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Research

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Relationship Between Serum Vitamin D Levels and Childhood Recurrent Tonsillitis

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ABSTRACT

Background: Many factors are associated with the development of recurrent tonsillitis. These include patient incompliance, premature cessation of antibiotherapy, inadequate antibiotic absorbance, bacterial tolerance, bacterial load, bacterial biofilms, and immune system deficiencies.
Objective: To compare between recurrent tonsillitis patients undergoing three to seven tonsillitis episodes per year within less than two years with controls having less than three tonsillitis episodes per year on the basis of vitamin D levels.
Study design: A retrospective review of clinical charts.
Methods: A total of 426 patients were enrolled in this study. The patients were divided into two groups according to the number of acute tonsillitis episodes: Those who had less than three episodes per year (Group A) and those with three to seven episodes per year (Group B). The patients in Group A were assigned to the control group. Each patient in Group B was considered as a potential candidate for recurrent tonsillitis. The total number of episodes of acute tonsillitis within one year, demographic characteristics of the patients and the mean serum 25-hydroxyvitamin D levels of both groups were compared.
Results: Group A consisted of 277 patients (132 women, 145 men; mean age 4.40±2.46 years; range 2 to 10 years), while Group B consisted of 149 patients (66 women, 83 men; mean age 5.22±2.26 years; range 2 to 10 years). The mean serum vitamin D levels of Group A and Group B were 57.83±23.10 nmol/L and 48.03±31.36 nmol/L, respectively. Serum vitamin D level of Group B was lower than the Vitamin D levels of Group A which was statistically significant (p=0.001, p<0.01, respectively).
Conclusion: This is the first study investigating vitamin D levels among patients for the diagnosis of recurrent tonsillitis during the follow-up. However, further prospective randomized-controlled studies are conducted to gain a better understanding as to whether vitamin D supplementation would reduce the tonsillectomy rates in the diagnosis of recurrent tonsillitis.

KEYWORDS: Vitamin D level; Children; Tonsillectomy; Recurrent tonsillitis.

INTRODUCTION

Acute tonsillopharyngitis is a clinical presentation which is usually characterized by clinical acute inflammatory manifestations such as hyperemic tonsils and pharynx, exudation, and ulceration.[1,2] Although this condition shows a viral etiological origin, approximately 5% to 17% of the cases are bacteriological which is mostly Group A β-hemolytic streptococci.[3] As previously described by Paradise et al, recurrent tonsillitis is defined as seven episodes of the condition within one year or five episodes in the preceding two years and more or three episodes in the preceding three years and more.[4,5] Many factors are related with the development of recurrent tonsillitis. These include patient incompliance, premature cessation of antibiotherapy, inadequate antibiotic absorbance, bacterial tolerance, bacterial load, bacterial biofilms, and immune system deficiencies.[3]

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It is well-established that vitamin D plays an important role in bone mineralization of the skeletal system. Serum levels of vitamin D may differ according to racial differences and seasonal changes. Afro-Americans and Hispanics have been reported to have lower vitamin D levels than Caucasians.[6] In the winter season, lower amounts of vitamin D synthesis occurs in the skin.[3,7] Solar ultraviolet B radiation (wavelength: 290-315 nm) penetrates the skin and converts 7-dehydrocholesterol to previtamin D3, which is rapidly converted to vitamin D3. Vitamin D from the skin and diet is metabolized by the liver to form 25-hydroxyvitamin D (25(OH) D). Then, 25 (OH) D is metabolized by the enzyme 25-hydroxyvitamin D-1α- hydroxylase (CYP27B1) to its active form, 1.25-dihydroxyvitamin D. Inadequate circulation may lead to the development of cancer, diabetes mellitus, cardiovascular diseases, and immune deficiencies.[8-10] In addition, vitamin D has a critical role in the production of surface anti-microbial peptides (AMPs), which plays an important role in innate immunity.[11] These peptides have a wide spectrum antimicrobial activity and directly prevent proliferation of microorganisms in a tissue.[12] Anti-microbial peptides are not only produced from neutrophils, but also produced from macrophages and natural killer (NK) cells. Also, they have been shown to play a critical role in the respiratory defense system.[12,13] Many recent studies have confirmed the positive correlation between low levels of vitamin D and increased incidence of upper respiratory tract infections (URTIs).[14-16]

In the present study, we aimed to compare recurrent tonsillitis patients undergoing three to seven tonsillitis episodes per year within less than two years with controls having less than three tonsillitis episodes per year with respect to the vitamin D levels.

METHODS

This retrospective study was conducted among a total of 426 children who were diagnosed with acute tonsillitis between June 2013 and June 2014 at our hospital, Otolaryngology-Head and Neck Surgery Department. The age of the patients ranged between 2 and 10 years. The inclusion criteria were as follows: The absence of complications due to acute URTIs or a condition requiring hospitalization, not receiving vitamin D in the depot or on daily basis within the past three months. The patients affected by chronic disease, who were unwilling to give a written informed consent or those with inaccessible medical data, were excluded from the study. All the patients were followed-up for at least one year and the total number of acute tonsillitis episodes was recorded. Serum 25 (OH) D levels, serum C-reactive protein (CRP), creatinine, serum calcium, total protein, albumin, and complete blood count was analyzed within the first three days of the first episode of acute tonsillitis. Serum 25 (OH) D level was determined using enzyme linked immunosorbent assay (ELISA) method. 25 (OH) D levels below 50 nmol/L was defined as a deficiency, between 50 to 80 nmol/L as inadequacy, between 80 to 250 nmol/L as normal, between 250 to 325 nmol/L as excessiveness, and greater than 325 mol/L as toxicity.[17,18] Normal values were between 0 to 0.50 mg/dL for CRP, 0.4 to 0.60 mg/dL for creatinine, 8.6 to 10.0 mg/dL for calcium, 6.4 to 8.3 g/dL for total protein, 3.5 to 5.2 g/dL for albumin, and 4000 to 11.000 cells/mm^3 for white blood cell counts (WBCs). According to the number of acute tonsillitis episodes they underwent, the patients were divided into two groups: Those who had less than three episodes per year (Group A) and those with three to seven episodes per year (Group B) in the last two years. The patients in Group A were assigned to the control group. Seven or more episodes within one year were defined as recurrent tonsillitis according to the Paradise criteria.[5] Recurrent tonsillitis was considered indicative of tonsillectomy and these patients were recommended for tonsillectomy. Each patient in Group B was considered as a potential candidate for recurrent tonsillitis. Age, sex, chronic diseases, total number of acute tonsillitis episodes per year, serum 25 (OH) D levels, body mass index (BMI), tonsil size, serum CRP levels, creatinine, serum calcium levels, total protein, albumin, and complete blood counts were recorded. The total number of acute tonsillitis episodes within one year, demographic characteristics and the mean serum 25 (OH) D levels of both groups were compared.

All patients were informed about the study and a written consent was obtained from each patient or parents of the patients. The study protocol was approved by the Institutional Ethics Committee (ethical committee number: 2014/64). The study was conducted in accordance with the principles of Helsinki Declaration.

STATISTICAL ANALYSIS

Statistical analysis was performed using the NCSS (Number Cruncher Statistical System) 2007 and PASS (Power Analysis and Sample Size) 2008 software (Utah, USA). Other than the descriptive statistical methods (mean, standard deviation, median, frequency, rate, minimum, maximum), the Mann-Whitney U test was performed to analyze the abnormally distributed quantitative data between the groups. The Yates continuity correction (Yates chi-square) test was performed to compare the qualitative data between the groups. p-values of <0.01 and <0.05 were considered as statistically significant.

RESULTS

A total of 426 patients were enrolled in this study. Group A consisted of 277 patients (132 women, 145 men; mean age 4.40±2.46 years; range 2 to 10 years), while Group B consisted of 149 patients (66 women, 83 men; mean age 5.22±2.26 years; range 2 to 10 years). The demographic characteristics of the groups have been summarized in Table 1.

The mean serum vitamin D levels of Group A and Group B were 57.83±23.10 nmol/L and 48.03±31.36 nmol/L, respectively. None of the patients had a serum 25 (OH) D level at toxic levels. The mean 25 (OH) D levels of Group B were found to be at the deficiency level, whereas Group A was at the

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Table 1: Patient Demographics.

	Group A (n=277) Mean±SD	Group B (n=149) Mean±SD	*p**
Age (year, mean±SD)	4.40±2.46	5.22±2.26	**0.012***
Serum CRP (ng/dl)	0.675±0.123	1.4±0.8	**0.079***
Creatinine (mg/dl)	0.82±0.4	0.78±0.2	**0.186***
Calsiyum (mg/dl)	9.3±1.1	9.4±1.4	**0.376***
Total protein (g/dl)	6.84±3.7	7.0±2.9	**0.028***
Albumin (g/dl)	4.3±3.3	4.8±2.2	**0.662***
WBC (10^3/mm^3)	11.9±4.7	13.3±4.4	**0.018***
BMI	14.7±3.8	16.4±4.4	**0.628***

*Man-Whitney U test

inadequacy level. Serum 25 (OH) D levels of Group B were lower than the levels of Group A and this difference was statistically significant (p=0.001, p<0.01, respectively) (Table 2). Of the patients in Group A and Group B, 145 and 83 were males, respectively. However, there was no statistically significant difference in the number of acute tonsillitis episodes between the groups on the basis of sex (p>0.05) (Table 3).

No statistically significant difference was observed either in terms of the mean CRP (ng/dL), creatinine (mg/dL), calcium (mg/dL), total protein (g/dL), albumin levels (g/dL), and WBCs (cells/mm^3) between groups.

The tonsil size according to the Brodsky Scale[19] and the mean 25 (OH) D levels have been shown in Table 4. Based on our results, lower 25 (OH) D levels were significantly associated with larger tonsil sizes (p=0.023).

DISCUSSION

The adaptive immune system is a complex system associated with the contribution of many cells.[20] Vitamin D plays a critical role in the adaptive immune system.[11] Effects of vitamin D on the immune system have been the subject of many researches, particularly focusing on its effects on the production of AMPs. Gombart et al[21] showed that 1, 25 (OH) D increased the production of cathelicidin peptides. These peptides have been demonstrated to have a protective role against URTIs in the previous studies.[22-24] In another study, Ball et al[13] compared tonsillectomies for recurrent tonsillitis and obstructive sleep apnea syndrome and concluded that AMPs of the tonsil surface epithelium, beta-defensin 1, 3 - and cathelicidin decreased in the recurrent tonsillitis group.

Table 2: Vitamin D Levels of the Study and Control Groups.

	Group A (227) mean±SD	Group B (149) mean±SD	*p**
Serum vitamin D levels (nmol/L)	57.83±23.10	48.03±31.36	**0.001***

**Man-Whitney U test
SD: standart deviation.

Table 3: Comparison of Sex of the Study and Control Groups According to the Yates Continuity Correction Test.

		Group A (277) (%)	Group B (149) (%)	*p**
Gender	Male	145 (63.6)	83 (36.4)	0.122*
	Female	132 (66.7)	66 (33.3)	

*Yates Continuity Correction Test

Table 4: Correlation between the Tonsil Size and Mean 25 (OH) Vitamin D Levels.

Groups/tonsil size	Grade 1(No)	Grade 2	Grade 3	Grade 4	
A (227)	65.8 (44)	61.5 (76)	53,0 (80)	49.7 (27)	p=0.023*
B (149)	53.4 (23)	50.2 (42)	43,5 (64)	40.4 (20)	
	p:0.622*	p:0.42*	p:0,882*	p:0.346*	

*p: Man-Whitney U test

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Lack of vitamin D receptors (VDR) were also shown to develop hypertrophy of subcutaneous lymph nodes due to the accumulation of mature dendritic cells in mice.[25] In addition, low levels of 1, 25 (OH) D were considered to decrease the inhibition of differentiation of dendritic cells, thereby, resulting in adenotonsillar hypertrophy.[11] Moreover, vitamin D-induced antiviral peptides were shown to be effective against the herpes simplex type 1, adenovirus, human immunodeficiency virus, and chickenpox virus as has been implicated in the previous studies.[26]

Furthermore, Science et al[27] demonstrated that a higher risk for viral URTIs which was confirmed by polymerase chain reaction (PCR) was associated with low vitamin D levels. The authors revealed that the risk for URTIs increased by 50%, when vitamin D levels were below 70 nmol/L, whereas the risk increased by 70%, when vitamin D levels were below 50 nmol/L. The authors concluded that young age and low levels of vitamin D increased the incidence of URTIs. Similarly, in our study, recurrent tonsillitis candidate group (Group B) was younger. In a study, Ginde et al[28] reported that adults with vitamin D levels of ≥75 nmol/L had fewer URTI episodes and children undergoing tonsillectomy due to recurrent tonsillitis had a mean serum vitamin D level of <75 nmol/L. In another study, Nseir et al[3] found a positive correlation between recurrent Group A streptococci (GAS) tonsillitis and vitamin D deficiency. In their study, the mean vitamin D level was 26±7 ng/mL (64.7±17.4 nmol/L) in the control group and 11.5±4.7 ng/mL (28.6±11.7 nmol/L) in the recurrent GAS group. Reid et al[11] found that low vitamin D levels were associated with dark skin, high body mass index, and large tonsil sizes. However, there was no significant relationship between BMI values and vitamin D levels. 25 (OH) D levels were significantly associated with the operating surgeon's classification technique of the tonsil size; however, multiple linear regression analysis showed that this association was not a major predictor of 25 (OH) D status. In the present study, we found a negative correlation between the tonsil size and 25 (OH) D status, consistent with the results of study of Reid et al.[11] Although, this may be a potential explanation, further studies are required to assess the association of larger tonsil sizes with lower 25 (OH) vitamin D status. In another study, Esteitie et al[6] measured the mean vitamin D levels as 28.4±7.7 ng/mL (70.7±19.2 nmol/L) in children undergoing adenotonsillectomy and 27.1±7.1 ng/mL (67.5±17.7 nmol/L) in the control group, suggesting no significant Vitamin D deficiency between the two groups. In addition, Yıldız et al[29] measured serum vitamin D levels as 142.7±68.1 nmol/L in patients with recurrent tonsillitis and 192.3±56.1 nmol/L in healthy controls. The authors suggested that the recurrent tonsillitis group had significantly lower vitamin D levels, compared to healthy children. In the same study, VDR polymorphisms were investigated; however, no significant difference was found between the groups. In their study, Aydın et al[7] showed that there was no significant difference between vitamin D levels and VDR polymorphism among children with recurrent tonsillitis and healthy subjects. They measured serum vitamin D levels as 176±79 nmol/L in the recurrent tonsillitis group and 193±56 nmol/L in the control group. Varying results of the studies may be explained by the several factors such as working groups, seasonal, personal or racial factors, vitamin D measurement methods, studied endpoints or VDR polymorphisms. Our study can be distinguished from previous studies, as it aims to demonstrate the relationship between the incidence of acute tonsillitis and vitamin D levels with a control group consisting of the same patient population. In the current study, we addressed patients with frequent acute tonsillitis episodes but not diagnosed with recurrent tonsillitis. The patients with three or more episodes of acute tonsillitis are also followed-up to evaluate whether they would continue to have more than three episodes and be diagnosed with recurrent tonsillitis in the next two or three years. This is the first reported study in the literature, directed towards investigating vitamin D levels among recurrent tonsillitis candidates. Furthermore, we divided the patients into two groups according to the number of episodes they underwent. Higher vitamin D levels in Group A than Group B suggest that vitamin D levels may have an influence on the frequency of episodes. As a result, several studies in the literature have led to the emergence of a new controversy. The question "if low levels of vitamin D increase the incidence of URTIs, can vitamin D supplementation reduce the incidence of upper URTI?" has been the subject of interest of many researchers. Recent studies on this subject produced different results. In randomized-controlled studies, vitamin D supplementation was shown to reduce the incidence of URTI.[30,31] On the contrary, Li-Ng et al[32] was unable to retrieve any data indicating that the supplementation therapy reduces the incidence of URTIs. In another study, Robertson et al[10] reported that there was no relationship between vitamin D levels and URTIs and concluded that vitamin D supplementation did not reduce the incidence of URTIs in the Norwegian population.

On the other hand, there are some limitations to this study. Firstly, the seasonal changes of vitamin D levels were ignored. Secondly, the vitamin D levels were measured only once. An ideal study should encompass vitamin D level measurements at the same seasonal period. Although our laboratory test results are consistent with the studies conducted worldwide, we obtained different results from other studies of Yıldız et al[29] and Aydın et al[7] which were carried out among the Turkish children. This may have been due to our ignoring the seasonal changes, laboratory testing and also not measuring VDR polymorphism. This can be also attributed to the small sample size and variable characteristics of the control groups of two other studies.

CONCLUSIONS

In this study, vitamin D levels of children who are potential candidates for recurrent tonsillitis and tonsillectomy were significantly lower than those with tonsillitis episodes less than three within one year. Evaluation of vitamin D levels in candidates for tonsillectomy may reduce the rates of tonsillectomy operations. However, we were unable to find any study investigating whether the vitamin D supplementation reduced the rates of tonsillectomy operations. Therefore, further studies are required to investigate that how much reduction in the operation rates

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would be obtained from the vitamin D supplementation. In addition, studies which determine optimal levels of vitamin D for adequate immune function in children are needed.

CONFLICTS OF INTEREST

No conflicts of interest was declared by the authors.

FINANCIAL DISCLOSURE

The authors declare that this case has received no financial support.

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