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Beneficial role for supplemental vitamin D_3 treatment in chronic urticaria: a randomized study

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ABSTRACT

Background: Observational reports have linked vitamin D with chronic urticaria, yet no randomized controlled trial has been conducted.

Objective: To determine whether high-dose vitamin D supplementation would decrease Urticaria Symptom Severity (USS) scores and medication burden in patients with chronic urticaria.

Methods: In a prospective, double-blinded, single-center study, 42 subjects with chronic urticaria were randomized to high (4,000 IU/d) or low (600 IU/d) vitamin D_3 supplementation for 12 weeks. All subjects were provided with a standardized triple-drug therapy (cetirizine, ranitidine, and montelukast) and a written action plan. Data on USS scores, medication use, blood for 25-hydroxyvitamin D, and safety measurements were collected.

Results: Triple-drug therapy decreased total USS scores by 33% in the first week. There was a further significant decrease (40%) in total USS scores in the high, but not low, vitamin D_3 treatment group by week 12. Compared with low treatment, the high treatment group demonstrated a trend ($P = .052$) toward lower total USS scores at week 12, which was driven by significant decreases in body distribution and number of days with hives. Beneficial trends for sleep quality and pruritus scores were observed with high vitamin D_3. Serum 25-hydroxyvitamin D levels increased with high vitamin D_3 supplementation, but there was no correlation between 25-hydroxyvitamin D levels and USS scores. There was no difference in allergy medication use between groups. No adverse events occurred.

Conclusion: Add-on therapy with high-dose vitamin D_3 (4,000 IU/d) could be considered a safe and potentially beneficial immunomodulator in patients with chronic urticaria.

Trial Registration: clinicaltrials.gov Identifier: NCT01371877.

Introduction

Chronic urticaria with or without angioedema (CU) is a common allergic skin condition associated with considerable morbidity and burden on health care expenditure.[1,2] CU is defined as urticarial wheals occurring daily or almost daily and lasting longer than 6 weeks. It has been estimated that 10% to 20% of the population develop an acute episode of urticaria in their lifetime and 1% to 3% develop CU.[1,3] Through a comprehensive approach, cutaneous symptoms sometimes can be ascribed to drug, food, aeroallergen, contact allergen, or autoantibodies to the high-affinity IgE receptor or to free IgE.[1,3] However, in most cases, the diagnosis remains idiopathic.[1,3] Treatment options are limited, and the mainstay of therapy is symptomatic control with antihistamines. Systemic corticosteroids, anti-leukotrienes, hydroxychloroquine, cyclosporine, dapsone, anti-IgE monoclonal antibody therapy, and other anti-inflammatory agents may be used, which themselves can pose substantial adverse events and cost.[3–6] A potential alternative and safe immunomodulator is vitamin D.

Vitamin D is essential for bone and mineral homeostasis, but vitamin D also regulates the growth and differentiation of multiple cell types and displays immunoregulatory and anti-inflammatory properties.[7] A possible role for vitamin D in the prevention or treatment of immune-mediated diseases, including cancers, cardiovascular diseases, arthritis, transplant rejection, and autoimmune diseases, has been suggested.[7] A role for vitamin D in allergic diseases gained attention after its potential causative role was

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proposed in anaphylaxis.[8] Vitamin D deficiency also has been linked with difficult-to-control asthma,[9,10] and vitamin D supplementation may alleviate atopic dermatitis.[11] Previously, the authors reported that serum 25-hydroxyvitamin D (25[OH]D) levels were significantly decreased in subjects with CU compared with those with allergic rhinitis.[12] There have been 2 observational reports suggesting that vitamin D supplementation might alleviate symptoms of CU.[13,14] A retrospective case series chart review found that approximately 70% of patients with low 25(OH)D (<32 ng/mL) and CU showed symptom alleviation after vitamin D_2 supplementation (50,000 IU/week) for 8 to 12 weeks.[13] A separate case study reported the resolution of CU after vitamin D_3 supplementation (2,000 IU/d for approximately 2 months) in a patient with profound vitamin D deficiency (25[OH]D 4.7 ng/mL).[14] To the authors' knowledge, there have been no randomized, prospective, blinded trials investigating whether vitamin D supplementation in patients with CU is beneficial, which was the objective of this study. Moreover, it is not known whether vitamin D supplementation decreases CU symptoms in patients with vitamin D sufficiency.

Sources of vitamin D include exposure to sunlight (ultraviolet light converts 7-dehydrocholesterol in skin to vitamin D_3), dietary intake (eg, fish, mushrooms, and fortified dairy products), and supplementation with vitamin D_2 (ergocalciferol) or vitamin D_3 (cholecalciferol).[7] Vitamin D_3, as opposed to vitamin D_2, is favored for increasing and maintaining steady-state 25(OH)D levels[15,16]; however, because of its half-life (2–3 weeks), supplementation with vitamin D_3 typically requires 12 weeks to restore depleted stores and/or reach a steady state.[17,18] For these reasons, this study was designed to determine whether add-on therapy with high-dose vitamin D_3 supplementation (4,000 IU/d) would improve clinical response and decease the medication burden in patients with CU compared with low-dose vitamin D_3 supplementation (600 IU/d) over 12 weeks.

Methods

Subjects

Adult patients (≥19 years of age) with physician-diagnosed CU were recruited through clinic populations at a tertiary care institution's internal medicine allergy and immunology clinics. Inclusion criteria required patients to have a history of urticaria and/or angioedema daily or almost daily for longer than 6 weeks. Patients were excluded if they were diagnosed with a pure physical urticaria, hereditary or acquired angioedema, hypercalcemia (>10.3 mg/dL), renal insufficiency (glomerular filtration rate <50 mL/min/1.73 m^2), primary hyperparathyroidism, sarcoidosis, granulomatous disease, or malignancy or were pregnant or lactating. Patients with CU having signs of dermatographism and/or delayed-pressure urticaria were not excluded. Patients with a history of intolerance to nonsteroidal anti-inflammatory drugs were included but warned not to take this drug class (acetaminophen was allowed). Patients with a history of alcohol-exacerbating hives were included but were counseled to avoid alcohol.

Study Design

This was a prospective, double-blinded, randomized, single-center clinical study approved by the center's institutional review board. Subjects and study personnel, including the principal investigator, were blinded in the study; the statistician had access to treatment assignments. The randomization method was randomized blocks with block sizes of 3 and 6 to ensure a balance in treatment assignment over time. The randomization list was generated with SAS 9.3 (SAS Institute, Cary, North Carolina) by the study statistician. All subjects provided informed written consent, and the study was registered at clinicaltrials.gov (NCT01371877). At the enrollment visit, subjects were randomized to low-dose vitamin D_3 (600 IU/d) or high-dose vitamin D_3 (4,000 IU/d) supplementation for 12 weeks. These doses of cholecalciferol were chosen based on the National Institute of Medicine's recommendations for safe upper limit and lower limit supplemental vitamin D_3 dosing in adult subjects.[19] Owing to the knowledge that 12 weeks would be necessary to safely restore depleted vitamin D stores and/or reach a steady state,[17,18] all subjects were provided a standardized treatment and a written action plan. The treatment algorithm was modified from the Third International Consensus Meeting on Urticaria (2008), a joint initiative of the Dermatology Section of the European Academy of Allergology and Clinical Immunology, the European Union–funded Network of Excellence, the Global Allergy and Asthma European Network, the European Dermatology Forum, and the World Allergy Organization position paper on CU.[20] Specifically, all subjects were provided with and instructed to take 10 mg of cetirizine twice daily and increase to 4 times daily as needed, 150 mg of ranitidine twice daily, and 10 mg of montelukast daily. Subjects also were provided with rescue prednisone use for intolerable or uncontrolled symptoms. The detailed written action plan included instructions for de-escalation and escalation of therapy based on symptoms. Briefly, subjects were to decrease the use of 1 allergy pill every 7 days if they were symptom free (step down) or increase (step up) if symptoms flared. The recommended order of de-escalation of allergy pills was ranitidine followed by montelukast followed by cetirizine. If at any point a subject's symptoms were "tolerable" but not resolved or symptom free, the subject was instructed to remain on the tolerable treatment regimen until the subsequent clinic visit. At 1 week after enrollment, a telephone interview was completed. At 6 weeks, a physician assessment (physician blinded to treatment arm) was conducted. If subjects had increased their use of rescue prednisone or had intolerable symptoms, an immunomodulatory therapeutic agent, hydroxychloroquine, was offered based on safety profile, cost, and principal investigator preference. At 12 weeks, the study was completed and patients received written notice of their treatment arm and laboratory results.

Data Collection

Blood was collected at enrollment and at 6- and 12-week clinic visits and processed at the institution's clinical laboratory for serum 25(OH)D, calcium, albumin, phosphorus, creatinine, serum urea nitrogen, inorganic phosphorus, and intact parathyroid hormone for study and safety end points. Spot urine for urine calcium also was collected for safety end points. Serum 25(OH)D levels were quantitated using tandem mass spectroscopy. All subjects completed an enrollment questionnaire with demographic information and a study-completion questionnaire. From the medical record, basophil CD203c expression (basophil activation marker associated with autoimmune CU[21]), thyroid-stimulating hormone, free thyroxine, antithyroid peroxidase antibody, antithyroglobulin, antinuclear antibody, and allergy skin prick test results, as available, were obtained. At enrollment, 1 week, 6 weeks, and 12 weeks, all subjects completed the Urticaria Symptom Severity (USS) score assessment[22] and allergy medications for CU were recorded. Briefly, the USS is an established questionnaire comprised of 12 questions that reflect the severity of urticaria, with the total USS ranging from 0 to 93, with a higher score indicating worsening of symptom severity.[22]

Safety Assessments

Safety monitoring was completed throughout the entirety of the study. Specific stopping rules and discontinuation of the study included pregnancy, a serum 25(OH)D level higher than 200 ng/mL, or a serum calcium level higher than 10.3 mg/dL. Safety guidelines

were implemented if the spot urine calcium level was higher than 30 mg/dL or the glomerular filtration rate was lower than 50 mL/min/1.73 m^2.

Statistical Analysis

Although there were no prior studies to accurately predict subjects' CU response to vitamin D_3 treatment, the authors arbitrarily designed this study to a predicted sample size of 38 to be 81.5% powered to detect a 40% difference between the 2 groups for the number of allergy medications used, and they calculated a 10% dropout rate. Subject characteristics for each group were summarized using descriptive statistics. Comparisons of categorical data were performed using the Fisher exact test. Continuous data were compared between the 2 groups using the Wilcoxon rank-sum test. To evaluate whether changes in USS score differed based on subject characteristics, baseline covariates were evaluated in separate repeated measures models, with each model including the covariate of interest, visit time, and the interaction of the covariate and visit time. If the interaction was significant, this would suggest that the change in total USS score differed based on the covariate. The Spearman correlation coefficient was used to determine the association of 25(OH)D levels at all encounters with USS score. A *P* value less than .05 was considered statistically significant. All statistical analyses were performed with SAS 9.3 (SAS Institute, Cary, North Carolina).

Results

Subject Characteristics

Forty-two patients were randomized to treatment with high-dose (4,000 IU) or low-dose (600 IU) vitamin D_3 daily, with 21 patients enrolled in each group. The baseline characteristics of these groups are listed in Table 1. There were no statistically significant differences in the distribution of these baseline characteristics between the 2 study groups ($P > .05$). Subjects were predominantly female, consistent with the known distribution of CU.[3] The race and ethnicity dominance was white, representative of the study geographic population. The average duration of CU was approximately 5 years, although the range was broad. The mean body mass index of this study population was high (overweight to obese), but the body mass index did not differ between treatment groups. Although not statistically significant, there were baseline differences observed between treatment groups. Namely, subjects randomized to the low vitamin D_3 treatment group reported an increased use of vitamin D supplementation before study enrollment, consumed more alcohol, and reported that alcohol worsened hives. Of note, at enrollment, all subjects were counseled about potential effects of alcohol (and nonsteroidal anti-inflammatory drugs) with hives. The frequency of autoantibodies was consistent with the reports from other CU studies.[23] Nine subjects (21%) were positive for antinuclear antibody, 9 (21%) were positive for basophil CD203c expression (>5%), and 8 (19%) were positive for thyroid autoantibodies.

Vitamin D Levels

At enrollment, subjects in the low vitamin D_3 treatment group had a nearly significant ($P = .052$) higher mean serum 25(OH)D level compared with subjects in the high vitamin D_3 treatment group. Specifically, the mean (SE) serum 25(OH)D level was 37.1 ng/mL (3.4 ng/mL) in the low vitamin D_3 supplementation group compared with 28.8 ng/mL (2.2 ng/mL) in the high vitamin D_3 treatment group (Fig 1). Subjects randomized to the high vitamin D_3 treatment group showed significant increases in 25(OH)D level over the course of the study, whereas subjects in the low treatment group showed no change in 25(OH)D levels (Fig 1). At 12 weeks (study completion), 25(OH)D levels were significantly different between groups, with a mean (SE) serum 25(OH)D level of 35.8 ng/mL (2.3 ng/mL) in the low vitamin D_3 treatment group vs 56.0 ng/mL (3.9 ng/mL) in the high vitamin D_3 treatment group ($P = .0003$). There was no correlation between 25(OH)D levels and USS score at baseline ($r = 0.07$, $P = .65$) or at week 12 ($r = -0.13$, $P = .45$).

Table 1
Baseline characteristics of study subjects[a]

	Vitamin D treatment group	
	600 IU/d (n = 21)	4,000 IU/d (n = 21)
Age (y), mean (range)	43.1 (19–79)	43.9 (20–72)
Sex, n (%)		
Male	6 (28.5)	3 (14.2)
Female	15 (71.4)	18 (85.7)
Body mass index, mean (SD)	30.5 (6.32)	30.6 (9.42)
Duration of hives (y), mean (range)	5.4 (0.3–25)	5.3 (0.2–20)
Race, n (%)		
White	19 (90.4)	20 (95.2)
African American	1 (4.7)	1 (4.7)
Asian	1 (4.7)	0 (0)
Highest grade level achieved, n (%)		
High school	2 (9.5)	4 (19.0)
College or greater	19 (90.4)	17 (80.9)
Vitamin D supplementation before study, n (%)	9 (42.8)	4 (19.0)
Vitamin D deficiency, serum 25(OH)D <20 ng/mL, n (%)	3 (14.3)	5 (23.8)
Consumed >12 drinks of alcohol in past month, n (%)	9 (42.8)	3 (14.2)
Alcohol reportedly makes hives worse, n (%)	7 (33.3)	4 (19.0)
Former smoker (>100 cigarettes in lifetime), n (%)	11 (52.3)	10 (47.6)
Current smoker, n (%)	5 (23.8)	6 (28.5)
Any past trips to ED for hives, n (%)	6 (28.5)	7 (33.3)
ANA positivity (>1:40 titer), n (%)	4 (19.0)	5 (23.8)
CD203c positivity (>5% expression), n (%)	5 (23.8)	4 (19.0)
Thyroid disease, n (%)	2 (9.5)	7 (33.3)
Any thyroid autoantibodies, n (%)	4 (19.0)	4 (19.0)
Positive allergy skin prick test result, any positive, n (%)	7 (33.3)	9 (42.8)

Abbreviations: ANA, antinuclear antibody; ED, emergency department; 25(OH)D, 25-hydroxyvitamin D.
[a]No statistically significant differences between groups ($P > .05$).

Medication Use and USS Score

The number and type of medications taken for hives were recorded at enrollment, 1 week, 6 weeks, and 12 weeks. There was

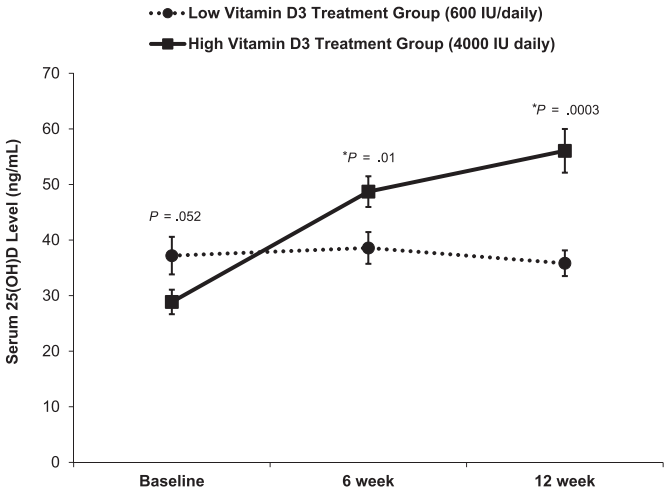

Figure 1. Serum 25-hydroxyvitamin D (25[OH]D) in the high and low vitamin D_3 treatment groups over time. Data are presented as mean and SE (*bars*), with statistical significance noted between treatment groups.

Table 2
Medication use for chronic urticaria in study subjects

	Vitamin D_3 treatment group		*P* value
	600 IU/d	4,000 IU/d	
Total number of allergy pills for CU, mean (SD)			
Baseline	4.6 (3.2)	2.8 (2.6)	.056
1 wk	5.7 (2.0)	5.5 (1.7)	.93
6 wk	5.1 (2.2)	5.4 (2.2)	.68
12 wk	4.9 (2.8)	5.0 (2.9)	.96
Medication use in past week at baseline, n (%)			
Any H_1 receptor antagonist	14 (66.7)	13 (61.9)	1.00
Any H_2 receptor antagonist	11 (52.4)	6 (28.6)	.24
Any leukotriene antagonist	6 (28.6)	2 (9.5)	.24
H_1 and H_2 receptor antagonists	8 (38.1)	5 (23.8)	1.00
H_1 receptor and leukotriene antagonist	6 (28.6)	2 (9.5)	.24
H_1 and H_2 receptor and leukotriene antagonists	3 (14.3)	2 (9.5)	1.00
Prednisone	4 (19.0)	5 (23.8)	1.00
Medication use in past week at 12 wk, n (%)[a]			
Any H_1 receptor antagonist	15 (88.2)	19 (90.5)	1.00
Any H_2 receptor antagonist	11 (64.7)	15 (71.4)	.73
Any leukotriene antagonist	14 (82.4)	16 (76.2)	.71
H_1 and H_2 receptor antagonists	10 (58.8)	15 (71.4)	.50
H_1 receptor and leukotriene antagonist	13 (76.5)	15 (71.4)	1.00
H_1 and H_2 receptor and leukotriene antagonists	9 (52.9)	13 (61.9)	.74
Prednisone	4 (23.5)	2 (9.5)	.37
Hydroxychloroquine	5 (29.4)	7 (33.3)	1.00

Abbreviation: CU, chronic urticaria and/or angioedema.
[a]At week 12, there were 17 subjects in the low vitamin D_3 treatment group and 21 in the high vitamin D_3 treatment group. At baseline, there were 21 subjects in each treatment group.

no difference in the primary outcome of number of allergy pills used on a daily basis between treatment groups at 12 weeks ($P = .96$; Table 2). Table 2 presents the distribution of the allergy medication classes taken at baseline and week 12 between the low and high vitamin D_3 treatment groups. There also was no difference in the number of subjects using the immunomodulator hydroxychloroquine ($P = 1.00$) or the number of subjects using prednisone ($P = .29$; Table 2).

At enrollment, there was no difference in total USS score between groups, but there were differences in total USS scores over time and between treatment groups (Fig 2). One week after enrollment, after the institution of a standardized triple-drug therapy (cetirizine, ranitidine, and montelukast), there was a 33% decrease in total USS score, regardless of vitamin D_3 treatment group randomization ($P = .001$). Then, subjects randomized to supplementation with high vitamin D_3, but not low vitamin D_3, showed a further, significant decrease (40%) in total USS score at study completion (12 weeks) compared with total USS score at 1 week after enrollment ($P = .02$). Subjects in the high vitamin D_3 treatment group showed a decreased total USS score (mean ± SE, 15.0 ± 2.9) compared with the low vitamin D_3 treatment group (24.1 ± 4.0), but this did not reach statistical significance ($P = .052$).

To delineate the specific symptoms or severity that were potentially driving these differences in total USS score between vitamin D_3 treatment groups at 12 weeks, results of the individual questions on the 12-point USS questionnaire were analyzed (Fig 3). Interestingly, subjects in the high vitamin D_3 treatment group reported decreased body distribution of hives on an average day ($P = .0033$), decreased body distribution of hives on the worst day ($P = .0085$), and decreased number of days with hives ($P = .03$) compared with subjects in the low vitamin D_3 treatment group (Fig 3). There also were trends toward decreased interference with sleep ($P = .07$) and degree of pruritus experienced ($P = .09$). There were no differences found in the average or maximum hours of hives experienced each day or in the number of antihistamines used daily. There also was no difference in the number of prednisone pills used daily or reports of interference of hives with work, school, or social life, although these question items were generally scored low.

Post Hoc Analysis of Effect of Baseline Characteristics in Predicting USS Response over Time

Baseline characteristics (Table 1) were considered covariates and analyzed by separate repeated measures models, irrespective of treatment group. Of these potential covariates, having any trip to the emergency department for hives ($P = .02$), grade level

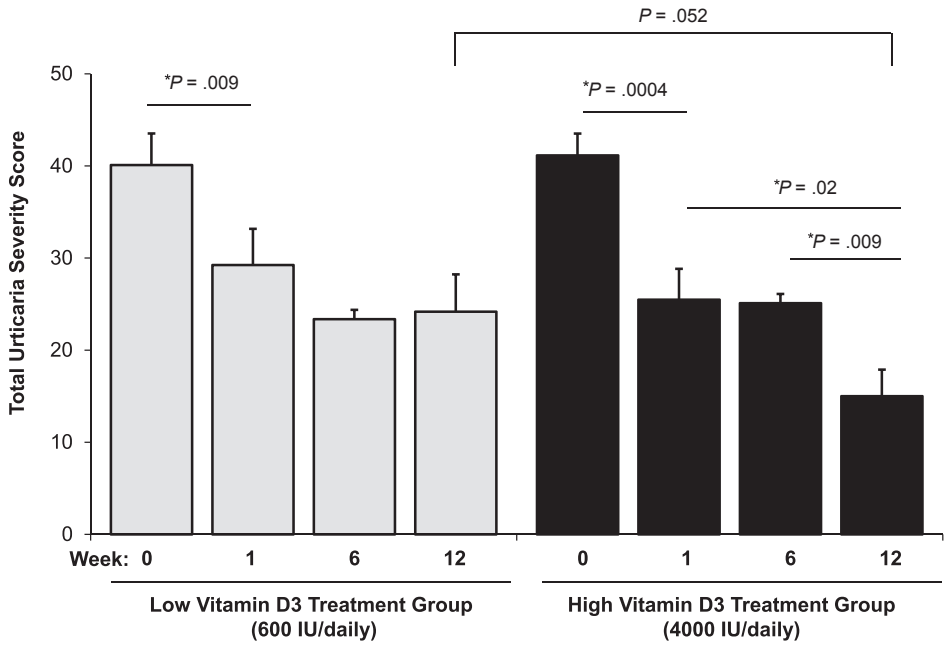

Figure 2. Total Urticarial Symptom Severity score over time in the high and low vitamin D_3 treatment groups. Data are presented as mean and SE (*bars*), with statistical significance denoted by *lines* and *asterisks*.

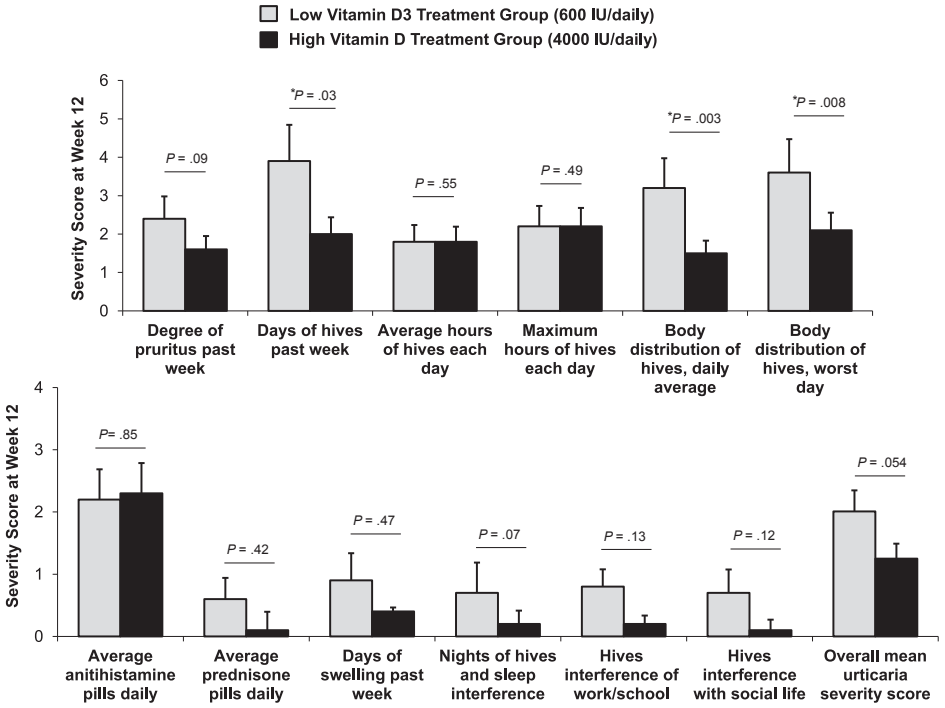

Figure 3. Individual Urticarial Symptom Severity score components shown between high and low vitamin D_3 treatment groups at week 12. Data are presented as mean and SE (*bars*), with statistical significance denoted by *asterisks*.

dichotomized as no college vs college ($P = .0033$), and baseline 25(OH)D levels dichotomized as vitamin D deficiency (<20 vs ≥20 ng/mL; $P = .038$) were found to be predictive of changes of USS score. However, the number of subjects in several of these group distinctions was small (Table 1), and statistical significance was lost when accounting for multiple comparisons for the covariates, including emergency department visits and vitamin D deficiency. There were no significant relations found for other potential covariates, including smoking status, thyroid autoantibodies, CD203c expression, any autoantibodies, body mass index, sex, alcohol use, duration of hives, prior use of vitamin D supplementation, and allergy skin test positivity.

Safety and Compliance

Vitamin D supplementation was well tolerated and no significant adverse events occurred. All subjects in the high vitamin D_3 treatment group completed the 12-week study, whereas 4 subjects in the low vitamin D_3 treatment group withdrew from the study. One withdrew because of pregnancy, and the remaining 3 withdrew for unknown reasons. There were 3 subjects (2 in the low treatment group and 1 in the high treatment group) with a 1-time spot urine calcium level higher than 30 mg/dL, which resolved on repeat measurement. There was 1 subject with a glomerular filtration rate lower than 50 mL/min/1.73 m^2 in the low vitamin D_3 treatment group, which showed resolution at repeat measurement. There was no evidence of hypercalcemia. Pill counts for vitamin D_3 supplements showed excellent compliance, with only 1 subject in the low vitamin D_3 treatment group showing less than 80% compliance.

Discussion

To the authors' knowledge, this is the first randomized, double-blinded, prospective interventional study demonstrating the potential beneficial effects for supplemental vitamin D_3 at 4,000 IU/d as a safe, add-on therapy in the treatment of CU for symptom relief. However, vitamin D_3 supplementation did not decrease the primary outcome of allergy medication use for CU. After accounting for standardization of medical therapy, high-dose supplementation of vitamin D_3 improved total USS scores over time in subjects with CU, whereas this benefit was not found with low-dose vitamin D_3 supplementation. This improvement was irrespective of baseline vitamin D status because the 25(OH)D level was not a criterion for enrollment. Therefore, these findings suggest that higher dosing of supplemental vitamin D_3 might be potentially beneficial and safe in CU, irrespective of a patient's vitamin D status. These randomized clinical study findings of a beneficial response with vitamin D support observations by others that vitamin D supplementation alleviates symptoms of CU in patients with low vitamin D levels.[14,24]

Because of the long half-life of vitamin D_3 (cholecalciferol), the 12-week study duration was designed to allow time for the appropriate attainment of a steady-state 25(OH)D while using recommended safe dosing regimens[10,15,19,22] that are readily available to the public. This design led to significant increases in serum 25(OH)D levels in the high vitamin D_3 treatment group by week 12 (Fig 1). Although there was no true placebo group, the low vitamin D_3 treatment group arguably served as an appropriate control because 25(OH)D levels remained unchanged. Given the slope of the increase in 25(OH)D in the high vitamin D_3 treatment group, it is possible that if the study length had been extended, there might have been further improvements in the USS score. Namely, vitamin D levels began to separate between groups at week 6 and most notably by week 12. Indeed, the significant decrease in USS score in the high vitamin D_3 add-on treatment group occurred from weeks 6 to 12, which was marked by a 40% decrease in the USS score. There was no further change in the USS score from weeks 1 to 6 or from weeks 6 to 12 in the low vitamin D_3 treatment group (Fig 2).

The total USS score was decreased in subjects treated with add-on high vitamin D_3 supplementation over time, and the difference in total USS score between the high and low treatment groups at

week 12 were nearly significant ($P = .052$; Fig 2). Data further suggested that high-dose vitamin D_3 supplementation might lessen the distribution of hives on the body and decrease the total number of days per week of hives. The authors had predicted that vitamin D_3 supplementation would lower the medication burden, but this was not observed. There was a nearly significant difference ($P = .056$) in baseline medication use, with the high vitamin D_3 treatment group on less medications at enrollment compared with the low vitamin D_3 treatment group, which might have skewed the findings. Next, trends toward symptom alleviation were observed for several other indices comprising the USS score (Fig 3); however, the quality-of-life outcome indices did not differ between groups. This discrepancy might be explained by subjects not scoring these quality-of-life measurements high at baseline or it might represent the need to use other quality-of-life questionnaires in future assessments. Nonetheless, these observations suggest the need for larger, longer, and multicenter studies to further understand the role of vitamin D in CU. Next, 25(OH)D levels and USS score were not correlated at any time points. The explanation for this observation is not entirely clear. High-dose vitamin D_3 supplementation might have produced important end-organ or downstream effects that cannot be completely ascribed to measured 25(OH)D levels. Vitamin D receptor gene expression and the expression of an enzyme important in vitamin D synthesis (cytochrome P450, family 24, subfamily A, polypeptide 1) was investigated in subjects' peripheral blood mononuclear cells at baseline and visit 3, but no significant associations were found (data not shown).

Multiple immunoregulatory effects of vitamin D by direct and indirect regulation of the immune system resulting in differentiation of multiple cells types and various anti-inflammatory properties have been described.[7] In atopic dermatitis, vitamin D has been recognized for its regulation and promotion of cathelicidin expression in the skin.[25] The etiology of CU is multifactorial and is likely traced to the complex immunoregulation milieu in the skin and peripheral tissues. Others have reported that $CD141^+$ dermal dendritic cells, which produce interleukin-10, induce regulatory T cells that might suppress skin inflammation.[26] Moreover, vitamin D_3–induced $CD141^+$ blood dendritic cells produce significantly larger amounts of interleukin-10 than $CD141^-$ dendritic cells.[26] In general, there is growing evidence supporting a role for vitamin D inducing T-regulatory cells,[27,28] and this mechanism might be important in understanding the role of vitamin D in CU. Another potential mechanism underlying the pathogenesis of CU is autoantibodies and thyroid autoantibodies. However, the authors did not find any interactions to support a differential response to vitamin D_3 therapy based on any autoantibody measurement as described in the "Results" section.

There was a 33% decrease in urticaria symptoms after 1 week of a standardized "triple-drug" therapy with higher dosing of cetirizine (2–4 times daily), ranitidine twice daily, and montelukast once daily. This significant and rapid alleviation of symptoms warrants highlighting. This treatment approach targets multiple mediators involved in CU pathogenesis.[3] H_1 and H_2 receptor antagonists have been used alone or in combination for the treatment of urticaria.[29] Several studies also have shown a significant benefit of the combination of H_1 receptor antagonist with leukotriene antagonists.[2,29,30] Khan and Lynch[29] reported a 48% improvement of urticaria symptoms when montelukast was added to H_1 and H_2 receptor antagonists. The present study supports the use of triple-drug therapy with H_1 and H_2 receptor and leukotriene antagonists to rapidly alleviate symptoms in patients with difficult-to-treat CU. However, it is not clear whether all 3 drug therapies were required to achieve symptom alleviation or whether 1 or 2 might be all that is required to improve symptom control. Thus, a prospective study may be warranted to investigate the impact of combination triple-drug therapy with H_1 and H_2 receptor and leukotriene antagonists in patients with CU.

There are several other limitations to this study. This sample consisted predominately of white female patients, which was representative of the geographic study area, but these findings may limit the applicability to other racial and ethnic populations. The authors may have underestimated the role of vitamin D because rates of vitamin D deficiency within African American and Hispanic populations are high, with vitamin D deficiency potentially affecting more than half of African Americans.[7] Another limitation to overgeneralizing the present findings is the overweight to obese habitus of the study population. Obesity is a well-recognized risk factor for vitamin D deficiency.[7]

In summary, add-on therapy with high-dose vitamin D_3 (4,000 IU/d) to subjects with CU resulted in a decrease in urticaria severity symptoms over time. This difference was most notable at 6 to 12 weeks of therapy. Triple-drug combination therapy with H_1 and H_2 receptor antagonists and leukotriene antagonist with any dosing of vitamin D resulted in a rapid decrease in urticaria symptoms. Collectively, add-on supplementation with high-dose vitamin D_3 could be considered a potentially safe and inexpensive immunomodulator to benefit patients with CU.

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