


The Role of Vitamin D Supplementation in The Prevention of Asthma Exacerbation

Laporan Kasus Berbasis Bukti

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ABSTRACT

Background: Asthma is a chronic inflammatory condition affecting the airways, marked by tissue changes and heightened bronchial sensitivity. Vitamin D, as an immunomodulator, may affect the inflammatory responses of the airways. Recent studies suggest that vitamin D supplementation has resulted in fewer exacerbations of asthma and improved lung function in both individuals with asthma and smokers. Other studies revealed a reduction of asthma exacerbations in corticosteroid-treated patients. This study sought to investigate whether vitamin D supplementation can decrease the frequency of asthma exacerbations. **Methods**: Literature research was done on three databases: PubMed, Cochrane Library, and ScienceDirect, related to the clinical question. Articles were chosen according to specific inclusion and exclusion criteria. All articles were critically appraised using the Oxford Center for Evidence-Based Medicine worksheet. **Results**: Three meta-analysis articles were critically appraised. The result is vitamin D supplementation can lower the incidence of asthma exacerbation, despite varying doses of vitamin D. **Conclusion**: Vitamin D supplementation was associated with a decrease in asthma exacerbations, despite varying doses of vitamin D. Vitamin D supplementation to corticosteroids can be considered potentially cost-effective and safe to prevent asthma exacerbations. Future studies should analyze the effect of vitamin D supplementation in long-term asthma therapy using the same dose.

Keywords: Asthma, asthma exacerbation, immunomodulator, vitamin D supplementation.

ABSTRAK

Latar belakang: Asma merupakan kondisi inflamasi persisten saluran napas, ditandai dengan perubahan struktur jaringan dan peningkatan sensitivitas bronkus. Vitamin D, sebagai imunomodulator, dapat memengaruhi respons inflamasi pada saluran pernapasan. Penelitian menunjukkan bahwa suplementasi vitamin D dapat mengurangi eksaserbasi asma dan meningkatkan fungsi paru, baik pada penderita asma maupun perokok. Penelitian lain mengungkapkan penurunan eksaserbasi asma pada pasien yang memerlukan pengobatan *corticosteroid*. Penelitian ini bertujuan untuk menyelidiki apakah suplementasi vitamin D dapat menurunkan frekuensi eksaserbasi asma. **Metode:** Pencarian literatur menggunakan tiga *database*: PubMed, ScienceDirect, dan Cochrane Library, terkait dengan pertanyaan klinis. Artikel dipilih berdasarkan kriteria inklusi dan eksklusi serta dilakukan telaah kritis menggunakan pedoman *Oxford Center for Evidence Based Medicine*. **Hasil:** Tiga artikel meta-analisis dinilai secara kritis. Hasilnya, suplementasi vitamin D dapat menurunkan risiko kejadian eksaserbasi asma, meskipun dosis vitamin D berbeda-beda. **Simpulan:** Suplementasi vitamin D berkaitan dengan penurunan eksaserbasi asma meskipun dosis vitamin D bervariasi. Suplementasi vitamin D sebagai tambahan pada terapi *corticosteroid* berpotensi hemat biaya dan aman untuk mencegah eksaserbasi asma. Penelitian selanjutnya sebaiknya meneliti pengaruh suplementasi vitamin D dalam pengelolaan asma jangka panjang serta menggunakan dosis vitamin D yang seragam. **Devina Sagitania. Peran Suplementasi Vitamin D pada Upaya Pencegahan Eksaserbasi Asma – Laporan Kasus Berbasis Bukti.**

Kata Kunci: Asma, eksaserbasi asma, imunomodulator, suplementasi vitamin D.

INTRODUCTION

Asthma is a common chronic respiratory disease. Currently, an estimated 1%-29% of the population in different countries suffers from asthma.[1] Asthma is a chronic inflammatory condition affecting the airways, with changes in tissue structure and heightened bronchial sensitivity. Many conditions can trigger asthma such as genetics, environmental factors, and psychological conditions. Asthma exacerbation is characterized by progressiveness in symptoms of wheezing, cough, chest tightness, shortness of breath, and a progressive episodic decrease in lung function. Frequent exacerbation triggers include exposure to allergens, air pollution, viral respiratory infections, and poor compliance with inhaled corticosteroids.[1] Alterations linked to asthma involve imbalances in both pro- and anti-inflammatory cytokines produced by Th1 and Th2 cells, persistent

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oxidative stress, heightened migration of cells into the bronchi, and increased sensitivity of the airways to stimuli.[2]

Vitamin D, as an immunomodulatory agent, may affect the inflammatory responses of the airways. A potential role of vitamin D in the management of asthma is through its capacity to suppress inflammation by controlling the movement, proliferation, and cytokine secretion of diverse immune cells such as eosinophils, neutrophils, and mast cells.[3] The production of pro-inflammatory cytokines such as IL-1β, IL-6, and TNFα may be decreased because of the anti-inflammatory effect of vitamin D.[2] Vitamin D also can release interleukin-10, an anti-inflammatory cytokine.[2]

In asthmatic individuals, an interaction between serum vitamin D (VD) levels (25-hydroxyvitamin D3 (25(OH)D)) and lung function has been shown in several studies.[4] Lower levels of VD have been associated with poorer asthma control as well as increased frequency of exacerbation, emergency department visits, and hospitalizations. Additionally, low VD levels have been linked to inadequate control of asthma, more frequent exacerbations, reduced lung function, and higher usage of medications.[3,5] Recent studies showed improvement of lung function and reduction of asthma exacerbations in both patients with asthma and smokers who take vitamin D supplements.[4] Other studies revealed vitamin D addition was associated with 36% lower asthma exacerbations in patients who need systemic corticosteroids.[6] A growing number of research studies suggest that vitamin D supplementation may enhance the effectiveness of corticosteroids in treating asthma and can reduce corticosteroids doses.[5,7,8] This study sought to investigate whether vitamin D supplementation could decrease the frequency of asthma exacerbation.

CASE

A 25-year-old female, BMI 30.04, was treated in the emergency department for anxiety and acute-onset dyspnea. The respiratory rate was 24/min, and oxygen saturation was 90%. Wheezes were heard on auscultation. Her past medical histories were asthma and anxiety disorder. The history of the patient's medication was formoterol fumarate 4.5 mcg and budesonide 80 mcg, one inhalation through a Turbuhaler twice daily, and tiotropium bromide 2.5 mcg puff once daily. The patient admitted that asthma often recurred, especially when she was anxious. The patient asks whether any other treatments, such as vitamins, can help prevent exacerbation.

CLINICAL QUESTION

The clinical question regarding whether vitamin D supplementation reduces asthma exacerbations was formulated into the PICO framework:

P (Patient): Individuals with asthma
I (Intervention): Vitamin D
C (Comparison): Placebo
O (Outcome): Reduction of asthma exacerbations
Design study : Meta-analysis

METHOD

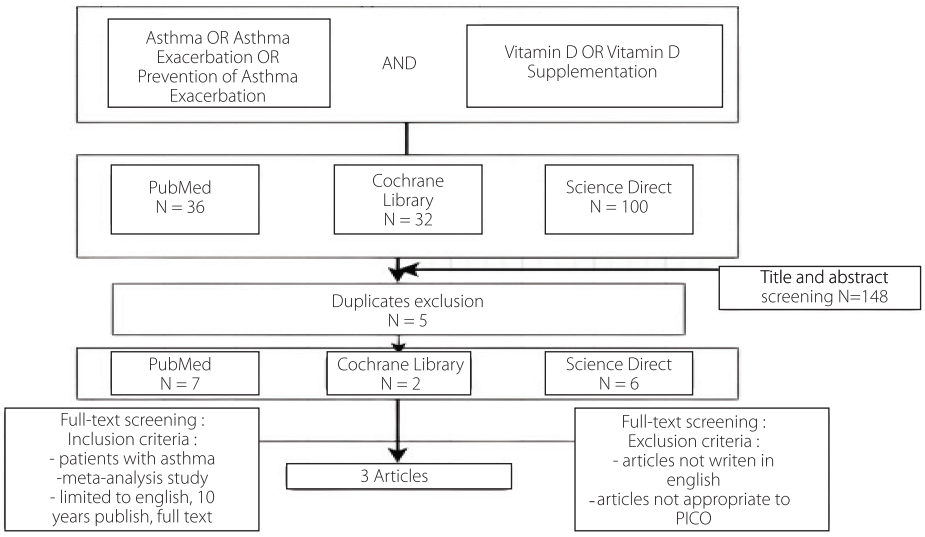
Literature searches were performed on March 1st, 2024, using the keywords "asthma,""asthma exacerbations," "vitamin D," and "prevention of asthma exacerbation" **(Table 1).** A literature search was done in three databases: PubMed, ScienceDirect, and Cochrane Library, related to the clinical question. The literature search strategy, results, and the inclusion and exclusion criteria are shown in **Scheme** Article selection was limited to the English full text of the meta-analysis study. Articles not written in English and not suitable with PICO were excluded. Critical appraisal was done of all articles based on the Oxford Center for Evidence-Based Medicine worksheet **(Tables 2, 3, and 4).**

RESULT

All 168 articles were acquired from three databases: PubMed, Cochrane Library, and ScienceDirect. Article selection was limited to meta-analyses studies. Three relevant studies were qualified for further assessment based on the selection and filtration stage. These studies were appraised using the Oxford center for evidence-based medicine

Table 1. Literature searching based on keywords.

Database	Keywords	Results
PubMed	{(Asthma [Title/Abstract]) OR (asthma exacerbations [Title/Abstract]) OR (prevention of asthma exacerbation[Title/Abstract])} AND {("vitamin D" [Mesh]) [Title/Abstract]) OR (Vitamin D supplementation (supplementation [Title/Abstract])}	36
Cochrane	(Asthma OR Asthma Exacerbation OR Prevention of Asthma exacerbation) AND (Vitamin D OR Vitamin D supplementation)	32
ScienceDirect	(Asthma OR Asthma Exacerbation OR Prevention of Asthma exacerbation) AND (Vitamin D OR Vitamin D supplementation)	100



Scheme. Flow chart of searching strategy.


worksheet and are considered to have good validity and relevance. All studies are meta-analyses with similarity of characteristics between the control group and intervention group.

In a meta-analysis study by Liu, *et al,* which included seven studies involving a total of 944 subjects, it was shown that vitamin D was related to a decrease in the rate of asthma exacerbations, despite a high level of significant heterogeneity (RR 0.60, 95% CI 0.41–0.88, I2 = 64%, p < 0.01). In the group of intervention, vitamin D was administered in different doses. The control group received an equivalent dose of placebo.[3] Every group also received inhaled corticosteroids, a standard treatment for asthma. In efforts to reduce heterogeneity, Liu, *et al,* conducted subgroup analyses of the included studies, taking into account variables like age, FEV1 values, and follow-up duration. In the children population subgroup analysis, supplementing vitamin D was correlated with a decreased frequency of asthma exacerbations (RR 0.46, 95% CI 0.30 to 0.70, I2 = 0%, p = 0.83). While in adults, there was no notable distinction observed between the control and intervention groups regarding the reduction of asthma exacerbations.

In the second study by Chen, *et al,* all eight studies showed the reduction of asthma exacerbation in the vitamin D supplementation group (RR 0.70, 95% CI, 0.59 to 0.83; p < 0.001), with very low heterogeneity (I2 = 0.00%, p = 0.823).[4] This reduction was statistically significant in both children and adults. Additionally, all participants were receiving various doses of corticosteroids as standard treatment; almost all studies were using inhaled corticosteroids (ICS), while several subjects were using oral corticosteroids.

In the third study by Jolliffe, *et al,* the effect of supplementing vitamin D on the reduction of exacerbation of asthma was investigated.[9] All subjects in both control

Table 2. Critical appraisal results: Validity.

Articles	Validity				
	Is PICO Clearly Explained?	Comprehensive Search	Appropriate Inclusion Criteria?	Studies Sufficiently Valid?	Similar Results from Study to Study?
Liu, *et al*, 2022.[3]	+	+	+	+	+
Chen, *et al*, 2020.[5]	+	+	+	+	+
Jolliffe, *et al*, 2019.[9]	+	+	+	+	+

Table 3. Critical appraisal results: Importance and level of evidence.

Articles	Importance: What were the Results?		Level of Evidence
	Pooled RR (95% CI)	Heterogeneity (p)	
Liu, *et al*, 2022.[3]	RR 0.60 (0.41–0.88)	I2 = 64%, p <0.01	1A
Chen, *et al*, 2020.[5]	RR 0.70 (0.59-0.83)	I2 = 0.00%, p = 0.823	1A
Jolliffe, *et al*, 2019.[9]	RR 0,69 (0,52–0,92)	I2=0·0%, p = 0.56	1A

Table 4. Critical appraisal results: Applicability.

Articles	Applicability		
	Patient Similarity	Feasibility	Benefit > Harm
Liu, *et al*, 2022.[3]	+	+	?
Chen, *et al*, 2020.[5]	+	+	+
Jolliffe, *et al*, 2019.[9]	+	+	+

*(+) stated in the article and done, (-) not done, (?) not clearly stated in the article. *CI: confidence intervals; RR: risk ratio; p < 0.05 is statistically significant, *The I2 statistic is used to evaluate the heterogeneity among the analyzed studies. The degree of heterogeneity is categorized according to specific I2 values: 25%, 50%, and 75% representing low, moderate, and high levels of heterogeneity, respectively.

Table 5. Study summary.

Author	Study Design	Subject	Results
Liu, *et al*, 2022.[3]	Meta-analysis	7 Randomized controlled trials (RCTs), 944 subjects (478 placebo and 466 intervention)	Supplementing vitamin D was correlated with a decline of the incidence of asthma exacerbations. (RR 0.60, 95% CI 0.41–0.88, high heterogeneity (I2 = 64%, p <0.01)
Chen, *et al,* 2020.[4]	Meta-analysis	8 Randomized controlled trials (RCTs) without mention of total subject	Supplementing vitamin D was correlated with a decline of the incidence of asthma exacerbations. The pooled RR 0.70 (95% CI, 0.59, 0.83; p <0.001), heterogeneity very low (I2 = 0.00%, p =0.823).
Jolliffe, *et al*, 2019.[9]	Meta-analysis	4 Randomized controlled trials (RCTs). Total 719 subjects	Supplementing vitamin D was correlated with a decline of the incidence of asthma exacerbations. Adjusted RR 0,69, 0,52–0,92, p =0.01; p heterogeneity =0.56

Abbreviations: CI: confidence intervals; RR: risk ratio; p <0.05: statistically significant.

and intervention groups received systemic corticosteroids, and several subjects also used inhaled corticosteroids as a standard treatment. Supplementation of vitamin D led to a noteworthy decrease in the frequency of exacerbation of asthma necessitating therapy with systemic corticosteroids (adjusted RR 0.69, 95% CI 0.52–0.92, p = 0.01; p heterogeneity=0.56). The studies' durations span from 15 weeks to 1 year. The summary of the studies can be seen in **Table 5**.

DISCUSSION

Asthma is a chronic condition of inflammation affecting the airways with changes in tissue structure and heightened bronchial sensitivity. Asthma is usually triggered by a combination of environmental factors, genetics, and possible association with psychological conditions. Poor response to inhaled corticosteroids is one of the complexities in asthma control and treatment that can influence asthma exacerbations.[2] Vitamin D, as an immunomodulatory, may affect the inflammatory responses of the airways; combining vitamin D supplementation with corticosteroids might enhance the protective effects of vitamin D due to its immunomodulatory properties.[4] Recently, there has been increasing attention to vitamin D, focusing on both its insufficiency and its contribution to immunity. The relationship between vitamin D supplementation and asthma has been investigated in numerous studies.[4]

According to the three studies that have been critically appraised, vitamin D supplementation has been linked to a lowered rate of asthma exacerbations when compared to placebo groups. In these three studies, participants in the intervention groups received different doses of vitamin D, while the control groups received a placebo. All subjects in both groups were also using corticosteroids as part of their standard asthma treatment. The subjects in the articles have a similarity with the case, in terms of age, disease, and therapy given. The patient in this case was using inhaled corticosteroids for her daily treatment before admission to the emergency department; this study is applicable to this case.

Liu, *et al*, demonstrated that vitamin D supplements were related to a decrease in the frequency of exacerbations of asthma, despite variations in the dosage of vitamin D across the studies. The doses ranged from vitamin D 500 IU, a single dose of vitamin D3 100,000 IU followed by 4,000 IU/day for 28 weeks, to vitamin D3 50,000 units administered fortnightly for 3 months, alongside standard treatment. The duration of follow-up varied between one week and twelve months.[3] However, the study had limitations. Variability in both the method and dosage of administering vitamin D among the studies was inevitable. Additionally, there was no uniformity in the basic anti-asthma treatment received by all subjects enrolled in different studies. Moreover, several studies examined in this analysis had small sample sizes, raising concerns about the reliability of the results. Furthermore, not all participants shared the same severity or causes of asthma. Despite these limitations, subgroup analyses were conducted to reduce heterogeneity for baseline factors such as age, FEV1 values, and follow-up duration. Sensitivity analysis consistently yielded reliable findings, enhancing the credibility of the meta-analysis results.

In the study by Chen, *et al*, various vitamin D dosages were employed; these included every day, every week, twice a month, 3.5 times a month, and a single high dose of long-acting oral vitamin D3. The administered doses spanned from 1,000 IU/week to 60,000 IU/week. The follow-up duration ranged from 2 to 12 months.[4]

In a meta-analysis study by Jolliffe, *et al*, the oral vitamin D dosage varied, including a daily oral dose of 2,000 IU/day, a combination of bolus and daily doses (100,000 IU bolus followed by 400–4,000 IU/day) in two studies, and a bolus of 120,000 IU once every 2 months. The lengths of the studies varied from 15 weeks to 12 months. The differences in vitamin D doses across studies may introduce bias.[3,4,9]

An important point to note is the potential for undesirable impact of vitamin D supplementation. Chen, *et al*, and Jolliffe, *et al*, indicate the safety of the administration of vitamin D (VD) both in adults and children. Jolliffe, *et al*, described no serious adverse events and no incident of renal stones or hypercalcemia at the doses administered between vitamin D and placebo groups.[4,9]

Subgroup analysis in Jolliffe, *et al*, study also highlights the usefulness of supplementing VD (vitamin D) in subjects with deficient VD levels, characterized by a baseline circulating 25(OH)D of <25 nmol/L, showing the significant lowering of exacerbation of asthma treated with systemic corticosteroids.[9] The strengths of this study include the great quality of the involved studies and a sufficient duration for participants assigned to receive vitamin D3 to achieve steady-state 25(OH)D concentrations. Only a small fraction of individuals randomly assigned had incomplete outcome data (2.4%), and the assessment of 25(OH)D concentrations was conducted using approved assays in laboratories participating in external quality assessment programs. The analysis included subjects with heterogeneous characteristics across multiple settings and incorporated recent data from a trial involving children with severe asthma, thereby enhancing both the internal and external validity of the findings. However, a limitation of the study is that the explanation of the funnel plot is constrained by the limited number of included studies. Nevertheless, the balanced distribution of results from smaller randomized controlled trials (RCTs) on both ends of the overall adjusted rate ratio offers some assurance that publication bias was likely not a significant concern in this meta-analysis.[9]

In subgroup analysis, Chen, *et al*, described that supplementing vitamin D lowered the rate of exacerbations of asthma among subjects with asthma who were treated with various doses of corticosteroids.[4] The limitations of this study include the analysis being based on a limited number of studies, suggesting that a larger sample size would be preferable, especially for assessing adverse events. Variations in dosing schedules for both vitamin D, and various doses and methods of corticosteroids could introduce bias into the results. The duration of sunlight exposure, baseline serum levels, the frequency of intake, and the dosage of each supplement can influence the status of vitamin D levels. While various methods of administering vitamin D aim to elevate serum concentrations to sufficient levels, some participants may still not achieve adequate serum vitamin D levels even with long-term supplementation.

Lower serum vitamin D concentrations have


been linked with a higher rate of asthma exacerbations, necessitating medical care and leading to multiple emergency department visits.[10] Vitamin D has an important contribution to the inhibition of inflammation by controlling the migration, proliferation, and cytokine release from various immune cells, including eosinophils, neutrophils, and mast cells.[3] Additionally, it lowers the production of inflammatory cytokines while increasing the secretion of the anti-inflammatory IL-10.[2] Vitamin D receptors have been detected in the respiratory system, including within epithelial smooth muscle cells.[2] A deficit of vitamin D exacerbates oxidative stress and the resistance of corticosteroids in severe asthma exacerbations.[3] Oxidative stress undermines the responsiveness to corticosteroids by impeding the function and expression of HDAC-2 (histone deacetylase-2) through serine hyperphosphorylation.[3] Vitamin D aids in asthma treatment by magnifying the anti-inflammatory effects of corticosteroids.[4] Corticosteroids are also involved in controlling the release of inflammatory chemokines. Co-administration of corticosteroids and vitamin D results in additive inhibition of inflammatory chemokines.[4]

Vitamin D supplementation has been linked to fewer asthma exacerbations. However, this review has several limitations, including the various doses and modes of administration of vitamin D in these studies, as well as inconsistency in the dose of standard anti-asthma therapy. Furthermore, the sample sizes in several studies might be insufficient to reliably ascertain the outcomes. Despite these limitations, heterogeneity was minimized by conducting subgroup analyses of included studies based on age, FEV1 values, and follow-up time. Although all three studies were deemed valid and applicable during critical appraisal, attention should be paid to the homogeneity of vitamin D doses and standard treatment doses, which should be standardized during the follow-up period. Subsequent research is required to explore the optimal dose of vitamin D supplement for subjects with asthma.

CONCLUSION

Vitamin D supplement regimen resulted in lower asthma exacerbations, despite varying doses of vitamin D used. Vitamin D as an addition to corticosteroids can be considered potentially cost-effective and safe to prevent asthma exacerbations. Subsequent studies ought to investigate the long-term impact of vitamin D in asthma treatment and to determine the optimal dosage of vitamin D supplementation for asthma patients with attention to standard treatment doses, duration of follow-up, larger sample size, and subject characteristics.

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