.5% ($n = 60$) of the patients were female. Additionally, 110 healthy controls of matched age and gender were included. The requirement for all participants was that they had not taken any vitamin D supplements over the last year before their vitamin D status was assessed. Vitamin D levels were classified into normal (>30 ng/mL), insufficient (20–30 ng/mL), and low (<20 ng/mL). According to this, all HS patients had low vitamin D levels (<20 ng/mL); the mean vitamin D level among patients was 8.4 ng/mL. Seetan et al. (20) did not find a significant correlation between vitamin D levels and disease severity ($r = 0.08$, $p = 0.406$), but there was a significant difference between patients' mean vitamin D levels and controls' mean levels (8.4 ng/mL vs 17.6 ng/mL, $p < 0.001$). The authors did not address how disease severity was measured.

One limitation is the cross-sectional design, which makes it difficult to establish a causal relationship between the results. Furthermore, the study included fewer patients than others, which makes it somewhat more challenging to generalize the results to other individuals with HS. Moreover, the blood samples were taken over a wide range of time, so different potential confounders could influence the vitamin D levels such as the amount of natural UVB rays or dietary habits.

Navarro et al. (21) performed a prospective case-control study to assess whether HS is associated with

disturbances in bone metabolism. For this purpose, they examined, among others, vitamin D levels in patients and a control group. Some 81 patients (mean age 45.6 ± 12.0, 50.6% female, 49.4% male) with HS were recruited from a dermatology outpatient clinic in a tertiary-care hospital in Santander, Spain. Additionally, 79 controls of similar age and sex were enrolled from either the Camargo cohort (27, 28) or they were hospital staff who consented to take part in the study. The severity of HS was estimated with the Hidradenitis Suppurativa-Physician Global Assessment (HS-PGA), Hurley staging, and International Hidradenitis Suppurativa Severity Score System (IHS4). In this study, an HS-PGA category <3 was classified as minimal to mild HS, whereas categories ≥3 were classified as moderate to severe manifestation. A minimal to mild HS was calculated for 28 patients (34.6%), and 53 (65.4%) had severe HS. On average, patients had been diagnosed with HS for 18.0 (9.5–25.5) years. For the blood samples, all participants were asked to fast for at least 8 hours before the sample was taken. Navarro et al. (21) found that patients with HS had significantly lower serum vitamin D levels than the control group (18.9 vs 24.9 ng/mL; $p = 0.001$), even after adjusting for age, sex, body mass index (BMI), fat percentage, diabetes mellitus, estimated glomerular filtration rate (GFR), serum C-reactive protein (CRP) levels, and month of the year ($p = 0.025$). Vitamin D deficiency was defined as serum levels <20 ng/mL. Considering this, 61.7% of HS patients and 35.4% of the controls had a deficiency

($p=0.001$), which means a 1.74 higher rate of vitamin D deficient subjects with HS. Furthermore, serum vitamin D levels were lower, but nonsignificant, in patients with severe HS (HS-PGA ≥ 3) compared with those with mild to moderate HS (HS-PGA < 3) (18.0 vs 20.8 ng/mL; $p=0.29$). Considering the IHS4 for HS severity, a similar nonsignificant observation was found. Patients with mild HS had mean vitamin D levels of 21.1 ng/mL, patients with moderate HS 19.3 ng/mL, and those with severe HS 15.6 ng/mL (mild vs severe HS; $p=0.07$).

The limitation of this study is the lack of information on the time of the year and, respectively, the season and recruitment interval, which might influence vitamin D production by natural ultraviolet B (UVB) exposure and dietary habits. Lastly, the results can lead to an association, but not to causality.

Sanchez-Diaz et al. (22) set up a cross-sectional study to assess intima-media thickness (IMT) in patients suffering from severe HS and to evaluate potential associated factors and biomarkers. They (22) took blood samples from recruited patients, including vitamin D, and assessed BMI, cardiovascular risk factors, and factors such as sociodemographic and biometric variables, and evaluated IMT via ultrasonography. A total of 50 patients with a clinical diagnosis of severe HS were inpatients at the Hidradenitis Suppurativa Clinic of the Virgen de las Nieves University Hospital in Spain. Their mean age was 38 (± 12.9 years), with a male/female ratio of 3:2. Mean duration of illness was 16.6 (± 13.54 years), mean age of onset was 21.83 (± 9.81 years). Disease severity was assessed using the IHS4 for inflammatory activity, Hurley classification for structural damage, and number of body areas affected by HS lesions. The mean IHS4 score was 21.6 (± 12.59), which indicates severe HS, and the mean vitamin D level was 19.80 ng/mL (± 7.08), indicating all participants had at minimum vitamin D insufficiency, but on average a deficiency. Considering vitamin D levels and severity of HS, the authors found that IHS4 scores were inversely and significantly correlated with vitamin D levels ($p=0.04$). Furthermore, an inverse association with vitamin D levels and the number of areas affected, IHS4 score, and Hurley stage in univariate analysis was found. The multivariate analysis revealed an inverse correlation between number of areas affected and vitamin D levels.

A limitation of this study was the cross-sectional design, making conclusions about causality impossible. Furthermore, the small sample size may have overlooked possible correlations. Moreover, the authors did not give information on what time of the year the vitamin D levels were taken, which might influence the vitamin D production by natural UVB exposure.

Moltrasio et al. (23) executed a retrospective cross-sectional study to assess correlations between CRP, IHS4, and especially vitamin D serum levels and disease severity of HS patients between June 2017 and February

2020. For this purpose, they recruited 250 patients at their Dermatology Unit in Italy on diagnosis of HS, before any specific treatment was initiated. The mean age of participants was 33.59 (± 0.89 years). Vitamin D serum levels were measured by an electrochemiluminescence immunoassay (ECL, Roche Diagnostic), whereas vitamin D levels ≤ 20 ng/mL were classified as deficient, 21–29 ng/mL as insufficient, and ≥ 30 ng/mL as sufficient. Mean vitamin D levels were 16.51 ± 0.3 ng/mL, 79.84% ($n=198$) patients were categorized as vitamin D deficient, 20.16% ($n=50$) were vitamin D insufficient, and 0.8% ($n=2$) were sufficient in vitamin D. Mean IHS4 was 10.6 ± 0.56 , indicating a moderate to severe HS. Moltrasio et al. (23) found a significant inverse correlation between vitamin D levels and IHS4 ($r=-0.76$, $p<0.0001$). Moreover, patients with vitamin D deficiency had higher IHS4 scores than patients with vitamin D insufficiency (12.59 ± 0.64 vs 3.06 ± 0.29 , $p<0.0001$), indicating a higher disease severity in patients with low vitamin D levels. Due to the low number of sufficient vitamin D patients, they were not included in the analysis.

One limitation of this study was the cross-sectional design, which makes conclusions regarding causality not possible. Furthermore, there was no adjustment of vitamin D levels for skin phototype, time of year, or geographic latitude, which might influence the vitamin D levels.

Fabbrocini et al. (24) executed a controlled cohort study to assess the correlation between vitamin D hypovitaminosis and disease severity of HS, and to explore the possible effect vitamin D supplementation could have on clinical responsiveness to prescribed therapy. Therefore, they measured serum vitamin D levels in patients and controls at baseline (T0) and after 6 months (T6) using ELISA assay. Forty patients ($n=26$ females, $n=14$ males) with a mean age of 27.3 (± 2.6 years) and 40 controls, who were matched with each patient for gender, age, BMI, and smoking status, were included.

Vitamin D deficiency was classified after the US Endocrine Society guidelines, assigning a deficiency at < 20 ng/mL; insufficiency at 21–29 ng/mL, and sufficiency at > 30 ng/mL (29). According to this, 31 patients (77.5%) were vitamin D deficient, 5 (12.5%) were insufficient, and 4 (10%) were sufficient. Compared with the control group, HS patients had significantly reduced vitamin D levels. Fabbrocini et al. (24) found an inverse association between vitamin D levels and clinical severity of HS, which was assessed by Sartorius score (SS). Patients with low vitamin D levels had an average SS score of 60 at baseline, whereas for those with vitamin D serum levels > 30 ng/mL at T6 the average SS score was 48, indicating a reduction of abscesses, nodules, and fistulas. All patients with vitamin D levels < 30 ng/mL ($n=36$) received oral supplementation of vitamin D (deficiency = 50,000 IU vitamin D/month, and insuf-

iciency=25,000 IU vitamin D/month) until their vitamin D levels were above 30 ng/mL. After 6 months (T6), 27 (75%) of the supplemented patients, who continued their previous therapy, had a significant reduction of SS scores (≥ 20 points), representing a significant improvement of the clinical condition of HS.

A limitation of this study was that the authors did not adjust the serum vitamin D levels for skin phototype, time of year, or geographic location, which might have had an impact on the measured vitamin D levels.

Ricceri et al. (25) conducted a pilot study to evaluate a possible association between vitamin D deficiency and specific demographic and clinical characteristics in HS patients. Therefore, they took blood samples in 22 patients with HS at the Dermatology Unit of Florence University, Italy. The authors did not make any specifications on the patients' age, sex, or disease severity. Ricceri et al. (25) found that all participants ($n=22$, 100%) had a vitamin D deficiency with serum levels < 30 ng/mL, of whom 19 (86%) had a severe deficiency with levels < 20 ng/mL. Furthermore, the deficiency in vitamin D had a mild correlation with the severity of HS ($r=-0.6$).

One limitation of this study was that many details of the sample as well as the disease severity were not disclosed, making it difficult to compare the results with other studies. Moreover, the authors did not state at what time of the year the blood samples were taken, or how the vitamin D levels were analysed, which again makes comparison difficult and may have influenced the vitamin D levels.

Guillet et al. (26) performed a pilot study to assess a possible association between vitamin D deficiency, HS, and disease severity. Furthermore, they aimed to analyse how vitamin D supplementation could improve inflammatory lesions in HS patients. Therefore, they set up a study with 2 phases: the first phase was intended for analysing vitamin D serum levels via ELISA in 22 patients and age, gender, and BMI matched healthy controls ($n=22$). For the second phase, 14 of the included 22 HS patients took vitamin D supplementation for 3 to 6 months and the clinical response was measured by assessing the decrease of inflammatory nodules. For supplementation, they used drinkable Uvedose® ampoules of 100,000 IU in line with the Research and Information Group on Osteoporosis. Patients were recruited at the Dermatology Department of Nantes Hospital, France, while controls were healthy donors at the French Blood Bank (FBB) of Nantes Hospital. Of the 22 patients (mean age 35 years), 14 (64%) were women and 8 (36%) were men. Their median duration of disease was 14 (6.0–45.3) years and the median age at disease onset was 16.5 (12.0–33.8 years). Furthermore, the disease severity was appraised by Hurley classification. Guillet et al. (26) found that all HS patients ($n=22$) had a vitamin D deficiency (< 30 ng/mL) and a median vitamin D level of 12.7 (95% confidence interval [CI]

6.3–21.5), whereas 91% ($n=20$) of the healthy controls had a deficiency in vitamin D and a median vitamin D level of 15.4 (95% CI 8.4–30.0). Eight patients had a severe vitamin D deficiency with levels < 10 ng/mL and at the same time deficiency severity was correlated to disease severity. Of the 14 supplemented patients in the second phase, 10 (71%) took vitamin D supplements from M0 to M3, and 4 (29%) took supplements from M0 to M6. They found a significant decrease in the number of nodules at M6 among the 14 supplemented patients, with a median decrease of 75% ($p=0.01133$). Therapeutic success for the number of nodules was obtained in 79% ($n=11$) patients.

Limitations within this study are the lack of power due to the small sample size and the study design without control vs placebo. Moreover, there was no matching on the phototype, which might have influenced the vitamin D levels. Furthermore, the authors did not provide any information on what time of the year the blood samples were taken, or what influenced the exposure to UVB and as a result vitamin D production.

DISCUSSION

This review has qualitatively synthesized the findings of 7 studies that examined the influence of vitamin D on HS. Every study included in the analysis reported that nearly all of the HS patients enrolled exhibited a deficiency in vitamin D (20–26), of which 3 found significantly lower vitamin D levels in patients than in controls (20, 21, 24). Furthermore, 6 studies evaluated that vitamin D deficiency was inversely correlated to clinical severity of HS (21–26). Only Seetan et al. (20) did not find a correlation between vitamin D levels and disease severity. Based on the current state of knowledge, we can conclude that patients with HS consistently have a deficiency in vitamin D, which is probably correlated with the severity of HS. However, it is not an isolated case that HS is associated with vitamin D deficiency, as this has also been observed in other T helper 1 (Th1) triggered skin conditions such as acne or psoriasis (30–32). Still, the exact role of vitamin D in HS remains unclear: some suggest hypovitaminosis D arises from comorbidities like obesity (33, 34), which is proposed to be 3.45 (95% CI 2.2–5.38) times more in HS patients than in control groups (35). Others believe inflammation is the initiator of vitamin D deficiency (36), and, once again, different studies suggested it is hypovitaminosis D, among other causes, that plays a crucial role in the pathogenesis of HS (16, 21, 26).

Two of the included studies conducted vitamin D supplementation on the recruited patients who had a vitamin D deficiency (24, 26). In both studies, vitamin D supplementation resulted in an improvement in patients' clinical condition. It should be noted, however, that each of these was a very small sample group. Guillet et

al. (26) reported therapeutic success in 11 (79%) of 14 supplemented patients, which meant a reduction in the number of inflammatory nodules, and Fabbrocini et al. (24) found a significant reduction of SS in 27 (75%) of 36 supplemented patients, which signifies a reduction in disease severity. A similar outcome was observed by Lim et al. (30), who supplemented vitamin D in patients with acne for 2 months in a randomized controlled trial. The number of inflammatory lesions decreased by 34.6% and showed a significant improvement compared with the control group, who received a placebo ($p < 0.05$). It appears that vitamin D contributes to the regulation of the immune system by inducing antimicrobial peptides in sebocytes and therefore presents anti-inflammatory effects in skin conditions (37). This would imply, in turn, that vitamin D could potentially play a significant role in the therapy for HS and other inflammatory skin diseases by reducing inflammation. In addition, vitamin D is suggested to lower HIF-1 α overexpression in mice (38). This seems important for HS, as a recently conducted study showed that HIF-1 α is elevated in HS patients and contributes to the hyperproliferation of keratinocytes and IL-17 (9). For now, the supplementation of vitamin D in HS remains a grade B recommendation with level III evidence, which is congruent with evidence based on non-experimental descriptive studies that align with the quality of the studies included in this review. This once again demonstrates the need for a randomized controlled trial on vitamin D supplementation in HS patients.

Limitations

A limitation of this review is that all studies included in the synthesis were case-control, pilot, or cross-sectional studies, which is why causality cannot be assessed. Furthermore, all included studies were of small sample size and some lacked control groups, which contributes to the difficulty of drawing concrete conclusions on how vitamin D might be connected to HS. Additionally, not all studies have considered potential environmental factors such as season or latitude when adjusting their vitamin D measurement results. As a result, the findings may not be generalizable and, in some cases, are thus difficult to compare.

Conclusion

The precise role of vitamin D in the development and progression of HS remains unclear. Nevertheless, hypovitaminosis D seems to be associated with HS and its disease severity, and vitamin D supplementation might be an adjunctive therapy option to reduce inflammatory nodules resulting from HS. As many studies have shown, most HS patients do have a vitamin D deficiency, which appears to correlate with higher disease severity. Therefore, it would be advisable to screen HS patients for vitamin D serum levels and, if necessary, to schedule

supplementation. Screening for vitamin D serum levels is non-invasive and inexpensive and could help improve the quality of life for patients with this debilitating disease.

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REFERENCES

- Zouboulis CC, Benhadou F, Byrd AS, Chandran NS, Giarmellos-Bourboulis EJ, Fabbrocini G, et al. What causes hidradenitis suppurativa? – 15 years after. *Exp Dermatol* 2020; 29: 1154–1170. <https://doi.org/10.1111/exd.14214>
- Sabat R, Jemec GBE, Matusiak L, Kimball AB, Prens E, Wolk K. Hidradenitis suppurativa. *Nat Rev Dis Primers* 2020; 6: 18. <https://doi.org/10.1038/s41572-020-0149-1>
- Wolk K, Join-Lambert O, Sabat R. Aetiology and pathogenesis of hidradenitis suppurativa. *Br J Dermatol* 2020; 183: 999–1010. <https://doi.org/10.1111/bjd.19556>
- Martorell A, Garcia-Martinez FJ, Jimenez-Gallo D, Pascual JC, Pereyra-Rodriguez J, Salgado L, et al. An update on hidradenitis suppurativa (part i): epidemiology, clinical aspects, and definition of disease severity. *Actas Dermosifiliogr* 2015; 106: 703–715. <https://doi.org/10.1016/j.ad.2015.06.004>
- Goldburg SR, Strober BE, Payette MJ. Hidradenitis suppurativa: epidemiology, clinical presentation, and pathogenesis. *J Am Acad Dermatol* 2020; 82: 1045–1058. <https://doi.org/10.1016/j.jaad.2019.08.090>
- Hessam S, Sand M, Gambichler T, Skrygan M, Ruedel I, Bechara FG. Interleukin-36 in hidradenitis suppurativa: evidence for a distinctive proinflammatory role and a key factor in the development of an inflammatory loop. *Br J Dermatol* 2018; 178: 761–767. <https://doi.org/10.1111/bjd.16019>
- Lima AL, Karl I, Giner T, Poppe H, Schmidt M, Presser D, et al. Keratinocytes and neutrophils are important sources of proinflammatory molecules in hidradenitis suppurativa. *Br J Dermatol* 2016; 174: 514–521. <https://doi.org/10.1111/bjd.14214>
- Schlapbach C, Hanni T, Yawalkar N, Hunger RE. Expression of the IL-23/Th17 pathway in lesions of hidradenitis suppurativa. *J Am Acad Dermatol* 2011; 65: 790–798. <https://doi.org/10.1016/j.jaad.2010.07.010>
- Agamia NF, Sorrow OA, Sayed NM, Ghazala RA, Echy SM, Moussa DH, et al. Overexpression of hypoxia-inducible factor-1 α in hidradenitis suppurativa: the link between deviated immunity and metabolism. *Arch Dermatol Res* 2023; 315: 2107–2118. <https://doi.org/10.1007/s00403-023-02594-6>
- Gulliver W, Zouboulis CC, Prens E, Jemec GB, Tzellos T. Evidence-based approach to the treatment of hidradenitis suppurativa/acne inversa, based on the European guidelines for hidradenitis suppurativa. *Rev Endocr Metab Disord* 2016; 17: 343–351. <https://doi.org/10.1007/s11554-016-9328-5>
- Zouboulis CC, Desai N, Emtestam L, Hunger RE, Ioannides D, Juhász I, et al. European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa. *J Eur Acad Dermatol Venereol* 2015; 29: 619–644. <https://doi.org/10.1111/jdv.12966>
- Hendricks AJ, Hsiao JL, Lowes MA, Shi VY. A comparison of international management guidelines for hidradenitis suppurativa. *Dermatology* 2021; 237: 81–96. <https://doi.org/10.1159/000503605>
- Kechichian E, Ezzedine K. Vitamin D and the skin: an update for dermatologists. *Am J Clin Dermatol* 2018; 19: 223–235.

- <https://doi.org/10.1007/s40257-017-0323-8>
14. Passeron T, Bouillon R, Callender V, Cestari T, Diepgen TL, Green AC, et al. Sunscreen photoprotection and vitamin D status. *Br J Dermatol* 2019; 181: 916–931. <https://doi.org/10.1111/bjd.17992>
 15. Brandao L, Moura R, Tricarico PM, Gratton R, Genovese G, Moltrasio C, et al. Altered keratinization and vitamin D metabolism may be key pathogenetic pathways in syndromic hidradenitis suppurativa: a novel whole exome sequencing approach. *J Dermatol Sci* 2020; 99: 17–22. <https://doi.org/10.1016/j.jdermsci.2020.05.004>
 16. Weber I, Giefer J, Martin KL. Effects of exercise and dietary modifications on hidradenitis suppurativa: a systematic review. *Am J Clin Dermatol* 2023; 24: 343–357. <https://doi.org/10.1007/s40257-023-00756-w>
 17. Kelly G, Sweeney CM, Fitzgerald R, O’Keane MP, Kilbane M, Lally A, et al. Vitamin D status in hidradenitis suppurativa. *Br J Dermatol* 2014; 170: 1379–1380. <https://doi.org/10.1111/bjd.12900>
 18. Lee JW, Heo YW, Lee JH, Lee S. Epidemiology and comorbidity of hidradenitis suppurativa in Korea for 17 years: a nationwide population-based cohort study. *J Dermatol* 2023; 50: 778–786. <https://doi.org/10.1111/1346-8138.16747>
 19. Kirsten N, Mohr N, Augustin M, Hilbring C, Girbig G, Neumann F, et al. Abstract 106: vitamin D and its correlation with the BMI and the MEDAS-Score in patients with hidradenitis suppurativa: results of a monocentric cross-sectional study. *J Dtsch Dermatol Ges* 2021; 19: 53.
 20. Seetan K, Eldos B, Saraireh M, Omari R, Rubbai Y, Jayyusi A, et al. Prevalence of low vitamin D levels in patients with hidradenitis suppurativa in Jordan: a comparative cross-sectional study. *PLoS One* 2022; 17: e0265672. <https://doi.org/10.1371/journal.pone.0265672>
 21. Navarro I, Gonzalez-Lopez MA, Sierra I, Olmos JM, Blanco R, Hernandez JL. Bone metabolism in patients with hidradenitis suppurativa: a case-control study. *Acta Derm Venereol* 2022; 102: adv00825. <https://doi.org/10.2340/actadv.v102.3504>
 22. Sanchez-Diaz M, Salvador-Rodriguez L, Montero-Vilchez T, Martinez-Lopez A, Arias-Santiago S, Molina-Leyva A. Cumulative inflammation and HbA1c levels correlate with increased intima-media thickness in patients with severe hidradenitis suppurativa. *J Clin Med* 2021; 10: 5222. <https://doi.org/10.3390/jcm10225222>
 23. Moltrasio C, Tricarico PM, Genovese G, Gratton R, Marzano AV, Crovella S. 25-Hydroxyvitamin D serum levels inversely correlate to disease severity and serum C-reactive protein levels in patients with hidradenitis suppurativa. *J Dermatol* 2021; 48: 715–717. <https://doi.org/10.1111/1346-8138.15797>
 24. Fabbrocini G, Marasca C, Luciano MA, Guarino M, Poggi S, Fontanella G, et al. Vitamin D deficiency and hidradenitis suppurativa: the impact on clinical severity and therapeutic responsiveness. *J Dermatolog Treat* 2021; 32: 843–844. <https://doi.org/10.1080/09546634.2020.1714538>
 25. Ricceri F, Pescitelli L, Di Cesare A, Rosi E, Prignano F. 053 OS11-02 – oral session: serum vitamin D in hidradenitis suppurativa patients: a pilot study. *Exp Dermatol* 2019; 28: 28.
 26. Guillet A, Brocard A, Bach Ngohou K, Graveline N, Leloup AG, Ali D, et al. Verneuil’s disease, innate immunity and vitamin D: a pilot study. *J Eur Acad Dermatol Venereol* 2015; 29: 1347–1353. <https://doi.org/10.1111/jdv.12857>
 27. Olmos JM, Hernandez JL, Garcia-Velasco P, Martinez J, Llorca J, Gonzalez-Macias J. Serum 25-hydroxyvitamin D, parathyroid hormone, calcium intake, and bone mineral density in Spanish adults. *Osteoporos Int* 2016; 27: 105–113. <https://doi.org/10.1007/s00198-015-3219-6>
 28. Martinez J, Olmos JM, Hernandez JL, Pinedo G, Llorca J, Obregon E, et al. Bone turnover markers in Spanish postmenopausal women: the Camargo cohort study. *Clin Chim Acta* 2009; 409: 70–74. <https://doi.org/10.1016/j.cca.2009.08.020>
 29. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2011; 96: 1911–1930. <https://doi.org/10.1210/jc.2011-0385>
 30. Lim SK, Ha JM, Lee YH, Lee Y, Seo YJ, Kim CD, et al. Comparison of vitamin D levels in patients with and without acne: a case-control study combined with a randomized controlled. *Trial PLoS One* 2016; 11: e0161162. <https://doi.org/10.1371/journal.pone.0161162>
 31. Barrea L, Savanelli MC, Di Somma C, Napolitano M, Megna M, Colao A, et al. Vitamin D and its role in psoriasis: an overview of the dermatologist and nutritionist. *Rev Endocr Metab Disord* 2017; 18: 195–205. <https://doi.org/10.1007/s11154-017-9411-6>
 32. Bergler-Czop B, Brzezinska-Wcislo L. Serum vitamin D level: the effect on the clinical course of psoriasis. *Postepy Dermatol Alergol* 2016; 33: 445–449. <https://doi.org/10.5114/ada.2016.63883>
 33. Afzal S, Brondum-Jacobsen P, Bojesen SE, Nordestgaard BG. Vitamin D concentration, obesity, and risk of diabetes: a mendelian randomisation study. *Lancet Diabetes Endocrinol* 2014; 2: 298–306. [https://doi.org/10.1016/S2213-8587\(13\)70200-6](https://doi.org/10.1016/S2213-8587(13)70200-6)
 34. Pereira-Santos M, Costa PR, Assis AM, Santos CA, Santos DB. Obesity and vitamin D deficiency: a systematic review and meta-analysis. *Obes Rev* 2015; 16: 341–349. <https://doi.org/10.1111/obr.12239>
 35. Tzellos T, Zouboulis CC, Gulliver W, Cohen AD, Wolkenstein P, Jemec GB. Cardiovascular disease risk factors in patients with hidradenitis suppurativa: a systematic review and meta-analysis of observational studies. *Br J Dermatol* 2015; 173: 1142–1155. <https://doi.org/10.1111/bjd.14024>
 36. Waldron JL, Ashby HL, Cornes MP, Bechervaise J, Razavi C, Thomas OL, et al. Vitamin D: a negative acute phase reactant. *J Clin Pathol* 2013; 66: 620–622. <https://doi.org/10.1136/jclinpath-2012-201301>
 37. Lee WJ, Cha HW, Sohn MY, Lee SJ, Kim DW. Vitamin D increases expression of cathelicidin in cultured sebocytes. *Arch Dermatol Res* 2012; 304: 627–632. <https://doi.org/10.1007/s00403-012-1255-z>
 38. An JH, Cho DH, Lee GY, Kang MS, Kim SJ, Han SN. Effects of vitamin D supplementation on CD4+ T cell subsets and mTOR signaling pathway in high-fat-diet-induced obese mice. *Nutrients* 2021; 13: 796. <https://doi.org/10.3390/nu13030796>
 39. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews *BMJ* 2021; 372: n71. <https://doi.org/10.1136/bmj.n71>