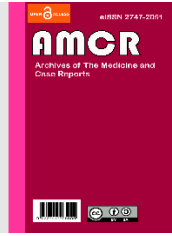




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The Association between Vitamin D Deficiency and Chronic Tonsillitis in Children: An Evidence Based Case Reports

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ABSTRACT

Background: vitamin D has an important influence on the host's immune system by modulating both innate and adaptive immunity and regulating the inflammatory cascade. Vitamin D deficiency may be related with reduced immunomodulation, specifically in preventing the occurrence of chronic tonsillitis. Objective: to identify the association between vitamin D deficiency with chronic tonsillitis in pediatric patients.

Methods: the search was conducted with advanced searching on PubMed® and Cochrane® according to the clinical question. The screening of title and abstract using inclusion and exclusion criteria, double filter, and reading full text led to six useful articles. The selected studies were critically appraised for validity, importance, and applicability. **Results:** three original articles were eligible for this evidence-based case report. All studies were considered to have good validity. All three studies reported an increased risk of chronic tonsillitis with the vitamin D deficiency and/or insufficiency.

Conclusion: Vitamin D deficiency may be associated with the increased risk of chronic or recurrent tonsillitis in children.

1. Introduction

Clinical scenario

A 10-year-old boy presented to the clinic with the chief complaint of difficulty swallowing food. Previously, the patient had consulted with an otolaryngologist and was diagnosed with chronic tonsillitis due to recurrent sore throat (5 times in the last 3 months). During recurrence, the patient had felt feverish.

The patient habitually consumes fried and spicy foods. The patient rarely spent time outdoors and often spent his time playing in front of the computer.

His parents were worried that the boy did not receive enough sunlight exposure, thus being in a state of vitamin D deficiency. The parent had asked whether the vitamin D deficiency was related to the recurring sore throat on the patient

Chronic tonsillitis is a recurrent and long-term inflammation of the tonsils without improvement of symptoms after administration of antibiotics.^{1,2} Chronic tonsillitis may be influenced by the pathogenic and immunity factors. Pathogenic factors refer to the characteristics of the pathogen associated with a higher ability to evade the immune system and remain viable in the host, while immunity factors refer to the characteristics of the patient associated with lower effectiveness in eliminating the pathogen.^{3,4}

Incidence rates of chronic tonsillitis in children varies according to the region. Haidara et al. had noted that there were approximately 40 million cases of chronic tonsillitis in the United States, 9 million cases in France, and 4 million cases in Spain.⁵ Previous reports by Ministry of Health in Indonesia had reported the estimated prevalence of chronic tonsillitis in children to



be 4.4%. Increasing incidence of chronic tonsillitis were reported compared to the previous decade.⁶

Vitamin D deficiency are often reported in patients with compromised immune system manifesting in upper tract respiratory infection; Shin et.al. had noted the prevalence of 91.3% of children presenting with vitamin D deficiency in recurrent adenotonsillitis.⁷ Reid et.al. had noted increased incidence of upper respiratory tract infection in patients with deficient serum vitamin D level (< 20 ng/mL).⁸ Conversely, Rao et al. had not found significant association with vitamin D deficiency with chronic tonsillitis.⁹ This report was aimed to describe the association between vitamin D deficiency with chronic tonsillitis in pediatric patients.

Clinical question

Clinical question: Are pediatric patients with vitamin D deficiency more likely to develop chronic tonsillitis when compared with pediatric patients without vitamin D deficiency ?

2. Methods

Article searching

Literature search was performed in electronic databases PubMed®, Cochrane®, on the 1st of January 2021. The keywords were inserted on the *MeSH Term* and *abstract/title* sections. The keywords were “chronic”, “recurrent”, “pediatric”, “children”, “tonsillitis”, “tonsillopharyngitis”, “Vitamin D”, “25-hydroxyvitamin D”, “25(OH)D”. Duplicate studies were eliminated with the help of EndNote application. After narrowing down literatures based on their titles and

abstracts with the PICO criteria, the full text literatures which met the eligibility criteria were critically appraised.

Article selection

Eligibility criteria

Article selection was based on the inclusion and

recurrent tonsillitis and children without chronic or recurrent tonsillitis; 2) the study design was cohort, case control or cross-sectional; 3) presence of vitamin D deficiency and/or insufficiency was assessed; and 4) publication within the last 10 years. The exclusion criteria were: 1) full text unavailable; 2) non-English article; 3) studies that recruits adult and pediatric patients without separate result for pediatric patient.

Critical appraisal

After literature selection, critical appraisal was done by consensus of all authors using several aspects based on Centre of Evidence-Based Medicine, University of Oxford for harm or etiology study. For the aspect of importance, the odds ratio (OR) is used to measure the ratio of the odds that an event. The formula is as follows:¹⁰

$$\text{Odd ratio} = \frac{(n) \text{ exposed cases} / (n) \text{ unexposed cases}}{(n) \text{ exposed non-cases} / (n) \text{ unexposed non-cases}}$$

The 95% confidence interval (CI) is used to estimate the precision of the OR. CI for ratio are calculated using the formula shown below:¹⁰

$$95\% \text{ CI} = \exp (\ln (OR) - 1.96 \times SE [\ln (OR)])$$

to

$$\exp (\ln (OR) + 1.96 \times SE [\ln (OR)])$$

for the Standard Error (SE) for ln(OR) is computed using the following equation:¹⁰

$$SE (\ln(OR)) = \sqrt{1 + \frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}$$

a = Number of exposed cases

exclusion criteria, which addressed the clinical question. The inclusion criteria were: 1) The subjects were children (aged < 18 years old) with chronic or



b = Number of exposed non-cases
 c = Number of unexposed cases
 d = Number of unexposed non-cases

3. Results

Following the search strategy, three original articles were eligible for this evidence-based case report.¹¹⁻¹³ The design and summary of result is available on Table 3. The critical appraisal is shown on Table 2. All article were case control studies with level of evidence 3.

All studies were considered to have good validity. Each group were similar and clearly defined although adequate follow up could not be done in this type of study. In terms of diagnostic tests for causation, the criteria were analyzed qualitatively, where the criteria ‘exposure preceding the onset of the outcome’ has to be fulfilled for the other criteria to be valid.

Unfortunately, that criteria is not fulfilled since vitamin D levels of the participants were not checked prior to diagnosing chronic tonsillitis.

From the aspect of importance, each study had an odds ratio (OR) above 1. The ORs were adjusted to per- protocol analysis for the critical appraisal. Only the study by Aydin et al.¹² showed a statistically significant result with a 95% confidence interval above 1. All studies were relevant to our case with similar subject’s characteristics.

Table 1. PICO criteria

PICO	
Population	Pediatric patients
Indicator	Vitamin D deficiency
Comparison	No Vitamin D deficiency
Outcome	Chronic or recurrent tonsillitis

Table 2. Resources and search strategy

Database	Search Strategy	Hits
PubMed	(((chronic[Title/Abstract]) OR (recurrent[Title/Abstract])) AND ((tonsillitis[MeSH Terms] OR (tonsillopharyngitis[Title/Abstract]))) AND ((children[Title/Abstract] OR (pediatric[Title/Abstract]))) AND (((vitamin d[Title/Abstract]) OR (25-hydroxyvitamin D[Title/Abstract])) OR (25(OH)D[Title/Abstract]))	6
Cochrane Library	#1 (children):ti,ab,kw OR (pediatric):ti,ab,kw OR (child):ti,ab,kw N:154879 #2 (vitamin D deficiency):ti,ab,kw N: 3967 #3 MeSH descriptor: [Tonsillitis] explode all trees and with qualifier(s): [diagnosis - DI] N: 16 #4 #1 and #2N:575 #5 #1 and #3 N:10 #6 (chronic):ti,ab,kw OR (recurrent):ti,ab,kw N: 213482 #7 #5 and #6 N: 3	3



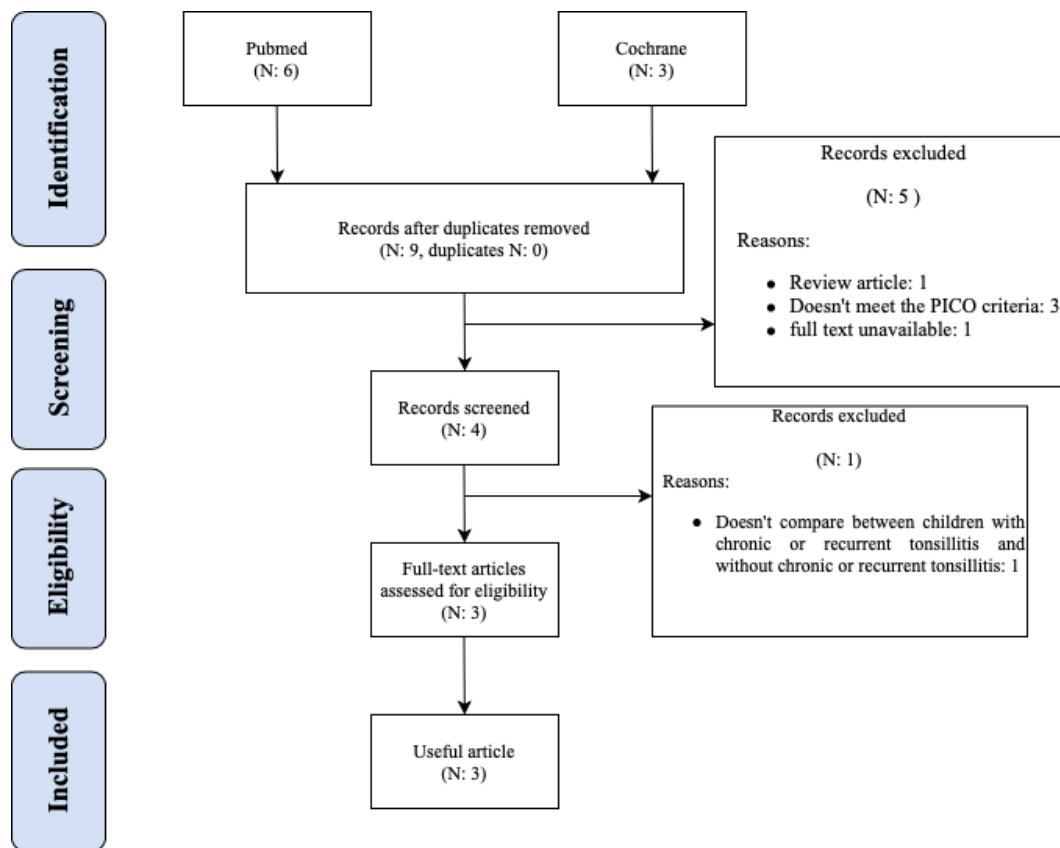


Figure. 1. Flow chart of literature searching

Table 3. Study characteristics VDR: vitamin D receptors

Articles	Study design	Population	Indicator
Aydin et al.12 (2011)	Case control	106 Children (2 – 12 years) with previous history of tonsillectomy (due to recurrent tonsillitis) and 127 children without history of tonsillectomy (due to recurrent tonsillitis) were recruited to the study.	Vitamin D levels, VDR gene polymorphism
Collak et al.13 (2014)	Case control	74 Children (2 – 12 years) with recurrent tonsillopharyngitis in outpatient clinics and 73 children without recurrent tonsillopharyngitis were recruited to the study.	Vitamin D levels.
Yildiz et al.11 (2012)	Case control	84 Children (2 – 10 years) with recurrent tonsillitis and 71 children without recurrent tonsillitis were recruited to the study.	Vitamin D serum, VDR gene polymorphism



Table 4. Critical appraisal.

Article, year	Level of evidence	Sample size	Validity				RR/OR (95% CI)	NN	Patient similarity
			Clearly defined	Equal measurement	Adequate follow-	Fulfill the criteria for causation			
Aydin et al.12, (2011)	3	23 3	+	+	-	-	VDI+D: OR 32.4 (1.9 – 551.4)	2	+
Collak et al.13, (2014)	3	14 7	+	+	-	-	VDD: OR 3.5 (0.8 – 15.0); VDI: OR 1.8 (0.4 – 7.4)	VD D: 3.3 VD I: 7. 6	+
Yildiz et al.11, (2012)	3	15 5	+	+	-	-	VDD: OR 7.9 (0.4 – 151)	2. 1	+

+ stated clearly in the article; - not being done; levels of evidence based on Oxford Centre for Evidence-based Medicine; RR: relative risk; OR: odds ratio; CI: confidence interval; NNH: number needed to harm; VDD: vitamin D deficiency; VDI: vitamin D insufficiency; VDI+D: Vitamin D insufficiency and deficiency

4. Discussion

Vitamin D deficiency may be related with reduced immunomodulation, specifically in preventing the occurrence of chronic tonsillitis. Available studies had shown that vitamin D has an important influence on the host's immune system by modulating both innate and adaptive immunity and regulating the inflammatory cascade.¹⁴⁻¹⁶ Vitamin D induces the expression of two antimicrobial peptides—cathelicidin and β -defensin—that are widely expressed in the body and play a key role in innate immunity owing to their chemotactic action and toxin neutralization. With this background, Vitamin D may have a preventive role in chronic or recurrent tonsillitis by inhibiting the formation of bacterial biofilms.^{15,16}

In this study, there were only three articles that met the eligibility criteria. These three articles were

case control studies which compared children with chronic or recurrent tonsillitis and children without chronic or recurrent tonsillitis. The appraised studies showed different vitamin D cut off levels to determine the risk for chronic tonsillitis. Yildiz et al.¹¹ used vitamin D deficiency ($< 50\text{nmol/L}$) as the risk factor for chronic tonsillitis. Collak et al.¹³ used vitamin D deficiency ($< 20\text{ng/mL}$, equal to $< 50\text{nmol/L}$) and insufficiency ($20 - 32\text{ng/mL}$, equal to $50 - 80\text{nmol/L}$) as risk factors for chronic tonsillitis. Meanwhile, Aydin et al.¹² employed a cut off level of Vitamin D levels below 80nmol/L , which is the combination of vitamin D deficiency and insufficiency. All three studies reported an increased risk of chronic tonsillitis with the vitamin D deficiency and/or insufficiency. However, only Aydin et al.¹² showed a statistically significant result with OR 32.4 (1.9 – 551.4). The calculated number needed to harm (NNH) from Aydin



et al.¹² is two, which means there is one child who suffered chronic tonsillitis in two children with vitamin D deficiency and/or insufficiency. The limitation to note is the sunlight exposure variance; while the included studies had attempted to perform the study in time periods where climate variation would be minimized, the application of the studies may not be fully applicable in Indonesia. Since Indonesia has a tropical climate and is located near the equator, Indonesians would receive more sunlight all year round compared with those far from the equator. While the studies were performed in subtropical regions, it may be inferred that sunlight exposure variances would affect the prevalence of vitamin D deficiency in different manner between both regions. Soesanti et al.¹⁷ however, suggested that 90.8% of healthy children in Indonesia had insufficient level of vitamin D, while 15% had vitamin D deficiency. Similarly, Collak et al.¹³ reported that 90.6% among the control group (Turkey children without chronic tonsillitis) had insufficient level of vitamin D. Meanwhile, prevalence of vitamin D deficiency in control group (33.8%) was higher than in Indonesian healthy children. Conversely, Aydin et al.¹² and Yildiz et al.¹¹ reported that none of the control group (Istanbul children without chronic tonsillitis and/or tonsillopharyngitis) had vitamin D deficiency or vitamin D insufficiency.

Another limitation of this report is the use of case control studies for appraisal, while the best evidence for etiology studies comes from cohort studies. Further prospective studies addressing vitamin D supplementation with or without duration of sunlight exposure in children who were diagnosed as tonsillitis with vitamin D deficiency in Indonesia (or other tropical countries), may be required to further consolidate the findings of the studies included in this report.

5. Conclusion

Vitamin D deficiency may be associated with the increased risk of chronic or recurrent tonsillitis in children. Additional prospective clinical trials may be required to ascertain whether vitamin D

supplementation would prevent the risk of chronic tonsillitis in children with vitamin D deficiency.

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