

Serum vitamin D levels in children with recurrent tonsillopharyngitis

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ABSTRACT

OBJECTIVE: In this study, we aimed to compare vitamin D levels of children with recurrent tonsillopharyngitis and healthy controls, and investigate the relationship between sociodemographic characteristics and serum vitamin D levels.

METHODS: Children with recurrent tonsillopharyngitis and healthy controls aged between 2, and 12 years who consulted to the outpatient clinics of Zeynep Kamil Maternity and Children's Diseases Training and Research Hospital from January to October 2012 were included in this study. Serum 25 (OH) vitamin D levels were studied by tandem mass spectroscopy (tandem ms) method. Risk factors which might be associated with vitamin D levels were questioned. Ethical approval was obtained from the Ethics Committee of Zeynep Kamil Maternity and Children's Diseases Training and Research Hospital and informed consent from the parents of the children.

RESULTS: A total of 147 children; 74 (50.3%) patients and 73 (49.7%) controls were included in our study. Age, gender and demographic characteristics did not differ significantly between the two groups. Vitamin D levels in patients with recurrent tonsillopharyngitis and controls were 19.7±8.7 ng/ml and 23.6±9.2 ng/ml, respectively ($p<0.01$). Although duration of vitamin D usage was shorter in children with recurrent tonsillopharyngitis, this difference was not statistically significant ($p>0.05$).

CONCLUSION: Vitamin D levels in children with ≥ 7 recurrent episodes of tonsillopharyngitis within the preceding year were significantly lower compared to the control group. We believe that serum vitamin D levels should be checked in children with recurrent tonsillopharyngitis and deficiencies should be treated.

Key words: 25-OH vitamin D, infection, recurrent tonsillopharyngitis, vitamin D

Tonsillopharyngitis is an important health problem in childhood because of potential development of its suppurative complications

(peritonsillary abscess, sinusitis, mastoiditis, otitis media, endocarditis, meningitis, and pneumonia) caused by group A beta- hemolytic streptococci,



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and also non-suppurative complications, in addition to the difficulties in the identification of the etiological agent (bacterial vs viral). In the literature, recurrent tonsillopharyngitis is defined as 7 or more well-documented, clinically important, adequately treated episodes of tonsillopharyngitis in the preceding year or 3 or more such episodes in each of the preceding 3 years or 5 or more such episodes in the preceding 2 years [1]. In the pediatric population tonsillopharyngitis is an important morbidity which adversely affects quality of life of the children, and parents because of its frequently recurrent symptoms, its treatment, and potential complications, and school absence it causes. In the United States of America in the year 1996 one of every 100 children had not reportedly attended their schools for a total of 152 days because of upper respiratory tract infections [2].

Comprehension of antiproliferative, prodifferentiative, proapoptotic, and immunomodulator functions of vitamin D whose deficiency was associated with only rickets for a long time has led to reconsideration of this vitamin regarding its newly discovered beneficial effects [3]. In studies performed, the role of vitamin D in decreasing the risks of many chronic diseases including prominently some types of cancer, followed by many autoimmune, infectious, and cardiovascular diseases are remarkable [4]. As revealed in many studies, vitamin D deficiency increases the risk of contracting many infections [5]. Vitamin D deficiency is reportedly a risk factor for the development of tuberculosis, otitis media, upper respiratory tract, and gripal infections [6, 7, 8].

In this study, we aimed to compare vitamin D levels in children who had recurrent episodes of tonsillopharyngitis, and in healthy children, and investigate the correlation between sociodemographic characteristics, and vitamin D levels.

MATERIALS AND METHODS

This prospective study included children aged between 2-12 years with recurrent tonsillopharyngitis and their age-matched healthy controls who consulted to the outpatient clinics of Zeynep Kamil Maternity and Children's Diseases Training and

Research Hospital from January to October 2012. The number of episodes of infections were determined based on patients' history of recurrent diagnoses of tonsillopharyngitis, hospital files, their prescriptions, and admission complaints. Demographic characteristics of the children, and their duration of vitamin D therapy during infancy were recorded.

Inclusion criteria for the study group were as follows: suffering from 7 or more well-documented, clinically important, and adequately treated episodes of tonsillopharyngitis in the preceding year or 5 or more such episodes in each of the preceding years or 3 or more such episodes in each of the 3 preceding years. For the control group inclusion criteria were determined as experiencing less than 7 such episodes in the preceding year, absence of any known chronic disease or any disease which might effect vitamin D metabolism or vitamin D therapy.

Blood samples were drawn from the children included in the study in order to analyze serum 25 (OH) D levels. Serum 25 (OH) vitamin D levels were analyzed using LC/MS/MS method which has been accepted as a reference method with higher sensitivity, and specificity. Waters® Micromass® Quattro Premier XE™ Tandem Quadrupole Mass Spectrometer was used for analyses.

Vitamin D deficiency, insufficiency, and adequacy were defined as the detection of vitamin D levels of <20 ng/ml, 20-32 ng/ml, and 32-100 ng/ml, respectively. Study population were divided into 3 groups based on the aforesaid vitamin D levels as groups with deficient, insufficient, and adequate vitamin D levels. Parameters as age, frequency of tonsillopharyngitis etc. were compared between groups.

SPSS (Statistical Package for Social Sciences 15; SPSS Inc., Chicago, IL, USA) program was used to evaluate study data. In intergroup comparisons for categorical variables chi-square, for comparisons of mean values between two or among three groups, Mann Whitney-U, and Kruskal-Wallis tests were used, respectively. The results were evaluated at accepted level of significance of $p < 0.05$, and within 95% confidence limit.

The approval for the conduction of the study was obtained beforehand from The Ethics Com-

mittee of Zeynep Kamil Maternity, and Children's Diseases Training and Research Hospital. Enlightened consent forms were signed by the parents who volunteered to participate in the study.

RESULTS

A total of 147 children; 74 (50.3%) patients and 73 (49.7%) controls were included in the study. Age, gender and demographic characteristics did not differ significantly between the two groups. Vitamin D levels in patients with recurrent tonsillopharyngitis and controls were 19.7 ± 8.7 ng/ml and 23.6 ± 9.2 ng/ml, respectively ($p < 0.01$). Although duration of vitamin D usage was shorter in children with recur-

rent tonsillopharyngitis, this difference was not statistically significant ($p > 0.05$).

A total of 147 (girls, $n=71$; 48.3%) patients were included in the study. Study, and control groups consisted of 74 (50.3%) patients, and 73 (49.7%) healthy individuals, respectively. Study, and control groups were not significantly different as for age, gender, number of siblings, and duration of vitamin D use. In the recurrent tonsillopharyngitis group, vitamin D level was detected to be significantly lower when compared to the control group ($p < 0.01$). Duration of vitamin D use was shorter than the control group without any statistically significant difference between groups ($p > 0.05$) (Table 1).

TABLE 1. Comparison of vitamin D levels in patients who suffered from frequent episodes of tonsillopharyngitis, and the control group

| | Control group | | | Study group | | | p |
|---|---------------|-------|--------|-------------|-------|--------|--------|
| | Mean | SD | Median | Mean | SD | Median | |
| Age (mos) | 65.72 | 28.11 | 60.00 | 67.36 | 29.75 | 60.00 | 0.782 |
| Number of episodes of tonsillopharyngitis | 2.54 | 1.55 | 2.00 | 8.42 | 1.55 | 8.00 | 0.0001 |
| Vitamin D level (ng/ml) | 23.62 | 9.22 | 23.00 | 19.73 | 8.77 | 18.00 | 0.009 |
| Duration of vitamin D therapy (mos) | 9.91 | 5.81 | 12.00 | 9.38 | 6.29 | 12.00 | 0.693 |

SD: Standard deviation.

TABLE 2. Comparison of demographic characteristics of the patients based on vitamin D levels

| | Vitamin D deficiency <20 ng/ml | | | Vitamin D insufficiency 20-32 ng/ml | | | Vitamin D adequacy 32-100 ng/ml | | | p |
|-----------------------------|-----------------------------------|------|-----------|--|------|-----------|------------------------------------|-----|------------|--------|
| | n | % | Mean±SD | n | % | Mean±SD | n | % | Mean±SD | |
| Patients | 63 | 42.9 | | 74 | 50.3 | | 10 | 6.8 | | 0.0001 |
| Age (mos) | | | 70.8±29.6 | | | 65.2±28.5 | | | 48.5±17.3 | 0.05 |
| Gender (Female) | 34 | 47.9 | | 34 | 47.9 | | 3 | 4.2 | | 0.31 |
| Episodes of URTI | | | | | | | | | | |
| <7/yr | 25 | 33.8 | | 42 | 56.8 | | 7 | 9.5 | | 0.06 |
| ≥7/yr | 38 | 52.1 | | 32 | 43.8 | | 3 | 4.1 | | |
| Levels of vitamin D (ng/ml) | | | 13.8±4.15 | | | 25.4±3.36 | | | 43.2±10.11 | 0.0001 |

SD: Standard deviation; URTI: Upper respiratory tract infection.

Vitamin D level was deficient, insufficient, and adequate in 42.9 (n=63), 50.3 (n=74), and 6.8% (n=10) of the patients in the study population. Although in patients with vitamin D deficiency, household members, and episodes of tonsillopharyngitis were more numerous, and the duration of vitamin D use was the shortest relative to the control group without any significant difference between groups as for demographic characteristics ($p>0.05$) (Table 2).

DISCUSSION

Although our country takes advantage of the sunlight abundantly, vitamin D deficiency still continues to be an important health problem affecting pregnant, babies, and adolescents. American Academy of Pediatrics recommends administration of 400 IU oral vitamin D supplementation beginning from the neonatal period, and continuing all along the infancy [9]. Although vitamin D supplementation program has been implemented in our country, especially in rural areas vitamin D deficiency is frequently encountered [10].

Detection of vitamin D receptors in many tissues of the body has led to the conduction of new studies on the functions, and correlations of vitamin D which plays an important role in the bone-mineral metabolism with various disease states [11]. Vitamin D exerts its effects through activation of vitamin D receptors which regulate transcriptions of target genes responsible for biological effects of its active form 1,25 (OH)₂ D [12]. The presence of the receptor in immune system cells (dendritic cells, B-lymphocytes, T-lymphocytes, NK-cells, monocytes) has been demonstrated. Besides, genetic polymorphism in these cells which lead to modifications in the functions of immune cells has been indicated [13, 14, 15, 16]. Presence of vitamin D receptors in immune system cells, and various regulatory effects of these cells induced by stimulation of these receptors demonstrate the correlation between vitamin D, and especially with immune system of the upper respiratory tract [17].

Vitamin D has important roles in fighting against infectious agents, and in individuals with vitamin D

deficiency, increase in the predisposition, and frequency of especially respiratory tract infections has been demonstrated. In their case-controlled studies performed among Ethiopian children less than 5 years of age with rickets, Muhe et al.[18] reported an existence of a correlation between vitamin D deficiency, and development of pneumonia. Wayse et al.[19] reported that in India, subclinical vitamin D insufficiency in children less than 5 years of age is an important risk factor for the development of serious lower respiratory tract infection. In their series, Cannell et al.[20] indicated that the incidence of viral respiratory tract infection had increased in cases with vitamin D insufficiency. Recurrent nature of acute tonsillopharyngitis has been reported in 10-15% of the pediatric cases [21, 22, 23]. Yildiz et al.[11] detected recurrent tonsillopharyngitis in 4.7% of the children who referred to the polyclinics of general pediatrics. In the literature, lower vitamin D levels were detected in children who had suffered from frequent episodes of tonsillopharyngitis [11, 24]. In our study, we detected lower vitamin D levels in children who suffered from frequent episodes of tonsillopharyngitis in consistent with the literature findings.

Yildiz et al.[11] reported that in patients with insufficient vitamin D levels, annual incidence rates of disease were markedly higher, and indicated that its incidence decreased directly proportional with increases in serum 25-(OH) vitamin D levels. In the same study, despite serum vitamin D levels within normal limits in cases who had frequent episodes of tonsillopharyngitis, and in the control group, serum 25-(OH) vitamin D levels were significantly lower in the recurrent tonsillopharyngitis group (142.7 ± 68.1 nmol/L) when compared with the control group (192.3 ± 56.1 nmol/L).

In studies performed in adult patients similar outcomes have been found. Nseir et al.[25] detected significantly lower serum 25(OH) vitamin D levels in the group of patients who frequently suffered from group A beta-hemolytic streptococcal tonsillopharyngitis. Ginde et al.[26] detected the rate of URTI as 24, 20, and 17 % in patients with serum 25(OH) vitamin D levels of <10 ng/mL, 10-30 ng/ml, and ≥ 30 ng/ml, respectively with statisti-

cally significant differences between groups. These outcomes demonstrate decrease in the frequency of tonsillopharyngitis in parallel with an increase in vitamin D levels.

However, some studies have demonstrated lack of any correlation between vitamin D levels, and frequent infections. In a study performed by Aydın et al., [27] the authors couldn't find a significant difference between patients who experienced frequent episodes of tonsillitis and thus underwent tonsillectomies and the control group regarding serum 25 (OH) vitamin D levels. Detection of similar serum vitamin D levels in both groups was interpreted as lack of any correlation between recurrent tonsillopharyngitis, and serum vitamin D levels. Similarly, in other studies, various units of measurement, and cut-off values have been used for the definition of vitamin D deficiency. Since the definition of vitamin D deficiency has not been standardized, it is hardly possible to compare outcomes of our study with those of the others.

Serum 25 (OH) vitamin D levels less than 20 ng/ml (50 nmol/L) are defined as vitamin D deficiency, while serum vitamin D levels protective against infections, and those inducing immune system have not been clearly established yet [28, 29]. In our study, vitamin D levels were deficient, insufficient, and adequate in 42.9, 50.3, and 6.8% of the cases, respectively. The study population was divided into 3 groups as vitamin D deficient, insufficient, and adequate groups, and any significant difference was not detected between groups as for demographic characteristics, number of episodes of tonsillopharyngitis experienced, and duration of vitamin D use.

Vitamin D levels in children are influenced by maternal, and environmental factors as daily diet, and sunlight [11, 27]. Protective role of vitamin D support against some diseases, predominantly upper, and lower respiratory tract infections in pregnancy, early childhood, and advanced age has been demonstrated [30, 31, 32]. However, controversial outcomes have been reported against protective role of vitamin D in upper respiratory tract infections [33, 34, 35]. Li-Ng et al. have demonstrated that daily 2000 IU vitamin D supplement for the

adults during winter months did not decrease the frequency, and severity of URTI [34]. Avenell et al. detected that administration of daily 800 IU vitamin D supplement decreased the incidence of infection at a rate of 10-15% without any statistically significant difference [35]. To reveal the correlation between vitamin D, and respiratory tract infection clearly, studies standardized according to seasons, dietary habits, the amount of sunlight exposure received by the countries, and regional clothing habits are needed.

One limitation of our study is that only a single measurement of vitamin D levels which show seasonal variations during the study period may not fully reflect vitamin D levels of the children.

In our country, vitamin D deficiency is an important public health problem which is often seen in pediatric cases with frequent tonsillopharyngitis. We think that in children with frequent tonsillopharyngitis, as a result of treatment of deficiencies detected with measurement of serum vitamin D levels, frequency of diseases, and healthcare expenses will decrease.

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