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REVIEW

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Is There any Association between Vitamin D Deficiency and Recurrent Tonsillopharyngitis? An Updated Systematic Review

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ABSTRACT

Introduction: *It has been theorized that vitamin D deficiency is directly associated with the occurrence of recurrent tonsillopharyngitis. The purpose of this study was to investigate the potential association between vitamin D levels and recurrent tonsillopharyngitis.*

Methods: *We searched the databases of PubMed, Scopus and Cochrane Central Register of Controlled Trials (CENTRAL) until the 15th of August 2023. Original articles of any study design assessing the correlation between recurrent tonsillopharyngitis and vitamin D levels in both pediatric and adult patients were considered. Serum 25-hydroxyvitamin D level was the measured outcome. Quality assessment was carried out by using the Newcastle-Ottawa scale (NOS) for observational studies.*

Results: *Eleven observational studies with a total of 2 503 participants were included in this systematic review. The qualitative synthesis revealed a possible association between recurrent tonsillopharyngitis and vitamin D deficiency. All studies, except one study, demonstrated a statistically significant association between the two conditions. As per our quality appraisal, all papers were deemed to be of moderate or good quality.*

Conclusion: *This study shows a potential association between vitamin D deficiency and the development of recurrent tonsillopharyngitis. Future studies should not only investigate this association in a more comprehensive manner but also assess the prevention potential of vitamin D supplementation on tonsillopharyngitis pathogenesis.*

Keywords: systematic review, vitamin D, recurrent tonsillitis, recurrent tonsillopharyngitis.

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INTRODUCTION

Tonsillopharyngitis (TPS) is the acute infection of the palatine tonsils and pharynx, which manifests with erythema, exudation or ulceration (1). It is caused by a variety of pathogens (2), with viral infections accounting for 50-80% of acute cases. However, approximately 5-17% of those are attributed to bacterial infections, primarily group A β-hemolytic streptococci (GAS) (3), with higher rates during winter in temperate climates (2). Recurrent TPS is the repetitive inflammation of the palatine tonsils and pharynx, predominantly, or even exclusively, caused by bacteria (4). In the literature, Paradise *et al* define "recurrent tonsillopharyngitis" as experiencing seven or more well-documented, clinically important, adequately treated episodes within one year, or five episodes in the last two years, or three episodes in the preceding three years (5). Several studies elucidate the pathogens involved in recurrent TPS (4), with *Staphylococcus aureus* being the main culprit, given its high prevalence in tonsillar samples from affected patients (4, 6).

The pathogenesis of recurrent TPS remains unclear (7), with multiple potentially associated factors which are including patient non-compliance, premature antibiotic cessation, inadequate absorption, resistance, bacterial tolerance, load and immune dysfunction (8-10). Previous studies found genetic predispositions to immune response in recurrent TPS (11, 12). Moreover, biofilm formation, particularly by *Staphylococcus aureus*, may explain antibiotic therapy failure (13-16). Studies identified biofilms in tonsillar folds and adenoids, with higher prevalence in recurrent cases (14-16). This association suggests the role of biofilms in recurrent TPS, potentially contributing to functional antibiotic resistance despite the absence of specific mechanisms (4). Furthermore, the increase in TPS cases during the winter season is one of the observed trends (2). While the higher frequency of the disease during winter can be attributed to environmental factors such as spending more time indoors, attention is also drawn to the lack of sunlight during this period. Sunlight plays a significant role in maintaining adequate levels of vitamin D in the human body as it is primarily produced in the skin through exposure to ultraviolet light. To elaborate, vitamin D is synthesized from 7-dehydrocholesterol in the skin through ultraviolet light band B (UVB) exposure, resulting in the formation of vitamin D3 (cholecalciferol), an inactive precursor. During the winter season, when sunlight exposure is limited, the skin synthesizes lower amounts of vitamin D (17). Consequently, studies have established a link between recurrent TPS and reduced sunlight exposure during winter, leading to inadequate vitamin D synthesis in the human body during that specific season (18, 19). Moreover, the association between susceptibility to upper respiratory tract infections (URTIs) and vitamin D deficiency has been suggested for many years. Several studies have successfully correlated the low levels of vitamin D with the high incidence of URTIs (20-25).

The intricate pathophysiological connection between vitamin D deficiency and recurrent TPS, as well as upper respiratory tract infections (URTIs) in general, involves a complex interplay. The palatine tonsils assume a pivotal role in detecting airborne antigens, facilitated by macrophages residing within their crypts (26). These antigens are internalized by crypt epithelial cells and recognized by toll-like receptors (TLRs) present on the macrophages (27). Due to the distinct structural composition of pathogens compared to eukaryotic cells, TLRs can discern these differences (27). The expression of TLRs exhibits variability concerning recurrent TPS (28). Moreover, it has been observed that TLR activation was contributing to an elevated expression of the vitamin D receptor gene and vitamin D hydroxylase, both critical for vitamin D synthesis (29). When pathogens are detected, macrophages utilize externally acquired 25-hydroxyvitamin D through endocytosis to synthesize 1,25-dihydroxyvitamin D (30). This internally synthesized 1,25-dihydroxyvitamin D then binds to vitamin D receptors, prompting the production of surface antimicrobial peptides (AMPs) like defensin and cathelicidin (31). These AMPs assume a crucial role in innate immunity (32, 33). To delve deeper, AMPs serve as the primary defense against URTIs by identifying invading viral or bacterial agents. They play a crucial role in neutralizing toxins and exhibiting chemotactic activity (34). These peptides directly inhibit the growth of microorganisms in various tissues, showcasing a broad-spectrum antimicrobial activity that impedes microorganism proliferation (22, 35). In essence, the active form of vitamin D substan-

tially regulates the immune system of the human body (36).

Recognizing the pivotal role of vitamin D in immune function, this study aimed to assess levels of vitamin D in recurrent TPS by synthesizing data from various studies, to establish a potential association between them.

MATERIAL AND METHODS

The protocol of the present systematic review was registered with PROSPERO (CRD42023458859). Additionally, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, published in 2020, was followed (37).

Eligibility criteria

We included original trials assessing the correlation between vitamin D deficiency and recurrent tonsillitis or tonsillopharyngitis in both pediatric and adult patients. Studies examining the association between vitamin D deficiency and tonsillar hypertrophy as well as those evaluating patients who underwent adenoidectomy along with tonsillectomy for recurrent TPS or tonsillectomy for other reasons beyond recurrent tonsillitis were not included. Additionally, studies investigating patients suffering from other diseases along with recurrent TPS were also excluded from this systematic review. Additionally, only studies concerning measurements of vitamin D levels were considered. Finally, studies assessing the results of vitamin D supplementation in patients suffering from recurrent TPS were also excluded.

Outcome assessment

Serum 25-hydroxyvitamin D level was considered the primary outcome in our study and was reported in ng/mL.

Literature search

Two independent researchers (A.T. and K.T.) scanned the literature for published and unpublished studies examining the correlation between vitamin D deficiency and recurrent TPS. The databases of PubMed, Scopus and Cochrane Central Register of Controlled Trials (CENTRAL) were comprehensively assessed until the 15th of August 2023. Moreover, up to the same date, we searched for completed unpublished trials the registries of International Standard Randomized Controlled Trial Number (ISRCTN), ClinicalTrials.gov and Australian New Zealand Clinical Trials Registry (ANZCTR). Furthermore, reference lists from relevant articles were manually searched to identify additional studies. Of note, no language or age restrictions were applied. The search strategy included the terms: “tonsillitis” AND “Vitamin D”.

Selection of studies

Two investigators (A.T and K.T.) independently identified potentially relevant records through the systematic literature search. Following deduplication, the titles and abstracts of the remaining studies were screened for eligibility. The full text of the remainder of articles was evaluated for possible inclusion against our eligibility criteria. Any discrepancies between the two investigators were discussed and resolved through consensus.

Data extraction

Data extraction was independently conducted by two reviewers (A.T. and K.T.). From each eligible study, data extraction included the year of publication, country, study design and chronicity, and intervention groups. Data about participants’ characteristics such as age, sex, inclusion and exclusion criteria, the total number of participants and serum vitamin D levels were also extracted.

Quality assessment

The quality of studies was assessed by two researchers (A.T. and K.T.) utilizing the Newcastle-Ottawa scale (NOS) (38) for the case-controlled and cohort studies. Using the above-mentioned tool, each study is judged on eight items and categorized into three groups: selection of study groups; comparability of groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively.

RESULTS

Literature search

In total, 43 articles were identified in the literature search. After deduplication and title and abstract screening, 17 studies were considered relevant. Finally, 11 studies fulfilled the

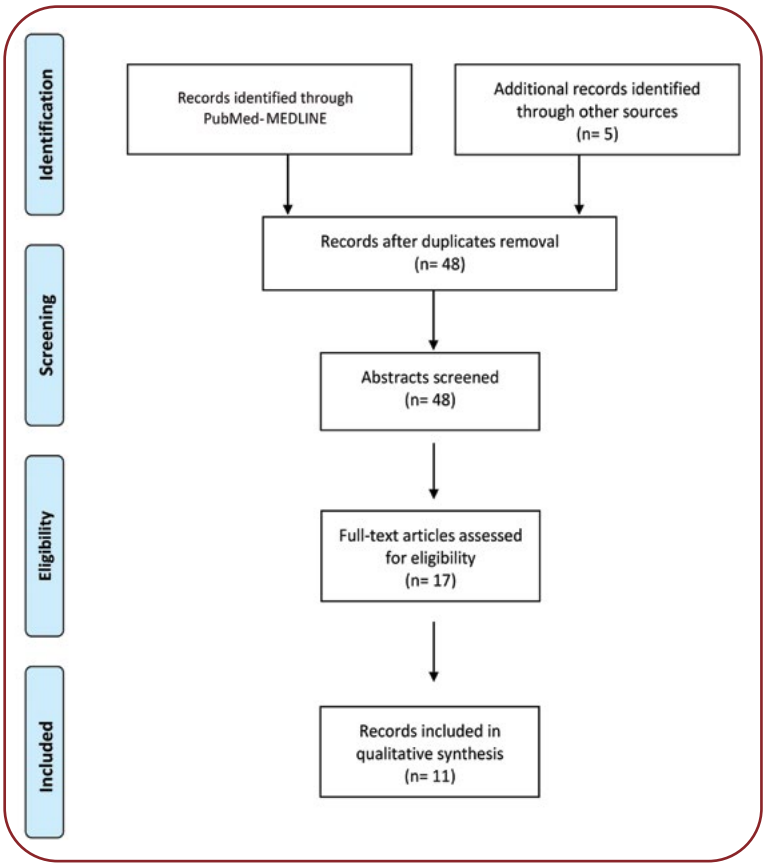

FIGURE 1. PRISMA flow diagram

eligibility criteria for inclusion in the present systematic review (Figure 1).

Study characteristics

Eleven studies with a total of 2 503 participants, which had been conducted in various countries globally, were included in the present systematic review. Four studies were carried out in Turkey (8, 17, 19, 39), two in India (40, 41), one in Israel (9), one in Italy (42), one in Iraq (43), one in Jordan (44) and one in Saudi Arabia (45). Both pediatric and adult patients were assessed. The included studies were both prospective and retrospective observational; nine of them were case-controlled and the remaining two cohort studies (Tables 1 and 2).

Quality assessment

With respect to the study quality, eight studies were graded 6/9 using NOS and thus were deemed to be of good quality, whereas three studies were graded 5/9 and thus were deemed to be of moderate quality (Tables 3 and 4).

A qualitative synthesis of the results

The common denominator of every study included in the present systematic review was the fact that patients with recurrent TPS had lower vitamin D levels than the control group, thus adequately associating those two conditions. In most studies, this correlation was statistically significant.

In a prospective case-control study, Aydin *et al* (17) reported that, in children who underwent tonsillectomy due to recurrent TPS, the average serum 25-hydroxyvitamin D level was lower (70.4±31.6 ng/mL) than that of healthy children in the control group (77.2±22.4 ng/mL). The difference in 25-hydroxyvitamin D levels between the two groups did not reach statistical significance (p=0.13). However, vitamin D insufficiency was more prevalent in children with recurrent TPS (18%). No vitamin D insufficiency was recorded in the control group. There was a statistically significant difference between groups ($p < 0.001$).

Furthermore, Yildiz *et al* (19) conducted a retrospective study which found that the difference in serum 25-hydroxyvitamin D levels between children with recurrent TPS (57.1±27.2 ng/mL) and healthy subjects (76.9±22.4 ng/mL) was statistically significant (p<0.001). In the study group, 4.7% of children had serum 25-hydroxyvitamin D in insufficiency levels, whereas none of those in the control group was in this category.

Another retrospective study examining the association between serum 25-hydroxyvitamin D and recurrent GAS TPS among adults was conducted by Nseir *et al* (9), who found that mean serum 25-hydroxyvitamin D levels among patients with recurrent GAS TPS were statistically significantly lower than the healthy controls (11.5±4.7 ng/mL *vs.* 26±7 ng/mL; p=0.001). After the adjustment of various confounders, including iron, diabetes mellitus, age, body mass index, calcium and serum creatinine, a significant association between vitamin D deficiency and recurrent GAS infection (p=0.001) was established.

Moreover, in a prospective study of children with recurrent TPS and their age-matched healthy controls, Collak *et al* (39) demonstrated that the difference in serum 25-hydroxyvitamin D levels between patients with recurrent TPS (19.7±8.7 ng/mL) and healthy controls (23.6±9.2 ng/mL) was significantly important

TABLE 1. Study characteristics

Study (year)	Country	Type of study	Intervention groups	Inclusion criteria	Exclusion criteria	Chronicity
Elbistanli (2017) (8)	Turkey	Retrospective case-control	277 patients with <three episodes of acute tonsillitis per year (Group A) and 149 patients with 3–7 episodes per year in the last two years (Group B)	1) Patients aged between 2–10 years; 2) absence of complications due to acute URTIs or a condition requiring hospitalization; 3) no supplementation of vitamin D within the past three months	1) Chronic diseases; 2) refusal for written informed consent; 3) inaccessible medical data	June 2013 – June 2014
Nseir (2012) (9)	Israel	Retrospective case-control	50 healthy individuals without a medical history of GAS tonsillopharyngitis and the members of this group were matched for age ± four years and gender with the study patients.	Individuals aged 18–60 years with recurrent tonsillopharyngitis	1) Non-GAS tonsillopharyngitis; 2) pregnancy; 3) renal failure (creatinine clearance rate <35 mL/min); 4) malignancy with life expectancy <1 year; 5) HIV infection; 6) splenectomy; 7) low compliance or low adherence with antibiotic use; 8) connective tissue diseases; 9) organ transplant; 10) chronic use of corticosteroid therapy; 11) vitamin D supplementation; 12) substance abusers	January 2007 – December 2009
Aydin (2010) (17)	Turkey	Prospective case-control	106 children subjected to tonsillectomy due to recurrent tonsillitis and 127 healthy children	For the recurrent tonsillitis group: 1) >six episodes of acute tonsillitis in 12 months or >3 episodes of acute tonsillitis in a year for two consecutive years; 2) no chronic or syndromic disease; 3) no nutritional problems; 4) no supplementation of multivitamin or vitamin D in the last year; 5) family signed consent form; 6) not known immune deficiency For the control group: children between 2–12 years, treated by the Pediatrics clinic	1) History of tonsillectomy; 2) chronic systemic disease; 3) vitamin D supplementation; 4) history of frequent tonsillopharyngitis; 5) history of frequent URTIs	N/A
Yildiz (2012) (19)	Turkey	Retrospective case-control	84 children with recurrent tonsillitis and 71 healthy children	1) >7 episodes of tonsillopharyngitis in one year; 2) symptoms of tonsillopharyngitis within the last seven days; 3) absence of conditions requiring hospitalization; 4) parental consent; 5) not known chronic diseases; 6) no supplementation of vitamin D during the last three months	N/A	April 2008 – April 2009
Collak (2014) (39)	Turkey	Prospective case-control	73 children with recurrent tonsillopharyngitis, and 74 age-matched healthy controls	For cases: ≥7 well-documented clinically important and adequately treated episodes of tonsillopharyngitis in the last year or ≥5 such episodes in each of the two preceding years or ≥3 such episodes in each of the three preceding years For controls: 1) <7 episodes of tonsillopharyngitis in the preceding year; 2) not known chronic disease; 3) not known disease affecting vitamin D metabolism	N/A	January 2012 – October 2012

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Saroch (2023) (40)	India	Prospective case-control	112 patients with <5 episodes per year (Group 1), 146 patients with >5 episodes per year (Group 2) in the last two years, 67 patients with otological complaints without tonsillar involvement as controls (Group 3)	Children between 5-15 years with recurrent tonsillitis without vitamin D supplementation within the past three months	1) Patients with blood sample inadequate for vitamin D testing; 2) patients with immunological diseases	November 2019 – January 2020
Rao (2020) (41)	India	Prospective cohort	60 children with chronic tonsillitis	1) Children between 5–15 years; 2) fulfillment of the criteria of Paradise; 3) no vitamin D supplementation	1) Syndromic children; 2) chronic systemic disease; 3) malnutrition or obesity or any other nutritional problems; 4) refusal of parents for their children to participate in the study	January 2018 – January 2019
Torretta (2015) (42)	Italy	Retrospective case-control	108 children with history of recurrent tonsillitis and 201 healthy controls	Caucasian children living in Milan with recurrent tonsillitis based on the criteria of Paradise	N/A	N/A
Sahar (2022) (43)	Iraq	Prospective cohort	Cases: 20 patients with recurrent tonsillitis (T group) who underwent tonsillectomy Controls: 20 healthy children	1) 3-7 reported episodes of recurrent tonsillitis per year; 2) written informed consent form of patients	N/A	November 2019 – January 2020
Al-Rawashdeh (2022) (44)	Jordan	Retrospective case-control	Cases: 242 children with recurrent acute tonsillitis Controls: 262 healthy children	For cases: 1) patients fulfilling the Paradise criteria for recurrent tonsillitis; 2) no history of any other diseases or syndromes; 3) no surgical history; 4) no malnutrition or obesity; 5) no history of vitamin D supplementation For controls: 1) no history of recurrent tonsillitis or any other diseases or syndromes; 2) no surgical history; 3) no malnutrition or obesity; 4) no history of vitamin D supplementation	N/A	January 2017 – January 2020
Hussein (2022) (45)	Saudi Arabia	Retrospective case-control	100 adult patients with recurrent tonsillitis and 100 subjects with no prior history of recurrent tonsillitis	N/A	For cases: 1) allergic rhinosinusitis; 2) systemic disorders; 3) chronic conditions other than chronic or recurrent tonsillitis; 4) age <18 years; 5) recent supplementation with vitamin D or consumption of low-calorie diets in the past year; 6) uncontrolled thyroid or parathyroid conditions; 7) incomplete and/or missing data For controls: 1) history of tonsillectomy or frequent tonsillitis; 2) known chronic systemic disorder; 3) vitamin D supplementation; 4) history of frequent URTIs; 5) incomplete and/or missing data	June 2016 – May 2022

TABLE 2. Study characteristics. The data has been presented as mean ± standard deviation (SD) or median (range)

Study (year)	Age (range) (years)	Mean age ± SD (years)		Participants		Females/males		Serum 25-hydroxyvitamin D mean ± SD/median (range) ng/mL	
		Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Elbistanli (2017) (8)	2–10	5.22 ± 2.26 (Group B)	4.40 ± 2.46 (Group A)	149 (Group B)	277 (Group A)	66/83 (Group B)	132/145 (Group A)	13.85 ± 9.05 (Group B)	16.68 ± 6.66 (Group A)
Nseir (2012) (9)	18–60	41 ± 13	42 ± 12	54	50	24 / 30	23 / 27	11.5 ± 4.7	26 ± 7
Aydin (2010) (17)	2–12	7 ± 2.3	6.59 ± 2.8	106	127	31 / 75	58 / 69	70.4 ± 31.6	77.2 ± 22.4
Yildiz (2012) (19)	2–10	5.6 ± 2.4	6.1 ± 2.7	84	71	N/A	N/A	57.1 ± 27.2	76.9 ± 22.4
Collak (2014) (39)	2–12	67.36 ± 29.75 months	65.72 ± 28.11 months	74	73	N/A	N/A	19.73 ± 8.77	23.62 ± 9.22
Saroch (2023) (40)	5–15	7.23 ± 3.12	7.27 ± 3.41	112 (Group 1), 146 (Group 2)	67 (Group 3)	147 / 111	34 / 33	21.7 ± 6.5 (Group 1), 19.7 ± 6.1 (Group 2)	36.6 ± 5.7 (Group 3)
Rao (2020) (41)	5–15	9.82		60		34/26		1) Females: 17.05/Males: 19.23 2) 5 to 10 years patients: 18.60/11 to 15 years patients 17.04	
Torretta (2015) (42)	N/A	71.4 ± 36.1 months	51.1 ± 27.8 months	108	201	42 / 66	86/115	22.0 ± 8.7	24.6 ± 7.8
Sahar (2022) (43)	4.5–14	N/A	N/A	20 (Group T)	20	7 / 13 (Group T)	12 / 8	17.5 ± 5.3 (Group T)	28.9 ± 6.1
Al-Rawashdeh (2022) (44)	2 - 14	5.5 ± 2.2	5.8 ± 2.3	242	262	112 /130	124 / 138	16.6 ± 7.3	26.1 ± 16.4
Hussein (2022) (45)	22 - 34	N/A	N/A	100	100	53 /47,	41 / 59	Median (IQR): 16 (12-21)	Median (IQR): 24.8 (16.2-29.1)

TABLE 3. Quality assessment of case-controlled studies utilizing the Newcastle–Ottawa scale (NOS)

	Elbistanli (2017) (8)	Nseir (2012) (9)	Aydin (2010) (17)	Yildiz (2012) (19)	Collak (2014) (39)	Saroch (2023) (40)	Torretta (2015) (42)	Al-Rawashdeh (2022) (44)	Hussein (2022) (45)
Selection									
Is the case definition adequate? (maximum 1 ✱)	✱	✱	✱	✱	✱	✱	✱	✱	✱
Representativeness of cases (maximum 1 ✱)	✱	✱		✱	✱	✱	✱	✱	✱
Selection of controls (maximum 1 ✱)	✱	✱	✱		✱	✱	✱	✱	✱
Definition of controls (maximum 2 ✱)	✱	✱	✱	✱		✱	✱	✱	✱
Comparability									
Comparability of cases and controls on the basis of the design or analysis (maximum 2 ✱)	✱	✱	✱	✱	✱	✱	✱	✱	✱
Exposure									
Ascertainment of exposure (maximum 1 ✱)									
Some method of ascertainment for cases and controls (maximum 1 ✱)	✱	✱	✱	✱	✱	✱	✱	✱	✱
Non-response rate (maximum 1 ✱)									
Total score (out of 9 ✱)	6	6	5	5	5	6	6	6	6
Power	**Adequately powered**	**Adequately powered**	**Adequately powered**	**Adequately powered**	**Adequately powered**	**Adequately powered**	**Adequately powered**	**Adequately powered**	**Adequately powered**

TABLE 4. Quality assessment of cohort studies utilizing the Newcastle–Ottawa scale (NOS)

	Rao (2020) (41)	Sahar (2022) (43)
Selection		
Representativeness of the exposed cohort (maximum 1 ✱)	✱	✱
Selection of the non-exposed cohort (maximum 1 ✱)	✱	✱
Ascertainment of exposure (maximum 1 ✱)		
Demonstration that outcome of interest was not present at start of study (maximum 2 ✱)	✱	✱
Comparability		
Comparability of cohorts on the basis of the design or analysis (maximum 2 ✱)	✱	✱
Exposure		
Assessment of outcome (maximum 1 ✱)	✱	✱
Was follow-up long enough for outcomes to occur (maximum 1 ✱)	✱	✱
Adequacy of follow up of cohorts (maximum 1 ✱)		
Total score (out of 9 ✱)	6	6
Power	**Adequately powered**	**Adequately powered**

($p<0.01$). Serum 25-hydroxyvitamin D level was deficient, insufficient and adequate in 42.9%, 50.3% and 6.8% of the patients in the study population.

In a study investigating the serum 25-hydroxyvitamin D levels in children with recurrent TPS in Milan, Torreta *et al* (42) reached the same conclusion. In comparison with healthy individuals, the mean serum 25-hydroxyvitamin D levels in the study group of children with recurrent TPS were significantly reduced (22.0±8.7 ng/mL *vs* 25.6±7.8 ng/mL, $p=0.03$). The proportion of children with insufficient or deficient serum 25-hydroxyvitamin D levels was higher in the group with recurrent TPS (81.5% and 6.5%, respectively) than in the control group (75.1% and 3.5%), although the difference was not significant.

In a retrospective review of clinical charts, Elbistasnli *et al* (8) sought to compare the mean serum 25-hydroxyvitamin D levels between patients experiencing 3–7 episodes of recurrent TPS per year, within less than two years, with individuals experiencing less than three episodes of TPS per year. The mean serum 25-hydroxyvitamin D levels were 13.85±9.05 ng/mL for the first group and 16.68±6.66 ng/mL for the second group. The difference between the two groups was statistically significant ($p=0.001$).

Additionally, the study by Rao *et al* (41) examined the levels of serum 25-hydroxyvitamin D in 60 children with recurrent TPS, of which 40 (66.7%) subjects were found to have a deficiency and 20 (33.3%) insufficiency. The mean level of 25-hydroxyvitamin D (17.99 ng/mL) ranged between 9.13 and 28.58 ng/mL.

In a retrospective comparative analysis, Hussein *et al* (45) examined whether serum 25-hydroxyvitamin D levels were a risk factor for recurrent TPS among adult patients. Thus, 100 adult patients with recurrent TPS were recruited as cases, while the control group comprised 100 subjects with no prior history of recurrent TPS. The median serum 25-hydroxyvitamin D levels were 16 ng/mL (range 12–21) in the case group and 24.8 ng/mL (range 16.2–29.1) in the control group. The statistical difference was significant ($p<0.001$). A deficiency in serum 25-hydroxyvitamin D was found in 68% of patients in the case group and only 50% of controls; the situation was different for insufficiency, since those levels of serum 25-hydroxyvitamin D were detected in 24% of cases and 50% of controls.

Additionally, a part of the study of Sahar *et al* (43) investigated the relationship between patients with recurrent TPS who underwent tonsillectomy and healthy controls. The serum 25-hydroxyvitamin D level in the control group (28.9±6.1 ng/mL) showed a highly significant difference ($p < 0.01$) when compared with the patient group (17.5±5.3 ng/mL).

In their study, Saroch *et al* (40) divided the patients into three groups according to the number of episodes of recurrent TPS. Patients experiencing less than five episodes of tonsillitis per year were included in Group 1, whereas those with five or more episodes per year were classified in Group 2. Group 3 consisted of controls with no tonsillar involvement. The mean serum vitamin D levels of Groups 1, 2 and 3 were 21.7±6.5, 19.7±6.1 and 36.6±5.7, respectively. The serum 25-hydroxyvitamin D level in Group 1 was statistically significantly lower ($p=0.0034$) than Group 3. Similarly, upon comparison, serum 25-hydroxyvitamin D levels in Group 2 were also statistically significantly lower than Group 3 ($p=0.0023$). The number of patients with a deficiency of vitamin D was 99 in the case group and 22 in the control group. The number of patients with inadequate vitamin D was 84 in the case group and 20 in the control group. The total number of patients with sufficient vitamin D levels was 75 in the case group and 25 in the control one.

Finally, Al-Rawashdeh *et al* (44) conducted a study in which they compared children aged between 2 to 14 years suffering from recurrent TPS (case group) with healthy children of the same age who were recruited from the local community (control group). Among cases, 39.7% of subjects experienced at least seven episodes of tonsillitis per year; patients' mean level of serum 25-hydroxyvitamin D was 16.6±7.3 ng/mL, and overall, 72.3% of them had deficient levels, 20.3% insufficient levels and 7.4% sufficient levels. For controls, the mean serum 25-hydroxyvitamin D level was 26.1±16.4 ng/mL. with 34.7% of participants having deficient levels, 41.6% insufficient levels and 23.7% sufficient levels. The mean serum 25-hydroxyvitamin D level was significantly higher in the control group than the case group ($p < 0.0001$).

DISCUSSION

Vitamin D plays a crucial role in various bodily functions. Alongside its primary function of regulating calcium absorption in the small intestine, and thus, its involvement in bone metabolism and calcium homeostasis, recent research has delved into its significance in the immune system. The present systematic review thoroughly examines vitamin D levels in a substantial cohort of patients with recurrent TPS. In total, 11 studies have been included in the qualitative synthesis, encompassing diverse countries worldwide and enrolling both pediatric and adult subjects. The present systematic review effectively establishes a possible association between reduced serum vitamin D levels and recurrent TPS. Each included study has associated these two conditions with statistical significance, barring the findings by Aydın *et al* (17), which indicated no significant link between vitamin D levels and recurrent TPS.

The measurements in our study were based on serum 25-hydroxyvitamin D levels. We deemed this parameter the most suitable for evaluating vitamin D levels in the body due to its extended half-life of approximately 20 days (46). In contrast, the biologically active form, 1,25-(OH)2 vitamin D, has a much shorter half-life of only 3–6 hours, and its circulating blood level is significantly lower compared to 25-hydroxyvitamin D. Consequently, it is not preferred for assessing serum vitamin D levels (47, 48).

Moreover, despite different methods and criteria for defining vitamin D levels, in our study vitamin D levels were assessed using the currently categorized vitamin D levels by the Endocrine Society guidelines, which suggested that levels of 25-hydroxyvitamin D in the circulating blood ≤20 ng/mL reflected vitamin D deficiency, those ranging between 21–29 ng/mL vitamin D insufficiency and those ≥30 ng/mL vitamin D sufficiency (49).

Notably, studies by Aydin (17) and Yildiz (19), which were conducted on Turkish children, reported significantly higher levels of 25-hydroxyvitamin D compared to other studies. This discrepancy across studies may stem from various factors, including differences in personal or racial characteristics, laboratory techniques for vitamin D measurement, seasonal variations and absence of VDR polymorphism assessment. Ideally, each study should measure vitamin D levels during the same seasonal period to account for seasonal fluctuations. The rationale for assessing seasonal changes in serum vitamin D levels lies in reduced sunlight exposure during winter compared to summer. Additionally, other factors influencing vitamin D levels, such as dietary habits, sleep patterns, body composition, outdoor activity and overall health status, should be taken into consideration to mitigate potential biases among studies.

The results of the qualitative synthesis were further reinforced by the study conducted by Shrestha *et al* (50). In their prospective cross-sectional study, the authors observed that the incidence of recurrent TPS was 40.9% among patients with low levels of vitamin D (<30 ng/mL) but only 18.1% among those with optimal levels of vitamin D (>30 ng/mL). However, in contrast to most similar studies, Esteitie *et al* (51) reported that there were no differences in vitamin D levels between children undergoing adenotonsillectomy and those subjected to unrelated elective procedures. As a result, this pilot study did not reveal an association between serum vitamin D levels and the necessity for adenotonsillectomy.

Furthermore, in a previous systematic review and meta-analysis on the same topic, published by Mirza *et al* (18), the quantitative synthesis of four studies demonstrated a statistically significant reduction of vitamin D levels in patients with recurrent TPS as compared to healthy controls. The odds of vitamin D insufficiency were significantly higher in patients with recurrent TPS than in controls. Our systematic review added further six studies in the qualitative synthesis, all of them associating with statistical significance the low levels of vitamin D with recurrent TPS, which further strengthened the evidence that vitamin D levels are associated with recurrent TPS.

Furthermore, although our study exclusively focuses on assessing the association between vitamin D and recurrent TPS, deficiency of 25-hydroxyvitamin D predominantly impacts the occurrence and progression of other chronic diseases. Research has demonstrated close links between vitamin D levels and the onset and advancement of numerous chronic conditions, with its deficiency being linked to a heightened risk of malignancies (52), autoimmune diseases (53), metabolic disorders (54) and cardiovascular diseases (55). Also, a consistent correlation exists

between low levels of 25-hydroxyvitamin D and the susceptibility to upper respiratory tract infections (URTIs) (8, 34, 56). Studies have established connections between vitamin D levels and conditions such as adenotonsillar hypertrophy, TPS, PFAPA syndrome and otitis media with effusion (33, 57-59). It has also been observed that the general incidence of URTIs inversely correlates with vitamin D deficiency (22).

It is important to note that inadequate exposure to sunlight is not the sole cause of 25-hydroxyvitamin D deficiency. Vitamin D levels can also be influenced by dietary factors (17, 19). Nonetheless, over 90% of systemic vitamin D originates from the skin, while only 10% comes from dietary intake (53). Interestingly, a recent study revealed that, even in sunny regions, the incidence of 25-hydroxyvitamin D deficiency was ranging from 23% to 44% (47). However, the association between low vitamin D levels and other variables is still under investigation, yielding controversial data so far. Reid *et al* (33) discovered a significant association between low vitamin D levels and dark skin, high body mass index (BMI) and large tonsil size. Conversely, Rao *et al* (41) reported that gender, age, tonsillar and adenoid hypertrophy did not show a statistically significant association with vitamin D levels ($p > 0.05$). Similarly, Al-Rawashded *et al* (44) found no association between age and vitamin D levels ($p = 0.165$). On the other hand, BMI exhibited a correlation with vitamin D levels ($p < 0.0001$), aligning with findings from previous studies (60). In addition, Nseir *et al* (9) established a significant association between male gender and serum 25-hydroxyvitamin D, whereas Torreta *et al* (42) found no significant relationship between serum 25-hydroxyvitamin D levels and either gender or BMI. Lastly, Elbistanli *et al* (8) correlated lower 25-hydroxyvitamin D levels with larger tonsil size ($p = 0.023$). Conversely, Hussein *et al* (45) did not identify a significant relationship between serum 25-hydroxyvitamin D and tonsil size.

Now, the question that remains is whether vitamin D supplementation could decrease the incidence of URTIs. Divergent outcomes concerning the protective role of vitamin D against URTIs have emerged. Two double-blinded randomized controlled trials investigating vitamin D supplementation highlighted a reduction in URTI incidence (61, 62). Conversely, one randomized controlled trial found no benefit of vitamin D supplementation in lowering the occurrence of symptomatic URTIs (63). To elaborate, Li-Ng *et al* demonstrated that daily supplementation of 2 000 IU of vitamin D during the winter did not diminish the frequency and severity of URTIs in adults (63). In another study, Robertson *et al* reported an absence of correlation between vitamin D levels and URTIs and concluded that vitamin D supplementation did not curtail the URTI incidence within the Norwegian population (64). Furthermore, Awwad *et al* (65) conducted a hospital-based randomized prospective case-control study involving 80 children with recurrent tonsillitis and vitamin D deficiency. Among them, 40 received 50,000 IU of vitamin D weekly for 3–6 months, while the other 40 received 5 mL of distilled water as a placebo. The vitamin D group exhibited a statistically significant rise in serum vitamin D concentration after vitamin D supplementation compared to its initial concentration ($p < 0.001$). Vitamin D insufficiency elevated the risk for recurrent TPS ($p < 0.05$), as recurrent TPS was significantly more common in children with vitamin D deficiency compared to those who received vitamin D. These findings suggested a potential beneficial effect of vitamin D in patients with recurrent TPS. Moreover, it is hypothesized that vitamin D levels might be altered in patients with chronic tonsillar disease, involving an intricate interplay between innate and acquired immunity as well as bacterial load. Such an association implies that addressing vitamin D deficiency potentially reduces the rates of tonsillitis, tonsillectomies and subsequent postoperative complications (66). Overall, given the conflicting above-described evidence, controversy exists over whether vitamin D supplementation could diminish the incidence of recurrent TPS and URTIs in general.

Study strengths and limitations

Despite the sufficient number of studies reviewed by us here, totalizing 2 503 participants, we recognize that there are a few limitations which may potentially affect the robustness of our conclusions. Ideally, each study included in the present review should have conducted measurements of vitamin D levels during the same seasonal period, considering that sunlight exposure significantly differs between winter and summer seasons. Additionally, in most of the in-

cluded studies, serum vitamin D levels were measured only once per subject, neglecting the seasonal fluctuations in its levels. Furthermore, there are additional potential factors linked to vitamin D levels that were not considered in each of the included studies, such as dietary habits, body fat, sun exposure, etc, which could introduce some bias.

Implications for future research

Further large-scale studies are needed to investigate the relationship between vitamin D levels and the frequency of recurrent TPS, with standardized measurements and taking into consideration its seasonal variations. Additionally, further prospective randomized controlled studies assessing the effect of supplementation with vitamin D on the incidence of recurrent TPS are strongly suggested.

CONCLUSIONS

In conclusion, the present systematic review highlights a potential association between recurrent TPS and vitamin D deficiency. Given the outcomes of the present study, we advocate the screening of vitamin D levels in individuals with recurrent TPS. Further prospective randomized controlled studies assessing the effect of supplementation with vitamin D on the incidence of recurrent TPS are strongly suggested.

Ethical statement

No human or animal subjects or private, protected, or culturally significant research locations were used for the execution of this study. Thus, ethical approvals or informed consent were not applicable. ❑

Conflicts of interest: none declared.

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