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The Effect of Adjunctive Vitamin D Supplementation on Disease Severity in Chronic Spontaneous Urticaria: A Literature Review

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ABSTRACT

Vitamin D has been investigated as an adjunctive treatment for chronic spontaneous urticaria (CSU), although an association between low vitamin D concentrations and CSU does not establish that supplementation improves disease severity. This review aimed to critically evaluate the evidence regarding adjunctive vitamin D supplementation and disease severity in CSU, including its effects on quality of life, safety, and clinical applicability. A narrative literature review was conducted through targeted scholarly searches and verification of relevant primary studies, evidence syntheses, and international guidelines, with searches completed on 31 October 2026. Randomized trials were distinguished from uncontrolled before–after studies, while observational and mechanistic findings were considered contextual evidence. Several studies reported reductions in urticaria activity and symptom severity following supplementation. A placebo-controlled trial involving vitamin-D-deficient patients demonstrated improvement in UAS7, whereas comparisons of high- and low-dose supplementation did not consistently demonstrate superiority in final disease severity outcomes. Improvements in quality of life were reported in some studies, but medication-sparing effects remained uncertain. Interpretation was limited by small or selected populations, heterogeneous outcome measures, active-dose comparators, and short follow-up periods. Furthermore, hypercalcemia and renal lithiasis were reported in individual trials. In conclusion, adjunctive vitamin D may reduce short-term disease activity in some patients with CSU, particularly those with low vitamin D status. However, the magnitude and durability of its benefits, optimal supplementation regimen, and predictive value of baseline vitamin D levels remain uncertain. Current evidence does not support routine high-dose supplementation for all patients or its use as a replacement for established CSU treatments.

Keywords: chronic spontaneous urticaria; vitamin D supplement; biological plausibility of vitamin D

INTRODUCTION

Chronic spontaneous urticaria (CSU) is defined by the persistent occurrence of wheals, angioedema, or a combination of both for over six weeks without a specific identifiable cause. It is primarily a condition caused by mast cells, characterised by diverse inflammatory and autoimmune processes. The international urticaria guideline recommends validated patient-reported measures for assessing disease activity and treatment response [1].

Modern second-generation H1-antihistamines remain the initial pharmacological treatment, with dose escalation when symptoms remain uncontrolled. Further treatment is guided by response, eligibility, availability, and the benefit–risk profiles of targeted or immunomodulatory therapies.

The updated international guideline incorporates omalizumab and discusses additional options, including dupilumab and remibrutinib, while reserving ciclosporin for selected refractory disease [1]. Against this treatment background, the present review evaluates nutritional supplementation in terms of incremental benefit beyond appropriate CSU therapy, rather than improvement over time alone.

Vitamin D has attracted interest because of its effects on immune regulation and reports of lower circulating 25-hydroxyvitamin D [25(OH)D] concentrations in patients with CSU. However, published reviews describe substantial variation in the relationship between vitamin D status and disease activity, as well as in supplementation schedules and clinical endpoints [2,3].

A low serum concentration may represent a contributing factor, a consequence of illness-associated behavior, or a correlate of other determinants of vitamin D status. The present review therefore treats observational associations separately from evidence of a supplementation effect.

Interventional findings also require careful interpretation. Rorie et al. reported a potentially beneficial signal with higher-dose supplementation, Mony et al. demonstrated improvement against placebo in deficient patients, and Nabavizadeh et al. found differing patterns for symptom severity and quality of life [4–6]. Together, these studies justify critical examination but do not establish a uniform treatment effect. This review evaluates the effect of adjunctive vitamin D on CSU severity while separating controlled clinical evidence from observational associations, mechanistic plausibility, and uncontrolled treatment responses.

METHODS

This article was developed as a narrative literature review, not as a systematic review. Targeted searches of an academic literature index were supplemented by checks of publicly accessible PubMed/PMC records, publisher websites, international guideline documents, and institutional repositories. The final search date was 31 October 2026. Search concepts combined chronic spontaneous urticaria or chronic urticaria with vitamin D, supplementation, adjunctive treatment, randomized trial, placebo, disease severity, UAS7, symptom severity, and quality of life. Supplied references were assessed for relevance, and additional primary reports and evidence syntheses were retrieved where needed.

Clinical supplementation studies in CSU were prioritized. Studies using the broader term chronic urticaria were retained where clinically relevant, but that terminology was not assumed to establish an exclusively CSU population. Observational studies of vitamin D status and mechanistic studies were used to inform background and interpretation, not to estimate therapeutic efficacy. Studies of unrelated interventions, including probiotic supplementation without a vitamin D intervention, were outside the scope.

Information was organized by study design, population, baseline vitamin D status, formulation, dose, duration, background therapy, comparator, severity outcome, quality-of-life outcome, and adverse events. Particular attention was paid to the distinction between within-group improvement and between-group treatment effects. Full reports were assessed where retrievable; otherwise, interpretation was restricted to the available primary abstract. Conference evidence was identified separately and was not treated as equivalent to a fully assessed journal report. Duplicate publication records were not considered independent studies. No protocol registration, duplicate independent screening, formal risk-of-bias scoring, or de novo quantitative pooling was undertaken.

NARRATIVE SYNTHESIS

1. Vitamin D status and CSU severity: association is inconsistent

Observational findings support an association between CSU and lower vitamin D status in many, but not all, populations. Importantly, lower concentrations in patients than in healthy controls do not necessarily imply a relationship with severity within the patient population. Tuchinda et al. found that only a subset of studies demonstrated a significant association between low vitamin D and high disease activity [2].

Recent studies illustrate this distinction. Tat et al. reported lower mean 25(OH)D in patients with CSU than in controls, but no statistically significant difference across disease-severity subgroups [7]. Conversely, one study reported an inverse correlation between vitamin D concentration and UAS7 in a cross-sectional CSU population [8]. The latter report also contains inconsistent descriptions of the boundary between low and deficient vitamin D categories; its findings are therefore most appropriately regarded as associative rather than as establishing a treatment-selection threshold. Neither study tested supplementation as an intervention.

These findings do not validate serum vitamin D as a stand-alone marker of CSU activity or a predictor of supplementation response. Sun exposure, season, body habits, dietary intake, and other determinants of vitamin D status may confound observed associations [2]. Therapeutic efficacy must therefore be judged primarily from controlled intervention studies.

2. Biological plausibility

Vitamin D has biological effects beyond mineral metabolism, including actions on immune cells that express vitamin D receptors. Its proposed relevance to CSU includes modulation of mast-cell function and inflammatory signaling [2]. In this review, these mechanisms are considered contextual evidence rather than clinical efficacy outcomes.

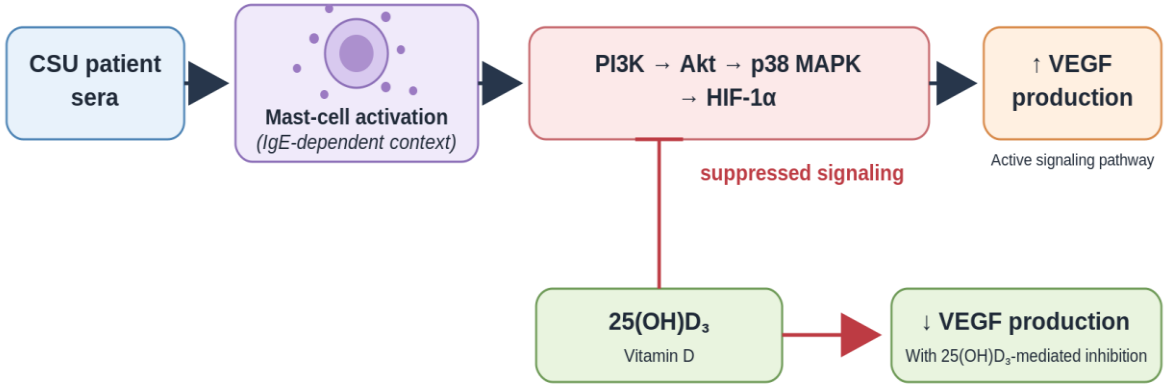


FIGURE 1: Proposed signaling pathway linking vitamin D to CSU-related mast-cell activation. Adapted from Zhaou et al. [9].

Zhao et al. investigated a specific pathway using sera from patients with CSU and mast-cell experiments. Patient sera stimulated vascular endothelial growth factor production through a PI3K/Akt/p38 MAPK/ HIF-1α signaling axis, and 25(OH)D3 suppressed this response, as illustrated in Figure 1 [9]. This finding provides mechanistic plausibility for an effect on mast-cell-associated inflammation. However, it does not establish which oral preparation, or dose, would reproduce that effect in patients, or whether pathway suppression mediates improvement in clinical severity.

3. Controlled supplementation studies

Rorie et al. conducted a double-blind randomized study involving 42 participants with chronic urticaria. Participants received vitamin D3 at 4,000 or 600 IU/day for 12 weeks, in addition to cetirizine, ranitidine, and montelukast [4]. Background therapy reduced the total Urticaria Symptom Severity (USS) score by 33% during the first week. The high-dose group subsequently experienced a further 40% within-group reduction. However, the comparison between the high- and low-dose groups for total USS at week 12 did not reach conventional statistical significance (P=0.052). Some hive-distribution and frequency measures favored higher dosing, but medication use did not differ. Accordingly, the study supports a possible benefit rather than definitive superiority of high-dose vitamin D on overall severity.

Mony et al. provide direct evidence from a randomized, double-blind, placebo-controlled trial in 120 patients with vitamin-D-deficient chronic urticaria [5]. Vitamin D was administered at 60,000 IU every two weeks for 12 weeks. The vitamin D group showed a significant reduction in UAS7 relative to placebo, accompanied by reduced inflammatory cytokines [5]. Accessible publisher extracts also reported lower medication use, but documented baseline imbalance in UAS7 and levocetirizine dose, with higher initial UAS7 in the vitamin D group. This imbalance complicates interpretation of the reported improvement. Baseline imbalance and incomplete numerical reporting prevented independent verification of the adjusted magnitude and precision of benefit.

Mohamed et al. conducted a randomized trial involving 77 patients with CSU who received either alfacalcidol (0.25 µg/day) or placebo for 12 weeks, while 67 healthy participants served as an observational comparison group. The available abstract summary reported that, compared with the placebo group, the intervention group demonstrated reductions in IL-6, hs-CRP, and TNF-α levels. Although the authors proposed a potential beneficial adjunctive role for alfacalcidol, the available abstract did not provide quantitative estimates of post-intervention disease severity outcomes for between-group comparisons. Therefore, improvements in biomarker levels cannot be directly equated with the magnitude of measurable clinical benefit.

Nabavizadeh et al. compared vitamin D3 at 28,000 versus 4,200 IU/week for 12 weeks in a double-blind randomized study [6]. Eighty participants were allocated, and 69 were followed through the study. USS decreased by 67.58% in the high-dose group and 50.05% in the low-dose group, but these percentages represent within-group changes. The between-group USS difference favored higher dosing at week six but was not significant at week 12. In contrast, CSU-specific quality-of-life scores favored the high-dose group at both points. Medication scores did not differ between groups. These findings suggest that quality-of-life improvement and superiority on final disease-severity scores should be discussed as distinct outcomes.

Rasool et al. evaluated vitamin D alone, antihistamine plus corticosteroid, and their combination [11]. Of 192 enrolled patients, 147 were included in the final evaluation. Vitamin D3 was given at 60,000 IU/week for four weeks; the medication regimen included hydroxyzine and deflazacort for six weeks. At six weeks, mean visual analogue scale scores were lower with combination treatment than with antihistamine plus corticosteroid alone, at 1.86 versus 3.3 (P=0.0203). However, attrition, the corticosteroid - containing background regimen, short follow-up,

and use of itch-oriented outcomes may limit application to current antihistamine-based CSU care.

The controlled evidence is not uniformly positive. Tuchinda et al. summarized a three-arm trial comparing vitamin D at 2,000 IU/day, 60,000 IU/week, or no supplementation with concomitant levocetirizine. No significant difference in mean UAS4 was reported among groups after 12 weeks [2]. Because the original report was not retrieved for direct assessment, this finding is retained explicitly as secondary-reported evidence rather than presented as a fully verified primary extraction. It nevertheless cautions against treating improvement during supplementation as synonymous with an incremental treatment effect.

4. Nonrandomized and uncontrolled studies

Boonpiyathad et al. studied 60 patients with CSU and 40 healthy controls [12]. Fifty patients with 25(OH)D below 30 ng/mL received ergocalciferol at 20,000 IU/day for six weeks alongside nonsedating antihistamines; ten vitamin-D-sufficient patients did not receive supplementation. Median UAS7 in the supplemented group decreased from 27 to 15, and the follow-up score was lower than in the non-supplemented group, whose median was 26. Quality of life also improved. However, allocation depended on baseline vitamin D status, creating non-exchangeable comparison groups. The study therefore supports a treatment hypothesis but cannot isolate an unbiased causal effect. Its very high supplementation dose should not be generalized as a standard CSU regimen.

Oğuz Topal et al. reported improvement in UAS4 and CSU-specific quality of life after vitamin D3 supplementation at 300,000 IU/month for three months in patients with low vitamin D [13]. Ariaee et al. likewise reported improved symptom severity and Dermatology Life Quality Index (DLQI) after eight weeks of vitamin D at 50,000 IU/week in a small, selected cohort [14]. The latter study had no concurrent control group. Such findings cannot distinguish supplementation effects from ongoing treatment, natural fluctuation, regression to the mean, or nonspecific study effects. They should be interpreted as supportive but lower-confidence evidence.

5. Recent evidence and the limits of accessible reporting

A more recent randomized trial of vitamin D3 added to bilastine was identified through a journal publication record [15]. The accessible conference abstract described 60 patients receiving bilastine 40 mg/day with either vitamin D3 60,000 IU/week or placebo for eight weeks. It reported better urticaria activity and control in the supplemented group. However, the objective referred to UAS7 while the results used the label UAS, and the abstract did not provide enough information to verify per-arm analyzed populations or the statistical model. The complete journal report was not available for assessment. Consequently, the conference findings are treated as provisional supporting evidence, not as a fully appraised confirmatory trial. The journal record and conference abstract were not counted as separate independent efficacy studies. The inability to assess the complete journal report leaves uncertainty about how much weight these recent results should receive in the overall synthesis.

DISCUSSION

1. What the evidence supports

The evidence suggests a possible short-term adjunctive benefit, with the most directly interpretable positive placebo-controlled result arising from a vitamin-D-deficient chronic urticaria population. It does not show that every patient with CSU benefits, that higher doses are consistently superior, or that supplementation produces sustained remission. The distinction is important because the high- versus low-dose studies by Rorie and Nabavizadeh did not demonstrate clear superiority on their final total severity outcomes, despite favorable within-group changes or secondary endpoints [4–6].

Published syntheses should also be interpreted according to the treatment contrast they actually analyzed. Li et al. reported substantial reductions in severity scores, but their methods describe the intervention analysis in terms of changes from pretreatment values, with marked heterogeneity and different severity instruments [3]. Those estimates should not be interpreted as a single, precise placebo-adjusted effect. The later systematic review by Siddiqui et al. also acknowledged inconsistent trial findings, methodological limitations, and insufficient long-term evidence [16]. Agreement among reviews does not overcome limitations in the underlying studies.

2. Patient selection, formulation, and dose

Low baseline vitamin D is a plausible context for benefit, but it is not yet a validated predictive biomarker. Mony et al. recruited deficient patients, while the intervention populations analyzed by Li et al. had average baseline concentrations below the sufficiency threshold used in that review [3,5]. These data provide limited information about patients who already have sufficient vitamin D. A larger improvement in a deficient cohort cannot, by itself, establish that baseline deficiency modifies the treatment effect; that question requires a controlled comparison across prespecified vitamin D strata.

The literature also does not establish an optimal CSU-specific regimen. Daily, weekly, fortnightly, and monthly schedules have been studied, using cholecalciferol, ergocalciferol, or a vitamin D analogue. Formulation, exposure, baseline status, and background treatment vary simultaneously across reports [2,3]. Consequently, cross-study differences cannot establish a reliable dose–response relationship. In particular, the high doses used in some small studies should be described as experimental regimens, not converted directly into routine prescribing recommendations.

3. Disease activity, quality of life, and medication burden

Disease activity and quality of life are related outcomes, but they are not identical. The Urticaria Activity Score over 7 days (UAS7) is a disease activity score that assesses the number of wheals and the severity of pruritus over a 7-day period, thereby reflecting the daily symptom pattern. The Urticaria Activity Score over 4 days (UAS4) follows the same principle but evaluates symptoms over a 4-day period. Meanwhile, some studies also report an additional outcome, the Total Urticaria Symptom Severity (USS), which represents the overall severity of urticaria symptoms and is used as an additional measure to monitor symptom burden, including the predominance of complaints such as itching and/or other symptom components, depending on the assessment instrument used in each study. Since different instruments measure different aspects of the disease and/or use different assessment periods, direct comparisons across studies may be difficult when these outcomes are combined without considering their differences.

The quality-of-life findings are encouraging, especially in the Nabavizadeh trial, but they do not establish medication-sparing efficacy. Neither Rorie et al. nor Nabavizadeh et al. found a significant between-group reduction in medication use or medication score [4,6]. Although medication reduction was reported in the accessible Mony study extracts [5], the available results do not establish a consistent medication-sparing effect across trials. Claims that vitamin D reliably reduces antihistamine requirements would therefore exceed the overall evidence. Similarly, follow-up limited to a short treatment period cannot establish prevention of relapses after supplementation stops.

4. Safety and clinical positioning

Short-term tolerability was reassuring in some reports, but supplementation cannot be described as uniformly risk-free. Rorie et al. reported no adverse events, and Boonpiyathad et al. reported no adverse effects during their short intervention [4,12]. In contrast, Rasool et al. documented hypercalcemia requiring withdrawal, and Nabavizadeh et al. excluded one high-dose participant because of renal lithiasis [6,11]. The latter observation does not establish causality, but it should not disappear from a safety synthesis. Long-term safety remains insufficiently characterized in the available literature.

The defensible clinical interpretation is therefore limited: correction of an identified vitamin D deficiency and use of vitamin D as a CSU-directed immunomodulatory treatment are not equivalent claims. Evidence supporting the former context does not automatically justify high-dose treatment in vitamin-D-sufficient patients. If supplementation is considered alongside CSU care, it should not delay appropriate treatment escalation or replace assessment with validated disease-activity measures. The current evidence is insufficient to endorse a universal CSU-specific dose, target concentration, or treatment duration [1–3].

5. Limitations and priorities for future research

This review is limited by its narrative design and targeted rather than exhaustive retrieval. Several primary studies were assessed through abstracts or limited publisher extracts because complete reports were unavailable, limiting independent evaluation of allocation methods, attrition handling, outcome definitions, and numerical effect estimates. A negative three-arm comparison was available only through a secondary synthesis, and the recent bilastine study could be assessed only through conference-level results and a journal record. No formal risk-of-bias or certainty grading was undertaken; the cautious interpretation presented here is a qualitative judgment, not a GRADE classification.

Future trials should define CSU rigorously, standardize background therapy, prespecify baseline vitamin D strata, and distinguish correction of deficiency from supplementation in sufficient patients. Where ethically appropriate, placebo-controlled comparisons should report absolute between-group differences with confidence intervals, validated activity and control outcomes, clinically interpretable responder proportions, quality of life, and rescue-medication use. Longer follow-up should assess relapses after treatment withdrawal and include systematic calcium-related safety monitoring. These priorities address the heterogeneity, incomplete comparative reporting, and short follow-up that currently limit clinical interpretation [2,3,17].

CONCLUSION

Adjunctive vitamin D supplementation may improve short-term disease activity and quality of life in some patients with CSU, particularly in populations with low baseline vitamin D. However, between-group severity benefits are not consistent across studies, and the magnitude of benefit is difficult to quantify because of heterogeneous designs, comparators, formulations, and outcome measures. The evidence remains insufficient to establish a standard CSU-specific regimen, a validated vitamin D threshold predicting response, medication-sparing efficacy, or durable remission. Vitamin D should therefore be regarded as a possible adjunct in selected circumstances, not an established replacement for guideline-directed therapy or a justification for routine high-dose supplementation in all patients.

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