SYSTEMATIC REVIEW

Philippine Journal of Allergy, Asthma and Immunology

The Clinical Efficacy of Vitamin D Supplementation for Allergic Rhinitis: A Systematic Review and Meta-analysis

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ABSTRACT

Objective: To conduct a systematic review and meta-analysis of all controlled studies of vitamin D for treating allergic rhinitis to determine the efficacy of vitamin D supplementation to patients with allergic rhinitis.

Methodology: A systematic search was conducted using PubMed, Cochrane, CENTRAL databases, and Google Scholar for articles published in journals from 2010 to February 2023. The change from baseline in the Total Nasal Symptom Score (TNSS) was the main outcome. A random-effects model was used to pool the results of the included studies. Separate subgroup analyses were performed for studies using TNSS-12 and TNSS-15.

Results: Eight studies were included, including seven randomized controlled trials and one prospective analytical observational study. The combined sample size across all studies was 635 participants, including adults and children. Studies utilizing the TNSS-12 and TNSS-15 scales consistently demonstrated that the group receiving vitamin D supplementation had lower severity scores than the control group. The standardized mean difference (SMD) showed a statistically significant improvement in TNSS compared to the baseline, with an average SMD of 6.27 (95% CI, 3.96 to 8.59).

Conclusion: Vitamin D supplementation significantly improves nasal symptom scores of allergic rhinitis. It can be considered an adjunctive therapy in the management of allergic rhinitis. However, larger-scale studies are needed to confirm this conclusion.

Keywords: Vitamin D, supplementation, adjunct, allergic rhinitis

INTRODUCTION

The most prevalent kind of chronic rhinitis, accounting for up to 30% of cases worldwide, is allergic rhinitis (AR). Based on the 2008 National Nutrition and Health Survey (NNHS), the overall prevalence of allergic rhinitis in the Philippines is 20%.[1] Allergic rhinitis is characterized by sneezing, itching, rhinorrhea, and nasal congestion, which can affect daily activities and quality of life. The standard treatment for allergic rhinitis includes antihistamines, intranasal corticosteroids, and immunotherapy.[2,3] However, the current lifestyle has led to people spending more indoors, leading to less sun exposure and less cutaneous vitamin D production. Based on the NNSH 2018, 60.6% of Filipino children aged 6-12 years were found to have vitamin D deficiency and insufficiency.[4]

Vitamin D is a pleiotropic hormone. Apart from controlling the metabolism of calcium and phosphorus, vitamin D exhibits potent immunomodulatory properties.Vitamin D inhibits T cell proliferation. It facilitates the induction of Foxp3+ T regulatory (T reg) cells and suppresses the development, differentiation, proliferation, and survival of Th17 cells in allergic airway inflammation. Vitamin D induces the switch from Th1 to Th2 and enhances the Th2 cell development. Furthermore, vitamin D suppresses plasma cell differentiation, immunoglobulin production, particularly IgE release, and the proliferation and death of activated B cells.

These data indicate there is a relationship between vitamin D and allergic rhinitis morbidity as all these factors mentioned decrease allergic rhinitis-related inflammation.[5,6]

Several studies have investigated the clinical efficacy of vitamin D adjuvant therapy in allergic rhinitis; however, the results are still controversial. Among them, two articles reported a negative association between vitamin D levels and AR,[7,8] while 2 reported a positive association[9,10] and another 2 reported no association between vitamin D levels and AR.[11,12] Therefore, we conducted a systematic review and meta-analysis with research published in the last 13 years to determine the overall efficacy of vitamin D adjuvant therapy in allergic rhinitis. To maintain clarity and coherence in this study, the terms "vitamin D supplementation" and "vitamin D adjuvant therapy" are used interchangeably to denote the administration of vitamin D as a therapeutic intervention adjunctive to standard treatment protocols.

Meta-analysis and systematic review are powerful tools for synthesizing and analyzing the available evidence from multiple studies. Meta-analysis involves combining the results of multiple studies to obtain an overall estimate of the effect size. In contrast, systematic review involves a comprehensive and rigorous search of the literature, followed by critical appraisal and synthesis of the evidence. A meta-analysis and systematic review of RCTs investigating the clinical efficacy of vitamin D adjuvant therapy in allergic rhinitis can provide a comprehensive and objective assessment of the available evidence.

This meta-analysis and systematic review will offer clinicians and patients a more comprehensive understanding of the clinical efficacy of using vitamin D as an adjunct therapy for allergic rhinitis. The results may influence clinical practices and guide future research in this area.

LITERATURE REVIEW

An increasing number of epidemiological studies have linked vitamin D levels with allergic rhinitis.

In a meta-analysis by Kim YH, the relationship between vitamin D levels and the incidence and prevalence of allergic rhinitis was investigated in 21 data sets extracted from 19 studies. They found no significant relationship between the incidence of allergic rhinitis and vitamin D levels. In children, the current vitamin D levels were associated negatively with the prevalence of allergic rhinitis and were lower in patients with allergic rhinitis than in controls; however, the same associations were not found in adults.[13] The results suggested that low vitamin D levels were caused by allergic rhinitis or existed together with allergic rhinitis but were not one of the predisposing factors of allergic rhinitis. One explanation for this relationship may be the lifestyle adjustments patients with allergic rhinitis make to avoid symptoms. Patients with allergic rhinitis may refrain from engaging in outdoor activities to avoid allergens that trigger or aggravate allergic rhinitis symptoms.[14] Because the synthesis of vitamin D in the skin requires sun exposure, reduced outdoor activity can lead to lower vitamin D levels.[15] Another explanation for the negative relationship between vitamin D levels and allergic rhinitis prevalence may be related to treatment. Allergic rhinitis can coexist with other conditions, such as asthma and atopic dermatitis, which may require repeated treatment with oral steroids for exacerbations or failure to respond to other therapies. The use of oral steroids can lead to vitamin D deficiency.[16] The use of inhaled steroids has been reported to be inversely correlated with serum vitamin D levels, possibly due to the increased renal metabolism of vitamin D with steroids.[17] In the meta-analysis by Kim YH et al., a comparison of vitamin D levels between patients with allergic rhinitis and controls showed that the vitamin D levels of patients with allergic rhinitis were significantly lower only in children but not adults. They concluded that prior vitamin D levels were not associated with developing allergic rhinitis; however, lower current

vitamin D levels were associated with higher allergic rhinitis prevalence only in children. There is insufficient evidence to support vitamin D supplementation for the prevention of allergic rhinitis.[6] Since the publication of the mentioned study regarding vitamin D levels in allergic rhinitis, multiple studies have emerged on whether vitamin D supplementation will help in treating these patients to reduce the severity of the disease spectrum.

Coban et al., aimed to clarify the relation between allergic rhinitis and the serum levels of 25-hydroxyvitamin D in the adult population and showed that patients with allergic rhinitis had significantly lower serum 25-hydroxyvitamin D levels compared to the control group. Thus, vitamin D supplementation as an adjunctive therapy may be considered in those patients.[18]

In a cross-sectional prospective study by Kumar et al.. regarding the association of vitamin D levels in allergic rhinitis, vitamin D deficiency (defined as serum 25(OH) D, <20 ng/mL) was statistically significant among patients with allergic rhinitis as compared to healthy controls. The deficiency was significantly more in moderate-severe patients than in mildly symptomatic patients. This suggests that suboptimal levels of vitamin D may modify the disease behavior. Vitamin D supplementation can be a useful therapeutic adjunct.[19]

OBJECTIVES

General Objective

To determine the clinical efficacy of vitamin D supplementation to patients with allergic rhinitis.

Specific Objectives

1. To investigate the overall effect size of vitamin D supplementation on the change in TNSS from baseline to post-intervention.
2. To investigate the effect of vitamin D supplementation on pre- and post-treatment vitamin D levels compared with placebo.
3. To identify and compare all relevant studies investigating vitamin D supplementation on top of standard of care on symptoms in patients with allergic rhinitis.

METHODOLOGY

Research Design

This study utilized a systematic review with a meta-analysis design to answer the research question, "Does vitamin D supplementation reduce symptom scores of patients with allergic rhinitis?"

Eligibility Criteria

Type of Studies

Randomized and non-randomized controlled trials were included. Studies were excluded if: 1) the population was not relevant to allergic rhinitis, 2) Symptom score was not taken, or 3) there were no original data.

Type of Participants

The study included allergic rhinitis patients with Vitamin D deficiency in both adult and pediatric populations. Allergic rhinitis was confirmed by a physician's clinical diagnosis in both adults and children.

Type of Intervention

a. Vitamin D supplementation
b. No vitamin D supplementation

Vitamin D supplementation was given in the studies. Those who were blinded were given a placebo in the same form and at the same time as the interventional vitamin D (oral form).

Types of Outcome Measures

Primary Outcome

Symptom control (symptom scores and symptom-medication scores for allergic rhinitis)

Search Methods for Identification of Studies

Information Sources

A systematic search was performed on PubMed, Cochrane Library, Herdin, and CENTRAL databases for articles published in peer-reviewed journals with at least twenty subjects from 2010 to February 2023. Personal communication with authors via email was done; however, none replied.

Search Strategy

Briefly, search terms included keywords for (allergic rhinitis) OR (rhinitis, allergic) OR (hay fever) AND ((vitamin D) OR (vitamin D3) OR (vitamin D3 supplementation) OR (vitamin D supplementation) OR (vitamin D adjunct) OR (cholecalciferol) OR (dihydroxy vitamin D) OR (hydroxyvitamin D). The language was not restricted to English alone. Filters for the time frame of 2010 to February 2023. No other filters were applied. For those that only abstracts are available, the primary investigator emailed the main authors; however, there were no responses.

Study Selection

The selection of studies for this systematic review was based on the titles and abstracts of relevant papers acquired in the article search process. The studies must be consistent with the objectives of the research to be

included. An outline was made prior to the selection of the articles.

Studies included were limited to peer-reviewed journals in any language. Included studies were randomized and non-randomized controlled trials. The inclusion of non-randomized studies was necessary to achieve a comprehensive assessment of the intervention's effectiveness across different study designs and populations. Non-randomized studies often contribute real-world evidence that complements findings from RCTs, offering insights into effectiveness under diverse conditions and in populations not typically represented in randomized trials. Cross-sectional studies, case series, case reports, and other gray literature were excluded. No crossover trials were included in this systematic review and meta-analysis. The study duration was not restricted and dependent on the data gathered by the authors, who would want to assess the difference between the intervention groups. The dates of the studies were limited to the year 2010 up to the present. All studies were ethically approved.

Data Extraction and Management

Data Extraction

From all the included articles, we extracted the following outcomes: study design, publication year, country, population characteristics, form of Vitamin D supplement, dose, frequency, levels of serum vitamin D, allergic rhinitis activity outcomes (severity, control status, and allergic rhinitis-specific quality of life).

Data Collection Process

The authors, together with an independent reviewer, extracted data from the reports of the studies that fulfilled both the inclusion and exclusion criteria. The data items extracted are shown in Table 1.

Data Items

Methods, participants, interventions, outcomes, and conclusion are summarized and seen in Table 1.

Table 1. Data items: Methods, participants, interventions, outcomes, and conclusion

Methods	Inclusion: Studies included were limited to peer-reviewed journals in any language. Included studies were randomized controlled trials. Exclusion: Cross-sectional studies, case series, case reports and other gray literature were excluded. No crossover trials were included in this systematic review and meta-analysis. The duration of the study depends on the data gathered by the authors which they would want to assess the difference between the intervention groups. The dates of the studies were limited to the year 2010 up to the present. All studies were ethically approved.
Participants	The selection of the participants depended on fulfilling the inclusion and exclusion criteria, this included both children and adults, males and females who had allergic rhinitis with either vitamin D deficiency or insufficiency. Countries where the studies were performed were not limited. The total number of participants enrolled depended on the capacity and the census of the hospitals where the authors of the studies gathered their study subjects. The number of participants who followed up and the drop-out rate were also noted.
Interventions	The study participants included patients with diagnosed allergic rhinitis. Supplementation of vitamin D was the interest of this study. No limitations are done on certain brands.
Outcomes	Symptom scores were analyzed using standardized mean difference since the studies had different instruments used to assess symptoms. Total Nasal Symptom Score (TNSS) is the sum of scores for each of; nasal congestion, sneezing, nasal itching, and rhinorrhea at each time point, using a four-point scale (0–3) TNSS is calculated by adding the score for each of the symptoms to a total out of 12. TNSS scale with a total of 15 included eye symptoms as an additional symptom.
Conclusion	The authors reported an association between allergic rhinitis and vitamin D supplementation with improvement of the symptom scores.

Measures of Treatment Effect

Data Synthesis

Tables 2, 3, and 4 illustrate how the results of the primary studies were summarized. All studies summarized the results qualitatively and quantitatively. Forest plots were generated using RevMan 5.3 and subjected to stat pooling.

Assessment of Risk of Bias in Individual Studies

The Cochrane Risk of Bias tool, which assesses random sequence generation, allocation concealment, participant and staff blinding, outcome assessment blinding, inadequate outcome data, and selective reporting, was used to determine the risk of bias for each study. None of the included studies had published study protocols available online.

Statistical Analysis

Descriptive statistics were used to summarize the outcomes of individual studies, and forest plots were generated to visually represent the study-specific effect sizes, their confidence intervals, and the overall pooled effect size.

The primary outcome of this meta-analysis was the change in total nasal symptom score (TNSS) from baseline.

Table 2. Patient demographics included in study

Study	Study Population	Demographic	Sample Size
Hassan et al,[27] Egypt, 2016	• Children (6-12 years) • Diagnosed with allergic rhinitis by ARIA guideline • Vitamin D deficiency	Age: 8.6 ± 3.4 years Gender: 50% male: 50% female	N = 100 E = 50 C = 50
Bakshaee et al,[26] Iran, 2019	• Patients aged 18-40 years diagnosed with allergic rhinitis by ARIA guideline • Vitamin D deficiency	Age: 29.6 years (experimental), 29.13 years (control) Gender: unspecified	N = 68 E = 35 C = 33
Upadhyay et al,[25] India, 2017	• Children (5-15 years) • Clinically diagnosed with allergic rhinitis • Vitamin D deficiency	Age: 8.6 years Gender: 23 (55%) male: 19 (45%) female	N = 42 E = 21 C = 21
Hembrom et al,[23] India, 2019	• Patients >12 years of age, diagnosed with allergic rhinitis moderate to severe persistent based on ARIA • Vitamin D deficiency	Age: 40.18 ± 7.81 (control), 39.40 ± 7.58 (experimental) Gender: 27 (42%) male : 37 (58%) female	N = 64 E = 32 C = 32
Velankar et al,[22] India, 2019	• Patients aged 15-60 years diagnosed with history of allergic rhinitis symptoms for at least 2 years • A positive skin test to 1 or more allergens • TNSS of at least 8 on screening • Vitamin D deficiency	Age: 34.26 (15-60) (control), 33.21 (15-59) (experimental) Gender: control: 52 (63.4%) male : 30 (36.59%) female experimental: 46 (54.8%) male : 38 (45.2%) female	N = 166 E = 84 C = 82
Bhardwaj et al,[20] India, 2020	• Patients aged 16-60 years diagnosed with allergic rhinitis based on ARIA • Vitamin D deficiency	Age: unspecified Gender: 38 (43.7%) male : 49 (56.3%) female	N = 87 E = 44 C = 43
Liu et al,[21] China, 2020	• Patients aged 13-53 years diagnosed with mild seasonal pollen allergic rhinitis according to guidelines published by Tianjin	Age: 27.3 ± 7.1 (control), 27.2 ± 8.8 (experimental) Gender: 29 (48.3%) male : 31 (51.7%) female	N = 60 E = 30 C = 30
Menon et al,[24] India, 2016	• Patients aged 18-60 • Diagnosed with allergic rhinitis • Vitamin D deficiency	Age: 32.17 ± 7.49 (control), 31.84 ± 6.55 (experimental) Gender: control: 13 (52%) male: 12 (48%) female experimental: 12 (52%) male: 11 (48%) female	N = 48 E = 23 C = 25

N = total, E = intervention, C = control

A random-effects model was used to pool the results of the included studies, with positive values indicating an improvement in TNSS. To account for differences in the number of items between TNSS-12 and TNSS-15, the standardized mean difference (SMD) was used, given that the TNSS-12 and TNSS-15 scales measured the same underlying construct, that the magnitude of the intervention effect was similar, and that the two scales are linearly related. Separate subgroup analyses were performed for studies using TNSS-12 and TNSS-15.

Another analysis was conducted to compare the post-intervention TNSS between the control group and the vitamin D supplementation group. In this analysis, negative values indicated a decrease in TNSS, signifying a reduction in symptom severity. Separate subgroup analyses were conducted for studies using TNSS-12 and TNSS-15.

Lastly, a pooled analysis was conducted to compare post-intervention vitamin D levels (in ng/mL) between the control and vitamin D supplementation groups.

RESULTS

Literature Search

A comprehensive search of relevant journals was performed via electronic databases using free text and MESH where applicable and with no language limit. The PRISMA Flowchart for the study selection and search approach is displayed in Figure 1.

A total of 241 studies were gathered; fifteen were included after excluding duplicates, book references, and unrelated studies. Eight studies were included after the inclusion and exclusion criteria; seven randomized control trials and one prospective analytical study were included. All eight studies were full papers. Two studies mainly focused on the pediatric age group (6-12 years and 5-15 years), while six studies included adults (18-40 years, 15-60 years, >12 years, 16-60 years, 13-53 years, and 18-60 years of age). There was significant heterogeneity in the doses of vitamin D used (Oral vitamin D 800-1000 IU/day or 50,000-60,000 IU/weekly) in the intervention groups. Both groups received standardized treatment according to the guidelines. The

Table 3. Design and methodology of included studies

Study	Duration of intervention	Intervention / Experimental (Form, dose, frequency, duration)	Control	Outcome measures	Study design
Hassan et al,[27] Egypt, 2016 (n = 100)	6 months	Oral vitamin D3 (cholecalciferol) 1000 IU/day Loratadine as needed 5 mg/day	Placebo Loratadine as needed 5 mg/day	Reflective total nasal symptom score (rTNSS) IgE (IU/ml) Vitamin D levels	RCT; double-blinded
Bakshaee et al,[26] Iran, 2019 (n = 68)	8 weeks	Weekly Pearl 50,000 IU vitamin D 1 pearl per week Plus cetirizine	Cetirizine plus placebo	Total symptom score Serum 25(OH)D (ng/ml)/ Vitamin D levels	RCT; double-blinded
Upadhyay et al,[25] India, 2017 (n = 42)	21 days	Oral vitamin D (cholecalciferol) 800 IU/day Fexofenadine (TNSS ≤10) or fluticasone nasal spray (TNSS ≥11)	Fexofenadine (TNSS ≤10) or fluticasone nasal spray (TNSS ≥11)	Total nasal symptom score (TNSS) Vitamin D levels Levels of vitamin D in various TNSS levels	RCT
Hembrom et al,[23] India, 2019 (n = 64)	2 months	Oral vitamin D 60,000 IU/week Levocetirizine, fluticasone spray and montelukast	Levocetirizin, fluticasone spray and montelukast	Allergy symptom score (ASS)	Prospective analytical observational study
Velankar et al,[22] India, 2019 (n = 166)	14 days	Oral vitamin D 60,000 IU weekly Fluticasone furoate nasal spray	Placebo and fluticasone furoate	TNSS Vitamin D levels	RCT; double-blinded
Bhardwaj et al,[20] India, 2020 (n = 87)	4 weeks	Oral vitamin D 60,000 IU weekly Fluticasone nasal spray	Placebo and fluticasone nasal spray	TNSS Post-treatment rhinitis control assessment test score	RCT
Liu et al,[21] China, 2020 (n = 60)	4 weeks	Vitamin D3 nasal drops 150,000 IU weekly Desloratadine 10 mg/day	Desloratadine 10 mg/day	TNSS Serum 25(OH)D (ng/ml) Peripheral blood eosinophil §L-4 levels	RCT
Menon et al,[24] India, 2016 (n = 48)	30 days	Oral vitamin D 1000 IU daily Azelastine intranasal spray	Placebo and azelastine intranasal spray	TNSS Vitamin D level	RCT; double-blinded

follow-up time ranged from 2 weeks to 6 months. Tables 3, 4, and 5 show the summary of the characteristics of the individual studies.

Study Characteristics

Tables 3, 4, and 5 summarize the patient demographics, design methodology, and summary results of each study included.

Critical Appraisal

The included studies were critically appraised based on randomization, follow-up, intention-to-treat analysis, blinding, baseline similarity, and equal treatment, as shown in Table 5. Studies were rated A if they satisfy all primary and secondary criteria. The rest of the studies were rated B if they did not fulfill one.

Risk of Bias in Included Studies

The general quality of the included studies based on biases is shown in Figure 2. Among the components, two stand out as the strengths of the studies. These are low risks in attrition and reporting bias. There were unclear risks in selection bias as most studies failed to specify how they performed randomization and allocation concealment. There is some performance and detection bias risk as some studies had no blinding.

Random Sequence Generation and Allocation (Selection Bias)

Only the study done by Bakshaee specified how they performed randomization and allocation concealment. All other studies have an unclear risk for selection bias, as randomization was only mentioned but not specified.

Blinding (Performance Bias and Detection Bias)

Half of the studies - Bakshaee, Hassan, Menon, and Velankar -performed blinding. However, as blinding was not performed in other studies, there was a high performance and detection bias risk.

Incomplete Outcome Data (Attrition Bias)

All of the studies collected have a low risk for attrition bias.

Selective Reporting (Reporting Bias)

All of the studies collected have a low risk for reporting bias.

Table 4. Summary of results of included studies

Study	TNSS score (Standard deviation)		Summary of results	Overall study outcome
	TNSS baseline	TNSS post-intervention		
Hassan et al,[27] Egypt, 2016 (n = 100)	C: 8.7 (1.60) E: 8.3 (1.40)	C: 2.72 E: 2.11	• Individual symptom scores (clinical & patient-reported) significantly improved in vitamin D supplementation group • Serum vitamin D levels improved with supplementation	Positive trial
Bakshaee et al,[26] Iran, 2019 (n = 68)	C: 26.78 E: 26.43	C: 26.08 (9.107) at 4 weeks C: 24.51 (9.040) at 8 weeks E: 22.39 (8.285) E: 18.7 (8.160)	• Symptom severity score showed no significant difference between the two groups at 4 weeks, whereas a significant difference was obtained between baseline and 8 weeks of treatment initiation • Vitamin D levels at 8 weeks of treatment in the study group indicated a statistically meaningful difference compared to baseline	Positive trial
Upadhyay et al,[25] India, 2017 (n = 42)	C: 11.04 (1.93) E: 10.6 (2.65)	C: 4.66 (1.99) E: 2.76 (1.6)	• Clinical improvement in terms of reduction in TNSS was significant in the post-Vitamin D supplemented group • Significant improvement of Vitamin D levels was found post-treatment in Vitamin D supplemented group	Positive trial
Hembrom et al,[23] India, 2019 (n = 64)	C: 13.93 (1.01) E: 14.06 (1.01)	C: 6.06 (0.87) E: 2.65 (1.12)	• Significant reduction in the allergy symptom score after vitamin D3 supplementation which alters the course of disease towards clinical improvement	Positive study
Velankar et al,[22] India, 2019 (n = 166)	C 11.92 (0.28) E 11.94 (0.24)	C: 6.43 (1.33) at 8th day C: 0.33 (0.61) at 14th day E: 7.74 (0.75) at 8th day E: 1.29 (1.58) at 14th day	• Significantly better response in total nasal symptom scores in the group which received vitamin D along with a steroid spray	Positive study
Bhardwaj et al,[20] India, 2020 (n = 87)	C: 12.5 (2.68) E: 11.64 (3.09)	C: 8.98 (1.01) E: 6.3 (1.45)	• Vitamin D supplementation showed better outcome in terms of difference in reduction of total nasal symptom score and average post treatment score	Positive study
Liu et al,[21] China, 2020 (n = 60)	C: 4.43 (1.54) E: 4.3 (1.49)	C: 3.37 (1.50) E: 2.07 (1.89)	• Patients who received vitamin D3 adjuvant therapy had a higher serum 25(OH)D level and lower AR symptoms score compared with antihistamine single treatment	
Menon et al,[24] India, 2016 (n = 48)	C: 10.17 (2.90) E: 9.92 (1.37)	C: 5.42 (7.78) E: 2.81 (3.04)	• There was significant improvement in the levels of serum vitamin D and highly significant reduction in the total nasal symptom score after supplementation	Positive study

C = control, E = experimental

Table 5. Quality of included studies

Study	Randomization	Follow-up	Intention to treat	Blinding	Baseline similarity	Equal treatment	Rating
Bakshaee et al.[26] (2019)	Yes	Yes	Yes	Yes	Yes	Yes	A
Bardwhaj et al.[20] (2020)	Yes	Yes	Yes	No	Yes	Yes	B
Hassan et al.[27] (2016)	Yes	Yes	Yes	Yes	Yes	Yes	A
Hembron et al.[23] (2019)	No	Yes	Yes	No	Yes	Yes	B
Liu et al.[21] (2020)	Yes	Yes	Yes	No	Yes	Yes	B
Menon et al.[24] (2016)	Yes	Yes	Yes	Yes	Yes	Yes	A
Upadhyay et al.[25] (2017)	Yes	Yes	Yes	No	Yes	Yes	B
Velankar et al.[22] (2019)	Yes	Yes	Yes	Yes	Yes	Yes	A

Assessment of Reporting Biases

The presence of reporting bias was determined through a funnel plot, provided that at least ten studies were evaluated. If an asymmetric funnel plot was obtained, then the presence of publication bias was possible. However, if fewer than ten studies were obtained, the Cochrane Handbook for Systematic Reviews of Interventions guidelines were used to assess biases.

Effect Estimate of Vitamin D Supplementation on Post-treatment Total Nasal Symptom Score

In the studies using the TNSS-12 scale, the vitamin D supplementation group had lower severity scores by a magnitude of 1.65 compared to the control (95% CI -2.84 to -0.46). The TNSS-12 Change in Baseline of 1.3 (95% CI 0.75 to 1.85) also suggests that the vitamin D group experienced a 1.3 unit change in the TNSS (severity) compared to the

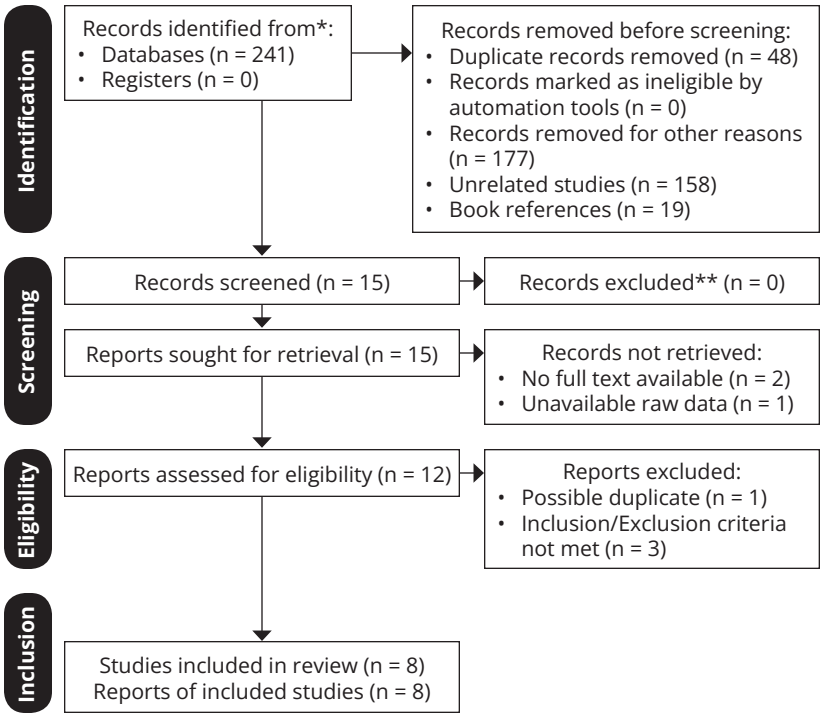

Figure 1. PRISMA flowchart of the search strategy and study selection.

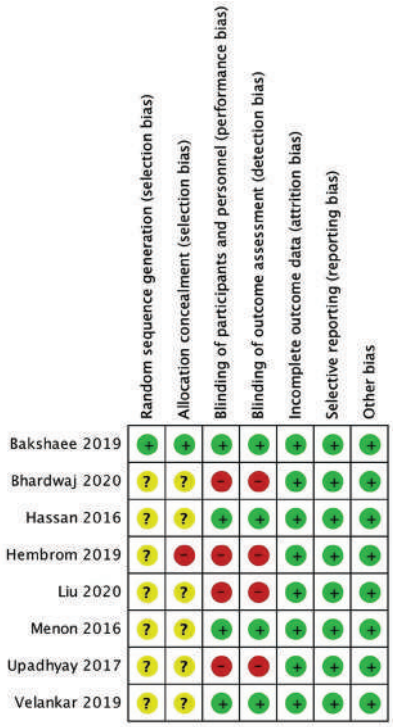

Figure 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

Table 6. Effect estimate of vitamin D supplementation on post-treatment total nasal symptom score (TNNS-12)

Outcome	Studies	Participants	Statistical method	Effect estimate
Post-treatment TNSS-12 [Score]	3	313	Mean difference (IV, random, 95% CI)	-1.65 [-2.84, -0.46]
TNSS-12 Change in Baseline	3	313	Mean difference (IV, random, 95% CI)	1.30 [0.75, 1.85]

Table 7. Effect estimate of Vitamin D supplementation on post-treatment total nasal symptom score (TNNS-15)

Outcome	Studies	Participants	Statistical method	Effect estimate
Post-treatment TNSS-15 [Score]	3	154	Mean difference (IV, random, 95% CI)	-4.21 [-8.98, 0.56]
TNSS-15 change in baseline	3	154	Mean difference (IV, random, 95% CI)	3.68 [2.48, 4.88]

control, indicating significant improvement from baseline (Table 6).

In the studies using the TNSS-15 scale, the vitamin D supplementation group had lower severity scores by a magnitude of 4.21 (95% CI -8.98 to 0.56) compared to the control. TNSS-12 Change in Baseline of 3.68 (95% CI 2.48 to 4.88) also suggests that the Vitamin D group had a 3.68 unit change in the TNSS score (severity) compared to the control also indicating significant improvement (Table 7).

All Forest plots did not cross the midline (Figures 3 and 4), indicating that all studies favor vitamin D supplementation.

Effect Estimate of Vitamin D Supplementation on Post-Treatment Vitamin D Levels

Five studies measured pre- and post-treatment vitamin D levels. An effect estimate of 11.16 (95% CI 5.99 to 16.34) states that vitamin D supplementation increases post-treatment vitamin D levels by 11.16 ng/mL on average (Table 8 and Figure 5).

The effect of Vitamin D and Placebo on Change from Baseline of Total Nasal Symptom Score

Results are based on six studies with 467 participants, and the effect estimate is expressed as the standardized mean difference (SMD) using a random-effects model. Vitamin D is associated with a statistically significant improvement in TNSS compared to the baseline, with an average SMD of 6.27 and a 95% confidence interval (3.96, 8.59) (Figure 6).

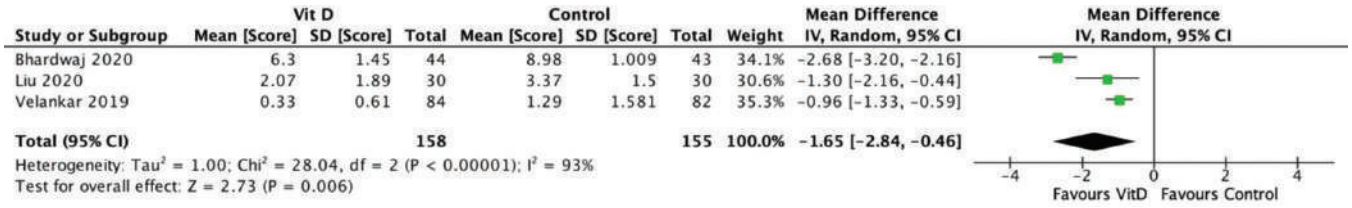

Figure 3. Forest plot using random effects model comparing the effect of vitamin D and placebo on post-treatment total nasal symptom score (TNNS-12).

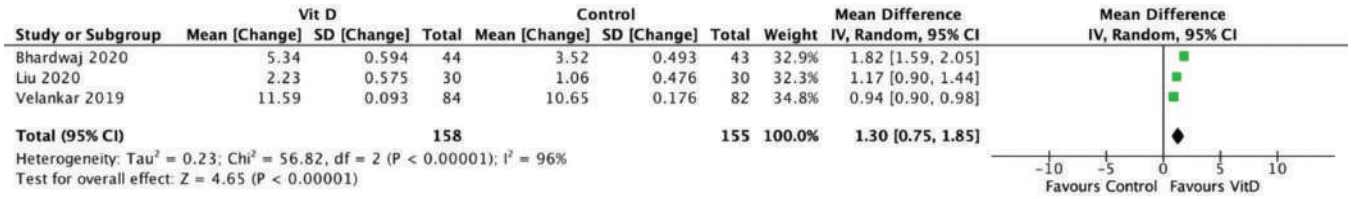

Figure 4. Forest plot using random effects model comparing the effect of vitamin D and placebo on change from baseline of total nasal symptom score (TNNS-15).

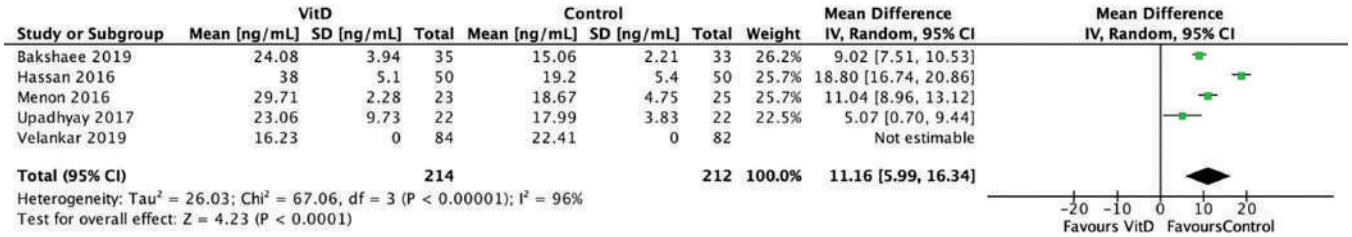

Figure 5. Forest plot using random effects model comparing the effect of vitamin D and placebo on post-treatment Vitamin D levels.

Table 8. Effect estimate of Vitamin D supplementation on post-treatment vitamin D levels

Outcome	Studies	Participants	Statistical method	Effect estimate
Post-treatment Vitamin D Levels [ng/mL]	5	426	Mean difference (IV, random, 95% CI)	11.16 [5.99, 16.34]

Six studies were collectively evaluated for the effect estimate of vitamin D supplementation on post-treatment total nasal symptom score; three of these studies (Bhardwaj, Liu, Velankar) used a TNSS of 12 assessing nasal congestion, sneezing, nasal itching, and rhinorrhea at each time point, using a four-point scale (0–3).[20-22] In contrast, the other three (Hembron, Menon, Upadhyay) used a TNSS of 15, which added eye symptoms to the total scoring.[23-25] All of these studies showed a significant decrease in post-treatment nasal symptom scores after vitamin D supplementation, with an average improvement in TNSS scores of 6.27 (95% CI 3.96 – 8.59) compared to the baseline. The study of Bakshaee used a different scoring system, using a total TNSS of 45.[26] According to their results, no significant difference was observed between the two groups regarding the mean score of symptom severity after four weeks of treatment (P = 0.073) due to the lack of time for vitamin D to induce its immunological effects. However, at the end of the 8-week treatment course, a significant decrease was observed in the intervention group in terms of the mean symptom severity score (P = 0.007). Hassan et al., also used a total TNSS score of 12 but was not included in the collective evaluation due to their study duration of 6 months (28 weeks).[27] Duration of treatment for the other studies ranged from 2 to 8 weeks (mean of 4.7 weeks). Their study, however, also showed improvement in the average patient-reported individual symptoms during the six months of treatment in the allergic rhinitis group who received vitamin D compared to the allergic rhinitis group who did not receive vitamin D.

DISCUSSION

This meta-analysis provides robust evidence to support the clinical efficacy of vitamin D supplementation in improving nasal symptom scores in patients with allergic rhinitis. Our findings are based on a comprehensive review of eight studies investigating vitamin D supplementation's effects on nasal symptom scores in vitamin D-deficient patients with allergic rhinitis. The results indicate that

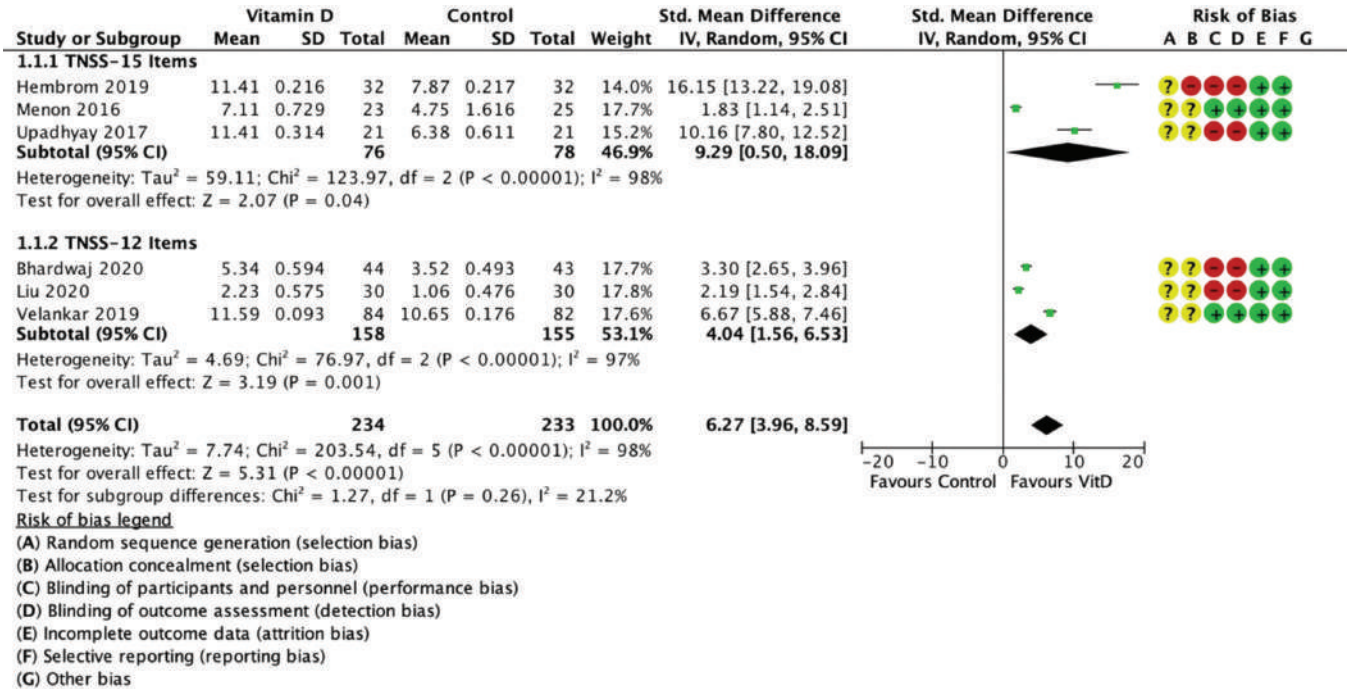

Figure 6. Forest plot using random effects model comparing the effect of vitamin D and placebo on change from baseline of total nasal symptom score.

adding vitamin D to the standard of care significantly improved nasal symptom scores in this group of patients compared to those who only received the standard of care. Overall, the meta-analysis suggests that vitamin D supplementation may be a promising adjunct treatment option for allergic rhinitis, potentially improving patient outcomes and reducing healthcare costs.

The pathogenesis of allergic rhinitis involves a complex interplay between various immune cells and mediators. It is suggested that a shift from a Th1 to Th2 phenotype in the proliferation of CD4+ T cells contribute to the pathogenesis of allergic rhinitis. Recent studies indicate that Th17 and Treg cells are important in the disease course of allergic rhinitis. Vitamin D plays a role in inhibiting the proliferation of T cells, facilitating the induction of Foxp3+ Treg cells, and suppressing the differentiation, maintenance, bioactivity, and transcription of Th17 cells.[6] Overall, while the exact mechanisms by which vitamin D modulates the immune response in allergic rhinitis are not fully understood, the available evidence suggests that vitamin D plays a role in the pathogenesis of allergic rhinitis and may have therapeutic potential in managing this condition.

According to practice guidelines and standard management protocols, allergic rhinitis is typically managed using a combination of medications, including antihistamines, intranasal corticosteroids, and leukotriene receptor antagonists. Despite these treatment options, many patients experience persistent symptoms, highlighting the need for additional therapies that can enhance symptom relief. Our meta-analysis suggests that vitamin D supplementation could be a promising adjunct therapy for patients with allergic rhinitis, as it has the potential to improve symptom control and reduce the need for more aggressive medical interventions. Moreover, the safety profile of vitamin D supplementation is well-established, and the cost of vitamin D supplementation is relatively low,[22,23] making it an attractive treatment option in the context of the high healthcare burden associated with allergic rhinitis. The prevalence of allergic rhinitis and the associated healthcare costs emphasize the importance of safe, effective, and affordable treatment options that can enhance patient outcomes and decrease healthcare spending. Our meta-analysis findings suggest that vitamin D supplementation may have a potential role as an adjunct treatment option for allergic rhinitis, which could reduce symptom severity and improve patient outcomes.[28,29] Studies included in this meta-analysis uniformly utilized the Total Nasal Symptom Score (TNSS) as a scale to measure symptom severity. The studies used the TNSS-12 or TNSS-15 scale to measure symptoms in patients with allergic rhinitis. All studies showed significant improvement in symptom severity in the vitamin D supplementation group compared to the control group. Forest plots showed that all studies favored vitamin D supplementation. Additionally, five studies measured pre and post-treatment vitamin D levels and found that vitamin D supplementation increased post-treatment vitamin D levels. Overall, the meta-analysis found a statistically significant improvement in TNSS with

vitamin D supplementation compared to the baseline. Compared to other studies investigating the effect of vitamin D supplementation on allergic rhinitis, our findings are consistent with several other published literature that have reported a significant improvement in symptom scores with vitamin D supplementation in other allergic conditions such as asthma and atopic dermatitis.[29] Although studies in other allergic conditions have reported conflicting results,[30,31] this was not the case in this meta-analysis wherein all eight included studies favored supplementation of vitamin D. However, the optimal dosing and duration of vitamin D supplementation in allergic conditions across all studies are still not fully established. The varying doses of vitamin D may lead to differential effects on outcomes such as serum vitamin D levels, bone health markers, or immune function, depending on whether the doses were sufficient to achieve therapeutic levels consistently across all participants. Additionally, the duration of follow-up is critical as it affects the assessment of both short-term responses and longer-term outcomes related to vitamin D supplementation. Shorter follow-up periods may capture immediate biochemical changes but could miss delayed effects on clinical outcomes or vice versa. Addressing this heterogeneity requires a nuanced approach. Conducting subgroup analyses based on dose ranges and follow-up durations can elucidate whether certain dose levels or durations are more effective or consistent in producing desired outcomes; however, it was not done in this study. Sensitivity analyses may also be warranted to assess the robustness of our conclusions across different scenarios of dose and follow-up duration variability.

A meta-analysis of 19 studies by Kim HY et al., regarding vitamin D levels in allergic rhinitis suggested that low vitamin D levels were caused by allergic rhinitis or existed together with it but were not one of the predisposing factors of allergic rhinitis.[13] They concluded that prior vitamin D levels were not associated with developing allergic rhinitis; however, lower current vitamin D levels were associated with allergic rhinitis prevalence rate, but only in children. The prevalence of serum vitamin D deficiency was significantly higher in patients with allergic rhinitis than in the normal population. In a study by Moradzadeh et al., the prevalence of severe vitamin D deficiency was significantly greater in patients with AR than in the normal population (30% vs. 5.1%; $p = 0.03$), demonstrating that there is an association between serum vitamin D levels and allergic rhinitis status.[32] This suggests a role of vitamin D supplementation in the treatment of patients with AR and no role in the prevention of allergic rhinitis.

Recent studies have shown that lower current vitamin D levels were associated with allergic rhinitis prevalence rate and symptom severity.[19,32] A study by Restimula et al., found evidence of a strong, negative relationship between serum vitamin D levels and allergic rhinitis incidence and TNSS. They established that vitamin D cut-off points correlated to AR were about 12.83 ng/mL (sensitivity = 80%; specificity = 100%).[33] Our study showed that vitamin D supplementation can significantly increase post-treatment vitamin D levels by an average of 11.16 ng/mL (95% CI 5.99 to 16.34). Thus, physicians should consider evaluating patients for vitamin D deficiency during allergic rhinitis management.

Based on the current meta-analysis and the available evidence, there is strong evidence to support vitamin D supplementation as a potential adjunct in the management of allergic rhinitis. The significant improvement in TNSS and the increase in post-treatment vitamin D levels seen in these studies suggest that vitamin D supplementation may provide a benefit to patients with allergic rhinitis.

CONCLUSION

Vitamin D supplementation can significantly improve nasal symptom scores in individuals with allergic rhinitis. It also significantly decreases post-treatment nasal symptom scores and significantly increases vitamin D levels after treatment. The current evidence supports the consideration of vitamin D supplementation as an adjunctive therapy in the management of allergic rhinitis.

Recommendation and Limitation of the Study

This study has certain limitations. The meta-analysis is limited to published studies and may be subject to publication bias. There was variability in vitamin D dosages and duration of treatment among the included studies, which may introduce heterogeneity that limits the conclusions' strength. The exclusion of unpublished studies may result in an overestimation of the clinical efficacy of vitamin D supplementation. Furthermore, the quality of the included studies varied, and some studies had a risk of bias, which could affect the validity of the results. A significant limitation of this study is the absence of attempts to contact the original authors for additional information regarding the studies included in the systematic review. This oversight raises concerns about the completeness and accuracy of the data utilized. Acknowledging this limitation is crucial as it underscores the potential impact on the reliability and comprehensiveness of the findings. Future research should consider incorporating strategies to directly engage with study authors to ensure a more thorough and robust systematic review process. Additionally, the study did not explore potential adverse effects or risks associated with vitamin D supplementation. To address these limitations, future studies should use standardized protocols for dosage and duration of intervention to reduce heterogeneity and improve the comparability of findings. There is a need for further research to explore the optimal dose and duration of vitamin D supplementation

in managing allergic rhinitis. Future studies should also investigate vitamin D supplementation's potential risks and adverse effects. Lastly, researchers should consider conducting studies on specific subpopulations, such as children or elderly individuals, to determine the efficacy of vitamin D supplementation in these groups.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

The authors declared no conflict of interest.

Funding Source

None.

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