



A Comparative Study of Vitamin D3 Insufficiency with Recurrent Tonsillopharyngitis and Without Tonsillopharyngitis

Inclub Dhungana

ENT Surgeon
Hetauda Hospital

INTRODUCTION

Repeated instances of tonsillopharyngitis are a common reason for children to visit the hospital.^{1,2} Recurrent tonsillopharyngitis is typically defined as experiencing at least 7 episodes in one year, 5 episodes per year for two consecutive years, or 3 episodes per year for three consecutive years.³ Numerous factors contribute to the development of recurrent tonsillopharyngitis, such as patient non-compliance, prematurely stopping antibiotic treatment, inadequate absorption of antibiotics, bacterial resistance, bacterial load, the presence of bacterial biofilms, and immune system deficiencies.⁴ It is worth noting that most cases are caused by viruses, and when it comes to bacterial cases, *Streptococcus pyogenes* is the most significant due to its potential for complications.

This study aims to determine the occurrence of vitamin D3 deficiency in children who suffer from repeated episodes of tonsillopharyngitis. The research investigates the importance of vitamin D in enhancing innate immunity through the production of surface antimicrobial peptides and its role in preventing bacterial biofilm formation.

Numerous recent studies have provided strong evidence supporting a direct link between low levels of vitamin D and an increased likelihood of upper respiratory tract infections^{5,6,7}

OBJECTIVE

TO ASSESS THE PREVALENCE OF VITAMIN D DEFICIENCY IN RECURRENT TONSILLOPHARYNGITIS PATIENTS AND COMPARE WITH NORMAL PATIENTS.

METHODOLOGY

Research Method: Quantitative type

Type of Study:

Hospital based Comparative study

Sampling Frame

Patients attending the department of ENT-HNS of National Medical College, Birgunj were assessed. Patient who satisfied the inclusion criteria was selected, from April 2022 to March 2023 for a period of 1 year

Study site:

Department of ENT-HNS in Collaboration to Central Laboratory, National Medical College and Teaching Hospital, Birgunj, Nepal.

Sample Size:-

$$N = AB$$

$$(E/S)^2$$

$$\text{where, } A = (1/q_1 + 1/q_2)$$

$$B = (Z_\alpha + Z_\beta)$$

$$E = \mu_1 + \mu_2$$

S = Standard deviation of vitamin D3 in recurrent tonsillopharyngitis

Where

$$Q_1 = 50\%$$

$$Q_2 = 50\%$$

$$Z_\alpha = 1.96$$

$$Z_\beta = 0.8146$$

$$\mu_1 = 23.6^8$$

$$\mu_2 = 19.7^8$$

$$S = 8.7^8$$

Putting this value in the above formula. The sample size calculated was 79 in each Recurrent Tonsillopharyngitis and Normal Group.

The study is a cross-sectional and hospital-based study undertaken for duration of 12 months. There are various limitations under which the study must be performed.

Time limitation: The duration of the study is 12 months, during which period the sample size may not be adequate enough to represent a statistically significant result with low error margin.

Selection Criteria:**Inclusion criteria:**

Patients attending the ENT & HNS OPD age group between (5-15Y)

Patients who fall under criteria for recurrent tonsillopharyngitis

Parental consent

Not on any vitamin d supplementation for past 3 months

Exclusion criteria:

Patients younger than 5 years and older than 15 years were not included.

Patients who had previous vitamin deficiency disorders.

Study variables:

Recurrent Tonsillopharyngitis , Non Tonsillopharyngitis , Age , Sex , Vitamin D3

Duration of study

Study duration was of one year (April 2022 to March 2023).

Tools and Techniques for Data collection:

Child of age 5-15 years with recurrent tonsillopharyngitis visiting ENT department was reviewed and identified retrospectively. Cases with a medical history of recurrent tonsillopharyngitis were compared to age- and gender-matched individuals without a medical history of recurrent tonsillopharyngitis. Recurrent tonsillopharyngitis was defined as three or more episodes of tonsillopharyngitis per year for a period of two consecutive years. Those who satisfied the inclusion criteria and exclusion criteria was selected and Vitamins D3 sample were collected.

According to American Academy of Pediatrics:

Vitamin D3 levels less than 20ng/ml was taken as deficient,

Vitamin D3 levels between 20-32ng/ml was taken as insufficient

Vitamin D3 levels between 33-100ng/ml was taken Normal

Vitamin D3 levels more than 100ng/ml was taken as hypervitaminosis

Statistical Methods: Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean +-SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance.

The following assumptions on data is made,

Assumptions:

1. Dependent variables should be normally distributed,

2. Samples drawn from the population should be random, Cases of the samples should be independent.

Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups, Non-parametric setting for qualitative data analysis.

Significant figures

+ Suggestive significance (P value: $0.05 < P < 0.10$)

* Moderately significant (P value: $0.01 < P < 0.05$)

** Strongly significant (P value : $P \leq 0.01$)

Statistical software: The Statistical software namely SPSS 25.0, and R environment ver.3.2.2 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

RESULTS

In our study, the majority of children in the case group were between the ages of 11 to 15 years, with 52 patients falling into this age group, followed by the 5-10 years age group, which had 30 patients. In the control group, consisting of children without tonsillitis, the most prevalent age group was also 11-15 years, with 48 children, and the 5-10 years age group, which included 34 children. The average age in our study was found to be 10.85 years.

Age distribution of Patients Studied

This study was conducted with a total of 164 participants, divided into two groups: 82 cases and 82 controls. Among the 82 cases, 54 were females and 28 were males. Of the 54 females in the case group, they were further categorized into two age groups. The first age group consisted of children aged 5 to 10 years, which included 19 females and 11 males.

The second age group encompassed children aged 11 to 15 years, comprising 35 females and 17 males. Similarly, within the control group of 82 participants, there were 34 females and 48 males.

Among the 34 females in the control group, they were also divided into two age groups.

The first age group comprised children aged 5 to 10 years, with 12 females and 22 males.

The second age group included children aged 11 to 15 years, with 22 females and 26 males.

Out of the 82 cases with recurrent tonsillitis, just 8 patients exhibited normal Vitamin D3 levels. In contrast, 33 cases had insufficient levels of Vitamin D3, and 41 cases had deficient levels. The average Vitamin D3 level among those with recurrent tonsillitis was calculated to be 22.6.

In the case of recurrent tonsillitis, it was observed that there was no noteworthy correlation between age and Vitamin D3 levels, with a p-value of 0.600. Similarly, the correlation between gender and Vitamin D3 levels was found to be insignificant, as indicated by a pvalue of 0.843. Furthermore, there was no significant relationship between Tonsillar Grade and Vitamin D3 levels, with a p-value of 0.485.

	type	N	Mean	Std. Deviation	Std. Error Mean
SERUM VIT D3	case	82	22.616	10.7630	1.1886
	control	82	40.671	11.7579	1.2984

Table 1: Mean Vitamin D levels of case and control

We conducted a comparison between two distinct groups: the "case" group, comprising individuals with recurrent tonsillitis, and the "control" group, which represents the overall healthy population. The "case" group exhibits a notably lower average Vitamin D level (22.616) in contrast to the "control" group (40.671). Table 1

		Levene's Test for Equality of Variances		Independent Samples Test				
		F	Sig.	t	df	Significance		Mean Difference
						One-Sided p	Two-Sided p	
SERUM VIT D3	Equal variances assumed	4.177	.043	-10.257	162	<.001	<.001	-18.0549
	Equal variances not assumed			-10.257	160.750	<.001	<.001	-18.0549

Table 2: SD of case and control

Levene's Test reveals that the variances between these groups are unequal, with a p-value of 0.043. The T-test further underscores a highly significant difference in means, with a p-value of less than 0.001. The mean difference is -18.0549, indicating that the "case" group significantly exhibits lower Vitamin D levels. The 95% Confidence Interval for this difference ranges from -21.5310 to -14.5788. In essence, individuals with recurrent tonsillitis tend to possess lower Vitamin D levels compared to the generally healthy population.

DISCUSSION

In Nepal, despite having an abundant amount of sunlight, vitamin D3 deficiency remains a significant health issue affecting both children and adults. This paradoxical situation can be explained by the presence of Vitamin D receptors (VDRs) in immune system cells and their regulatory effects on these receptors, which highlight the intricate relationship between vitamin D and the immune system.⁸

It has been established that vitamin D3 receptors are present in immune system cells such as dendritic cells, B-lymphocytes, T-lymphocytes, NK-cells, and monocytes. Vitamin D3 exerts its effects by activating these receptors, which, in turn, control the transcription of target genes responsible for the biological effects of its active form 1,25 (OH)₂ D.

Research by Gombart et al., demonstrated that 1,25 (OH) D increases the production of cathelicidin peptides. These peptides have been found to play a protective role against upper respiratory tract infections (URTIs), as previous studies have shown. In summary, the presence of VDRs in immune cells and their modulatory effects on various biological processes underscore the vital connection between vitamin D3 and the immune system, shedding light on its role in health and its potential impact on diseases and infections.⁸

Vitamin D plays a crucial role in bolstering the body's defense against various infectious agents, and research has consistently indicated that individuals with vitamin D deficiency are more susceptible to respiratory tract infections. Moreover, multiple studies have established a connection between vitamin D3 levels and patients who experience recurrent Tonsillitis. In our study, our primary objective is to evaluate the prevalence of vitamin D3 deficiency among children suffering from recurrent tonsilopharyngitis.

In our research, we categorized all the children into three groups based on their Vitamin D3 levels: normal, insufficient, and deficient. Among the 82 children in the control group, 59 had normal levels of Vitamin D3, 23 had insufficient levels, and none were classified as deficient. The average Vitamin D3 level in the control group was found to be 40.67.

Among the 82 cases of children with recurrent tonsillitis, only 8 of them had normal Vitamin D3 levels, while 33 children had insufficient levels, and 41 children had deficient levels of Vitamin D3. The mean Vitamin D3 level in the group with recurrent tonsillitis was determined to be 22.6.

In a study conducted by Collak and colleagues, involving a total of 147 patients (comprising 74 study patients and 73 control participants), they observed significantly lower vitamin D levels in the study group compared to the control group ($p < 0.001$). Among the patients in the study group, 63 (42.9%) were deficient in vitamin D, 74 (50.3%) had insufficient levels, and 10 (6.8%) fell within the normal range.⁹

This finding aligns with our own study, where we found that 50% of our participants, specifically 41 children, had deficient levels of vitamin D3.

In a separate prospective study conducted by Science and colleagues¹⁰, an investigation was carried out to examine the relationship between serum 25(OH)D levels and viral upper respiratory tract infections. The study's conclusion indicated that lower serum 25(OH)D levels were associated with an increased risk of viral upper respiratory tract infections.

Nseir et al.¹¹ conducted a study involving adults to investigate the relationship between vitamin D3 levels and recurrent group A streptococcal tonsillopharyngitis. They discovered that the average serum levels of 25(OH) vitamin D in individuals with recurrent GAS tonsillopharyngitis were significantly lower when compared to the control group (11.5 ng/ml \pm 4.7 vs. 26 ng/ml \pm 7; p=0.001). Furthermore, through a multiple regression analysis, they determined that having a serum 25(OH) vitamin D level below 20 ng/ml was associated with an increased risk of recurrent GAS tonsillopharyngitis, with an odds ratio of 1.62 and a 95% confidence interval ranging from 1.51 to 1.76 (p < 0.001).

In another study by Reid and colleagues¹², it was discovered that 78% of children in Auckland who underwent adenotonsillectomy had 25(OH) vitamin D levels below 75nmol.

They also concluded that low 25(OH) vitamin D levels were associated with factors such as darker skin, higher BMI, and larger assessed tonsil size

In their research, Aydin et al.¹³ did not observe a notable difference in serum 25(OH) vitamin D levels between individuals who experienced frequent tonsillitis episodes and the control group. Both groups exhibited similar levels of serum 25(OH) vitamin D.

In our own investigation, we did not identify any significant correlation between vitamin D3 levels and tonsil size (p value = 0.485). While we couldn't definitively establish a connection between tonsil size and low vitamin D3 levels, further assessments in future studies may provide more conclusive insights into this relationship.

Two randomized controlled trials have reported that vitamin D supplementation is effective in preventing upper respiratory tract infections^{14,15}. In contrast to these findings, Li-Ng and colleagues documented that vitamin D supplementation did not reduce the frequency and severity of upper respiratory tract infections in adults during the winter season.¹⁶

LIMITATIONS OF STUDY

Our study did have certain limitations. Since the vitamin D levels shows seasonal variation, ideally taking samples both in summer as well as winter would have been a better method in our study.

CONCLUSION

Notably, vitamin D3 deficiency is a significant health issue among children in our country, underscoring the necessity for further studies to establish a concrete link between low vitamin D levels and recurrent tonsillopharyngitis. Future investigations should also be designed to identify the optimal vitamin D levels

necessary for the effective functioning of the immune system. Building on our study, we recommend that children with recurring tonsillitis episodes be regularly screened for vitamin D3 deficiency and receive appropriate interventions, potentially contributing to improved health and a higher quality of life

References

1. Bisno AL. Acute pharyngitis: etiology and diagnosis. *Pediatrics*. 1996 Jun;97(6 Pt 2):949-54. PMID: 8637780.
2. Armstrong GL, Pinner RW. Outpatient visits for infectious diseases in the United States, 1980 through 1996. *Arch Intern Med*. 1999 Nov 22;159(21):2531-6. doi: 10.1001/archinte.159.21.2531. PMID: 10573043.
3. Vital and Health Statistics. Current estimates from the national health interview survey, 1996. Series 10, No. 200. Atlanta GA: Centers for Disease Control and Prevention, National Center for Health Statistics, October 1999.
4. Paradise JL, Bluestone CD, Colborn DK, Bernard BS, Rockette HE, Kurs-Lasky M. Tonsillectomy and adenotonsillectomy for recurrent throat infection in moderately affected children. *Pediatrics*. 2002 Jul;110(1 Pt 1):7-15. doi: 10.1542/peds.110.1.7. PMID: 12093941.
5. Sabetta JR, DePetrillo P, Cipriani RJ, Smardin J, Burns LA, Landry ML. Serum 25-hydroxyvitamin D and the incidence of acute viral respiratory tract infections in healthy adults. *PLoS One*. 2010 Jun 14;5(6):e11088. doi: 10.1371/journal.pone.0011088. PMID: 20559424; PMCID: PMC2885414.
6. Grant WB. Variations in vitamin D production could possibly explain the seasonality of childhood respiratory infections in Hawaii. *Pediatr Infect Dis J*. 2008 Sep;27(9):853. doi: 10.1097/INF.0b013e3181817bc1. PMID: 18645543.
7. Berry DJ, Hesketh K, Power C, Hyppönen E. Vitamin D status has a linear association with seasonal infections and lung function in British adults. *Br J Nutr*. 2011 Nov;106(9):1433-40. doi: 10.1017/S0007114511001991. Epub 2011 Jun 6. PMID: 21736791.
8. Gombart AF, Borregaard N, Koeffler HP. Human cathelicidin antimicrobial peptide (CAMP) gene is a direct target of the vitamin D receptor and is strongly up-regulated in myeloid cells by 1,25-dihydroxyvitamin D3. *FASEB J*. 2005 Jul;19(9):1067-77. doi: 10.1096/fj.04-3284com. PMID: 15985530.
9. Collak A, Bozaykut A, Demirel B, Sezer RG, Seren LP, Dogru M. Serum vitamin D levels in children with recurrent tonsillopharyngitis. *North Clin Istanbul*. 2014 Aug 3;1(1):13-18. doi: 10.14744/nci.2014.76486. PMID: 28058296; PMCID: PMC5175018.
10. Science M, Maguire JL, Russell ML, Smieja M, Walter SD, Loeb M. Low serum 25-hydroxyvitamin D level and risk of upper respiratory tract infection in children and adolescents. *Clin Infect Dis*. 2013 Aug;57(3):392-7. doi: 10.1093/cid/cit289. Epub 2013 May 15. PMID: 23677871; PMCID: PMC3888147.
11. W. Nseir et al. / *International Journal of Infectious Diseases* 16 (2012) e735–e738 doi: 10.1016/j.ijid.2012.05.1036005;289:F8–28.
12. Reid D, Morton R, Salkeld L, Bartley J. Vitamin D and tonsil disease--preliminary observations. *Int J Pediatr Otorhinolaryngol*. 2011;75:261–4, doi: 10.1016/j.ijporl.2010.11.012.
13. Aydin S, Aslan I, Yildiz I, Agachan B, Toptas B, Toprak S, et al. Vitamin D levels in children with recurrent tonsillitis. *Int J Pediatr Otorhinolaryngol* 2011;75:364–7.



14. Laaski I, Ruohola P, Mattilia V, Auvinen A, Vlikanin T, Pihlajamaki H. Vitamin D supplementation for the prevention of acute respiratory tract infections. A randomized double-blinded trial amongst young Finnish men. *J Infect Dis.* 2010;202:809–814. doi: 10.1086/654881.
15. Urashima M, Segawa T, Okazaki M, Kurihara M, Wada Y, Ida H. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in school children. *Am J Clin Nutr.* 2010; 91(5); 1255-1260. doi: 10.3945/ajcn.2009.29094
16. Li-Ng M, Aloia JF, Pollack S, Cunha BA, Mikhail M, Yeh J, Berbari N. A randomized controlled trial of vitamin D3 supplementation for the prevention of symptomatic upper respiratory tract infections. *Epidemiol Infect.* 2009 Oct;137(10):1396-404. doi: 10.1017/S0950268809002404. Epub 2009 Mar 19. PMID: 19296870.