THE EFFICACY OF VITAMIN D SUPPLEMENTATION TO REDUCE URTICARIA: SYSTEMATIC REVIEW

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Abstract

Urticaria is a condition of skin disorders. Based on the duration of symptoms, chronic urticaria occurs > 6 weeks. Chronic urticaria is caused by endogenous factors unrelated to an external physical stimuli. Vitamin D is an immunoregulatory hormone that activates innate and adaptive immune responses. A literature search was conducted in PubMed, ScienceDirect, SpringerLink, and ProQuest with a publication year limit of 2011–2023. The keywords used were "vitamin D deficiency and urticaria" and "vitamin D and urticaria". The present review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020. This review included four case reports from 2247 articles. All cases showed a low risk of bias. Two studies found were case-control studies that met the inclusion criteria. The Johanna Briggs Institute checklist was used to assess the risk of bias. The data were presented descriptively. Chronic spontaneous urticaria (CSU) is more common in women than men.. Patients CSU had < 30 ug/ml vitamin D level and experienced reduced urticarial symptoms after receiving vitamin D (p < 0, 001). Vitamin D2 supplement at 20,000 IU for 6 weeks alleviated urticarial symptoms in patients CSU. Alongside vitamin D, antihistamines, and corticosteroid were also recommended as a comination therapy, leading to a better clinical outcome. Vitamin D supplementation reduces symptoms in patients with CSU. A combination therapy with antihistamines and corticosteroid should be considered in clinical practice.

Keywords

Vitamin D deficiency, Chronic spontaneous urticaria

Introduction

Urticaria is an erythematous plaques with firm borders and itching sensations that are transient, and may occur on the entire skin surface.[1] Urticaria generally occurs during adulthood where women experience urticaria symptoms more often than men.[2] Based on duration of symptoms, urticarial is categorized into acute and chronic urticaria. Acute urticaria usually resolves within six weeks, while chronic urticaria persists for over six weeks.[3]

Chronic urticaria is not a life-threatening disease. However, if this condition is not adequatedly managed, it can affect a person's quality of life. Chronic urticaria is usually caused by endogenous factor unrelated to an external physical stimuli.[4] The etiology in cases of chronic urticaria is 55% idiopathic and 45% autoimmune. The pathogenesis of urticaria is a complex process involving mass cell activity, basophil cells, Th1/Th2 macrophage cell imbalance, and regulatory T cell function defects that contribute to the systemic inflammatory process.[5]

Previous studies have shown an association between vitamin D and the incidence of urticaria. Vitamin D is an immunoregulatory hormone important in activating innate and adaptive immune responses. This activation occurs at the nucleus and plasma membrane receptors of vitamin D on epithelial cells, mast cells, monocytes, macrophages, T cells, B cells, and dendritic cells.[6] In the innate immune system response, vitamin D improves antimicrobial defenses by stimulating the release of antimicrobial proteins such as chatelicidin and human b-defensin. [7] Meanwhile, in the acquired immune system response, the concentration of 25(OH)D3 in serum can activate T cells to release the enzyme CYP27B1, which functions to convert 25(OH)D3 into 1,25(OH)2D3, the active form of vitamin D.[6,7] Vitamin D can suppress dendritic cell maturation and inhibit Th1 cell proliferation by decreasing Th1 cytokine secretion, blocking Th17 proinflammatory cytokine secretion, and decreasing IL-2 production. In addition, vitamin D also inhibits the function of B lymphocytes in producing immunoglobulin E (IgE).[7]

In their study, Nasiri-Kalmarzi et al. showed that changes in vitamin D concentrations in the body can be a risk factor for the progression of chronic urticaria symptoms. There is a relationship between vitamin D and allergic diseases such as food allergies, rhinosinusitis, asthma, atopic dermatitis, and chronic urticaria. A case-control study conducted by Boonpiyathad et al. concluded that chronic urticaria was associated with low 25(OH)D concentrations and the highest prevalence in patients with vitamin D4 deficiency.[4]

In this systematic review, we will seek a systematic review of whether vitamin D supplementation can improve urticaria symptoms in patients with vitamin D deficiency and whether there is an association between patients with urticaria symptoms and vitamin D deficiency.

Materials and Methods

Study aim

This study aimed to find evidence that supplement vitamin D can reduce urticarial in patient with hypo vitamin D systematically. Moreover, this study seeks to explain the correlation between vitamin D deficiency and urticaria.

Determining clinical questions

Clinical questions

PICO

P: Patient with vitamin D deficiency

I: vitamin D supplement

C: Placebo

O: urticarial symptoms

Clinical questions: Does vitamin D supplementation reduce urticaria symptoms in patients with vitamin D deficiency?

Type of questions: interventional/ therapy

Research design: Systematic Review

Methods

This study used to present review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020. All the articles used data have already been published.

Eligibility

We used a systematic search of case control studies. Urticaria is one of the clinical manifestations of hypersensitivity. The urticaria in this study was chronic urticaria that often recurred for six weeks. The patient was also deficient in a vitamin D, with a vitamin D level <30 ug/mL. The publication year has a limitation period of 2011–2023. Studies using patients under 17 years old, patients with comorbidities, and pregnant patients were excluded. Also, studies written in languages other than English, without full text available, and with non-human subjects were excluded. Duplicate articles were resolved before title and abstract screening.

Search Strategy and Selection of Studies

We used a comprehensive systematic database search on September 20, 2023, in PubMed, SpringerLink, Science Direct, and Proquest. Relevant articles may be included by manual search or advance search. The keywords used in the search are “"Deficiency vitamin D AND urticaria” and “ Vitamin D AND Urticaria”. Titles and

abstracts of the articles to identify potentially eligible studies were independently screened for full-text review.

Article Extraction

We independently extracted relevant articles using a studies using a structured and standardized form. The following information was extracted: first author's name, publication year, patient's age, Vitamin D levels, dose ef vitamin D supplement, and outcome after therapy during follow-up.

Quality Assessment

We assessed the risk of bias using the Joanna Briggs Institute (JBI) critical appraisal checklist for case control studies.

Results

Study Selection

The search resulted in 2247 records, of which 2112 are irrelevant topic. And 26 articles was not use English. After title and abstract screening, 86 articles had inappropriate target samples, seven articles duplicate records, four inappropriate study design, seven articles were not retrieved. After that, we screened five articles with full text and the result: 2 articles did not use vitamin D supplement as a treatment, and 1 article was not a scientific publication. This systematic review included two published articles after the full-text assessment. PRISMA flow diagram presents the study selection process and the reasons for exclusion.

Quality assessment and Study Characteristic

All included case reports were assessed using a JBI critical appraisal checklist for case-control studies. The summarized critical appraisal checklist shows that the risks are generally low.

Clinical Characteristic

Chronic urticaria is urticaria that occurs for six weeks. In the study, patients experienced symptoms from 13 weeks to 42 weeks. The age range of patients who experience chronic urticaria is most common among adults. This is following the inclusion criteria of this systematic review. The age range in the study from 23 years to 55 years. Urticaria was often in women than men. All urticaria patients got vitamin D level examination. Vitamin D levels are divided into three categories: insufficiency (20–30 ng/mL), deficiency (<20 ng/mL), and insufficiency (<10 ng/mL). Patients in the study did not have comorbid disease factors that could risk reducing vitamin D levels, and there was no previous atopic history.

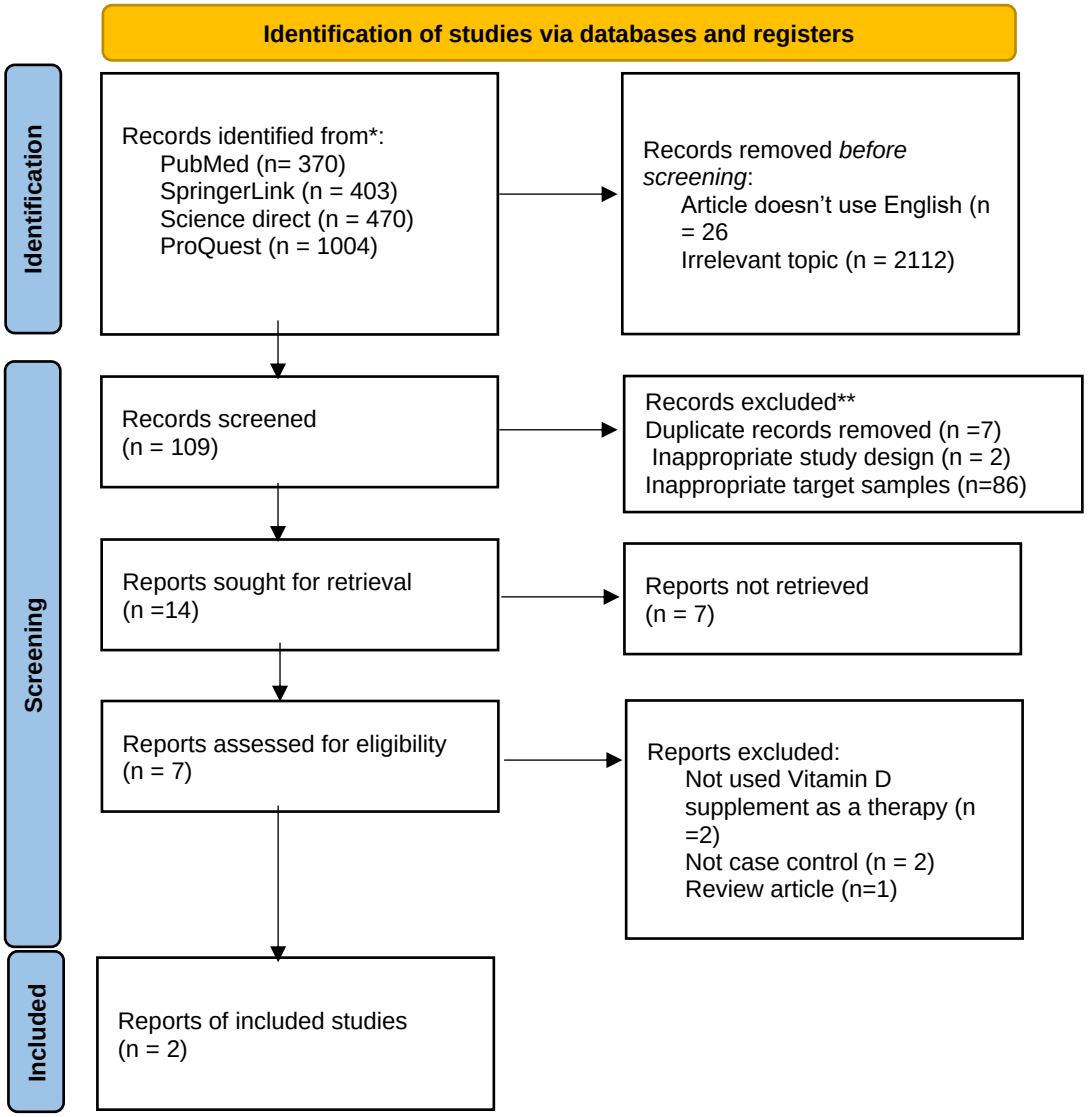

Figure 1. PRISMA Flowchart Body[8]

Table 1. Population, vitamin D levels before after treatment, outcome after treatment

Study,Year	Study design	Population (years)		Vitamin D levels (ng/ml)		Vitamin D supplement dosage			
		Control	CSU	Control	CSU	Control	CSU	Outcome	P value
Boonpiyatdh et al[4], 2016	Prospe ctive case control	40 Mean age 39±16 years	60 Mean age 39±16 years	Median 37 (33-52)	Median 13 (8-29) Vitamin D status: insufficiency 32% →20-30 deficiency 41% →20 deficiency 9% → <10	Placebo	Vit D2 20.000 IU	Median ratio of Levels vitamin D in CSU group 39 (28-62) ng/ml Median value of Levels vitamin D in control group 29 (20-55) ng/ml Median value UAS7 score 15 (2-44) Median value DLQ1 score 7 (1-27)	<0.001
Rasool et al[9], 2015	Rando mized case control	130 Mean (45.12 ± 7.65)	147 mean ± SD; 42.83 ± 8.52) Stratified of Vit D levels into 4 groups: Group 1 *Severe Deficiency* (<10 ng/mL) Group 2 *Deficiency* (10-20 ng/mL) Group 3 *Insufficiency* (20-30 ng/mL) Group 4	Mean levels group1: 7.310 ± 0.52 Group2: 15.26 ± 0.47 Group3: 23.98 ± 0.46 Group4: 47.78 ± 2.23	Mean levels Subgroups a: 16.98 ± 1.43 b: 17.04 ± 1.54 c: 18.95 ± 1.42	Placebo	Subgroups a: 48 patients got Vit D3 60.000 IU Subgroups b: 42 patient got Hydroxyzine 25mg/day for 6 weeks and Deflazacort 6mg/day for 6 weeks Subgroups c 57 patients got Vit D3 60.000 IU + antihistamin + corticosteroid	Mean value of vitamin D levels after treatment: Subgroup a: 56.74 ± 3.76 Subgroup b: 16.44 ± 1.50 Subgroup c: 41.73 ± 2.85 (p<0.0001) Mean value of VAS Score and 5-D Itchy Score: Significantly decreased in VAS in every groups	<0.0001

	Sufficiency (>30 ng/mL) randomized into 3 subgorups: Subgroups a (n:48) Subgroups b (n:42) Subgroups c (n:57)	(Hydroxyzine 25mg/day for 6 weeks and Deflazacort 6mg/day for 6 weeks + 60.000 iu /weeks for 4 weeks)	Significantly decreased in 5D itch score in every groups

Discussion

Urticaria is a erythematous plaque with firm borders, a temporary sensation of itching, which can occur on the entire surface of the skin.[1] The prevalence of urticaria generally occurs in adulthood. Chronic urticaria is not a life-threatening disease. However, if the condition is not treated properly, it can affect a person's quality of life. By using scientific journal reviews in searching 4 databases, 2 scientific studies were obtained with case-control studies with search limits from 2011–2023. It is expected that research in the past decade is the latest evidence that can be used as a reference.

Chronic urticaria is a type of urticaria usually caused by endogenous factors dan is unrelated to an external physical stimuli.[3] Vitamin D is an immunoregulatory hormone that important in activating innate and adaptive immune responses.[3] Previous studies, that vitamin D deficiency can trigger urticarial symptoms. In the study of patients with chronic urticaria, several examinations were carried out to rule out the possibility of precipitating factors outside of vitamin D associated with atopic disorders, such as the skin prick test, eosinophil examination, ANA-test (anti-nuclear antibody positive), and ASST (autologous serum skin test positive). In Roosol's study, two scores were used to assess the study's outcome: the 5-D scale and the VAS scale. The 5-D scale is a multidimensional questionnaire that assesses five aspects of pruritus: degree, duration, direction, disability, and distribution per 24 hours. 5-D scores range between 5 (no pruritus) and 25 (the most severe pruritus).[10] VAS was used as a method of pruritis assessment in CSU patients. Alternatively, UAS7 and DLQ1 are also applicable to assess pruritus symptoms in urticarial patients, as previously investigated by Boonpiyatdh et al.

In the study of Boonpiyatdh et al., vitamin D levels were examined in sample of 100 participants comprising, 40 control, and 60 CSU patients. In controls, vitamin D levels were higher than CSU, with a median of 37 ng/ml. CSU patients were futher into three categories: insufficiency with vitamin D levels of 20–30 ng/ml, deficiency with vitamin D levels <20 ng/ml, and severe deficiency with vitamin D levels <10 ng/ml. Three categories of CSU patients received vitamin D2 supplement therapy at 20,000 IU for six weeks. CSU patient experienced improvement in urticaria symptoms assessed through UAS7 and DLQ1. From the median UAS7 scores, 27 decreased to 15 ($p<0.001$). Meanwhile the median DLQ1 ranged from 12 to 7 ($p<0.001$). This finding implied that vitamin D supplementation can reduce urticarial symptoms. In addition, the outcome assessed was also the improvement of vitamin D levels after therapy, which increased to a median of 39 ng/ml from a median of 13 ng/ml.[4]

Based on a study by Rasool et al, which is using a randomized case-control study with a sampling of 277 patients, 130 control patients, and 147 CSU patients, Both CSU and control patients were examined for vitamin D levels. Control patients were divided into four groups with vitamin D levels described through mean values: group 1: 7.310 ± 0.52; group 2: 15.26 ± 0.47; group 3: 23.98 ± 0.46; and group 4: 47.78 ± 2.23. After being given a placebo, there was no significant change in vitamin D levels. CSU patients were divided into four groups after checking vitamin D levels: Group 1 with severe deficiency (<10 ng/mL), Group 2 with deficiency (10-20 ng/mL), Group 3 with insufficiency (20-30 ng/mL), and Group 4 with sufficiency (>30 ng/mL). Then the CSU group was randomly divided into subgroups A, B, C patients to receive different treatments.[9]

In subgroup A, 48 patients received D3 60,000 IU therapy. In subgroup B, 42 patients received Hydroxyzine 25 mg/day for six weeks and Deflazacort 6 mg/day for six weeks. In subgroup C, 57 patients received Hydroxyzine 25 mg/day for six weeks and Deflazacort 6 mg/day for six weeks + 60,000 IU/weeks for four weeks, as many as 57 patients. Improved vitamin D levels were assessed as the outcome. Of the three treatments, subgroup A experienced a significant increase with a mean value of 16.98 ± 1.43 to 56.74 ± 3.76 ($p<0.0001$). In addition, pruritus was also assessed using the 5-D score and VAS. The 5-D score and VAS significantly decreased after therapy. Furthermore, VAS scores were markedly different among the subgroups, with subgroup A as the reference ($p = 0.016$ and $p<0.0001$). The VAS score in subgroup C compared to subgroup B showed a significant difference ($p = 0.0203$). The 5-D itch score in subgroup A compared to subgroups B and C showed a significant difference ($p = 0.0116$ and $p<0.0001$). The 5-D itch score of subgroup C compared to subgroup B was also significantly different ($p=0.0382$). This shows that combination therapy is better in reducing urticaria symptoms.[9]

Conclusion

Chronic urticaria is not a life-threatening disease but a disease that can interfere with the quality of human life with symptoms of itching. There is a significant relationship between decreased vitamin D levels and urticaria. In the future, research and journal reviews using clinical trial studies are needed increase the value of higher-quality evidence to be applied to patients.

Competing Interests

None

Acknowledgments

Family and Sakinah Islamic Hospital, Mojokerto

References

1. Kayiran ME, Akdeniz N. Diagnosis and treatment of urticaria in primary care. North Clin Istanb 2019;6(1):93-99
2. Li Y, Cao Z, Guo J, Li Q, Su J. Effects of serum vitamin D levels and vitamin D supplementation on urticaria: a systematic review and metaanalysis. International Journal of Environmental Research Public Health 2021; 18(9), 4911
3. Rorie A, Poole JA. Vitamin D supplementation: a potential booster for urticarial therapy. Expert Review of Clinical Immunology 2014; 10 (10), 1269-1271
4. Boonpiyathad T, Pradubpongsa P, Sangasapaviriya A. Vitamin D supplements improve urticarial symptoms and quality of life in chronic spontaneous urticaria patients: A prospective case-control study. Dermato-endocrinology, e1; January 2014; Landes Bioscience.
5. Mony A, Chandrashekar L, Rajappa M, Munisamy M, Sahoo JP, Selvarajan S. Effect of vitamin D supplementation on clinical outcome and biochemical profile in South Indian population with vitamin D-deficient chronic urticarial – A randomized double-blind placebo controlled trial. Clinica Chimica Acta 2020; 504, 1-6
6. Mohamed AA, Hussein MS, Salah EM, Eldemery A, Darwish MM, Ghaith DM, et al. Efficacy and safety of active vitamin D supplementation in chronic spontaneous urticaria patients. Journal of Dermatological Treatment 2020; 1-22
7. Tuchinda P, Kulthanan K, Chularojanamontri, Arunkajohnsak, Sriussadaporn S. Relationship between vitamin D and chronic spontaneous urticaria: a systematic review. Clinical and Translational Allergy 2018; 8:51
8. the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) . Flow Diagram For Systematic Review 2020. Avalaible on: http://prisma-statement.org/documents/PRISMA_2020_checklist.docx
9. Rasool, Roohi, Khalid Z M, Irfan A S, Qayser Y, Imtiyaz A B, et al. Chronic Urticaria meritz serum vitamin D evaluation and supplementation: a randomized case control study. *World Allergy Organization Journal*. 2015; 8:15
10. Elman S, Hynan L S, Gabriel V, Mayo M J. The 5-D Itch Scale: A New Measure Of Pruritus. *Br J Dermatol.* 2010; 162(3): 587–593.