ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

DOI: 10.24179/kbbbbc.2017-56598

The Role of Vitamin D in Patients with Otitis Media with Effusion

Efüzyonlu Otitis Media Tedavisinde D Vitamininin Rolü

Yusuf DÜNDAR,[a]
Yasemin TİMURKAYNAK,[a]
Erol DEMİRBAŞ,[a]
Mehmet BİRİNCİ,[b]
Zerrin ÖZERGİN,[b]
Fatih AKCAN,[c]
Engin DURSUN[b]

[a]Clinic of Ear, Nose and Throat, Rize State Hospital,
[b]Department of Ear, Nose and Throat, Recep Tayyip Erdoğan University Faculty of Medicine, Rize
[c]Department of Ear, Nose and Throat, Düzce University Faculty of Medicine, Düzce

Received: 03.06.2017
Received in revised form: 02.04.2018
Accepted: 01.10.2018
Available online: 09.11.2018

Correspondence:
Yusuf DÜNDAR
Rize State Hospital, Clinic of Ear, Nose and Throat, Rize, TURKEY/TÜRKİYE
ysfdndr@gmail.com

ABSTRACT Objective: Vitamin D has multiple functions other than calcium metabolism. However, there exists a paucity of data to explain the role of Vitamin D deficiency in patients with otitis media with effusion (OME). **Material and Methods:** This retrospective review of OME with 320 patients was conducted from 2014 to 2016. The case files of patients with OME were analyzed retrospectively and patients were included in the study if 25(OH)D levels were available. Physician documented visit records were identified and statistical analysis was performed by using SPSS version 21 (IBM, Armonk, NY). **Results:** Of the initial 320 patients with OME, 67 patients had 25(OH)D levels available. 18 out of 67 patients were excluded from the study based on exclusion criteria further detailed in the study. A total of 30 boys (61.2%) and 19 girls (38.8%) were included with mean age 5.85±2.74 years. The mean 25OHVitaminD level was 16.87. 18 of 49 patients had 25OHVitaminD deficiency (Group 1). 31 patients had 25OHVitaminD level ≥15 (Group 2). The mean duration of treatment was 6.83 weeks and 3.80 weeks in Group 1 and Group 2 respectively (p: 0.010). 8 of 18 patients (44.4%) in the Group 1 underwent ventilation tube insertion while 4 of 31 patients (12.9%) underwent ventilation tube insertion in the Group 2 (p: 0.018). There was no statistical significance between the subgroups addressing to age, sex, primary symptom, history of smoking at home, type of house heating. **Conclusion:** There is a significant association between 25OHVitaminD deficiency and treatment outcomes of OME.

Keywords: Otitis media with effusion; ventilation tube insertion; vitamin D; hypovitaminoz

ÖZET Amaç: D vitamininin kalsiyum metabolizmasının yanı sıra bir çok fonksiyonu olmakla beraber Efüzyonlu Otitis Media (EOM) ve D vitamin eksikliği arasındaki ilişki tam olarak açıklığa kavuşturulamamıştır. **Gereç ve Yöntemler:** 2014-2016 yılları arasında EOM tanılı 320 hasta dosyası retrospektif olarak incelendi ve eğer hastadan herhangi bir nedenle 25(OH)D seviyesi çalışılmış ise çalışmaya dahil edildi. Hastaların kontrollerindeki fizik muayene bulguları ve laboratuvar verileri SPSS-21 (IBM, Amarok, NY) programı ile analiz edildi. **Bulgular:** 320 EOM tanılı hastanın 67'sinde 25(OH) D seviyesinin çalışılmış olduğu görüldü. 67 hastanın 18'i dışlama kriterleri nedeni ile çalışmadan çıkarıldı. 30 erkek (%61,2) ve 19 kız (%38,8) hasta çalışmaya dahil edildi. Ortalama yaş 5,85±2,74 yıl ve ortalama 25(OH)D seviyesi 16,87 idi. 49 hastanın 18'inde 25(OH)D eksikliği tespit edilmiş olup bu hastalar Grup 1'i; 25(OH)D seviyeleri ≥15 olan 31 hasta ise Grup 2'yi oluşturdu. Ortalama tedavi süreleri sırası ile Grup 1 ve Grup 2'de 6,83/hafta ve 3,80/hafta idi (p: 0,010). Grup 1'deki 18 hastanın 8'ine izlem sırasında ventilasyon tüpü tatbiki uygulandı ((%44,4), buna karşın Grup 2'deki 31 hastanın 4'üne (%12,9) takipleri sırasında ventilasyon tüpü tatbik edildi (p: 0,018). Gruplar arasında yaş, cinsiyet, primer şikayet, evde sigara kullanımı ya da ev ısınma aracı açısından istatistiki olarak fark elde edilemedi. **Sonuç:** 25(OH)VitaminD eksikliği ve EOM tedavi sonuçları arasında anlamlı bir ilişki bulunmaktadır.

Anahtar Kelimeler: Efuzyonlu otitis media; ventilasyon tüpü tatbiki; D vitamin; vitamin eksikliği

Active vitamin D receptors have been identified in many tissues: ovaries, skin, stomach, thymus, pancreas, kidney, parathyroid glands and lymphocytes. These finding support the fact that Vitamin D has lots of different functions other than calcium metabolism. Vitamin D receptors have been described in all cells of the immune system and particularly in those cells that produce antigen.[1] Vitamin D thus has an important role in immune-regulation. An up-regulation of the microbicidal effects of monocytes and macrophages has been described in the event of a Vitamin D enriched environment.[2,3] The association of Vitamin D deficiency and upper respiratory tract infections (URI) has been reported by several studies.[4,5] Group A streptococcal infections, pneumococcal infections and meningococcal infections are often seen in Vitamin D deficiency and these, being the most common bacterial infections, are very sensitive to the microbicidal effects of Vitamin D.[6]

Otitis media with effusion (OME) is an inflammatory process in the middle ear that is the most common infection after URI. The incidence of OME has a seasonal variation and is seen more commonly in winter since URI promotes the risk of OME. This increased incidence rate is associated with Eustachian tube dysfunction and recurrent respiratory tract infections.[7,8] Several studies support the correlation between Vitamin D deficiency and recurrent otitis media and this association might be related to the immune-stimulating effects of Vitamin D. However, there is no enough data to understand the role of Vitamin D deficiency in the pathophysiology, treatment, resistance to treatment, and clinical progress of OME.

The presented study was performed at "East Black Sea Region" that receives poor sun exposure because of climate condition (41.2°N). Vitamin D deficiency occurs very often in this region.[9,10] The purpose of current study was to investigate the clinical role of Vitamin D in OME.

MATERIAL AND METHODS

The retrospective review of 320 patients with OME was conducted at the Otolaryngology department in a referral center from January 2014 to January 2016 after obtaining approval from the institutional ethics committee. The study group consisted of children who were diagnosed with OME based on physical examination and tympanogram findings. Loss of light reflex on the tympanic membrane, presence of a glue-like effusion in the middle ear, retraction of the tympanic membrane and type B or type C tympanogram were accepted as positive signs of OME. All case files of patients with OME were analyzed retrospectively and patients were included in this analysis if 25(OH)D levels were available during the treatment period. Exclusion criteria included the following: craniofacial abnormality, presence of chronic diseases, acquired or congenital immunodeficiency, history of ventilation tube insertion, and history of adenotonsillectomy. Figure 1 represents a flow chart that summarizes the patient selection process that was utilized. Data collection included the following parameters: sex, age of onset, duration of symptoms, history of previous treatments, physical examination findings, tympanogram types and laboratory findings. Physician documented visit records were evaluated and duration of treatment and indications of surgery during the treatment was noted. Patients were divided into two sub-groups depending on the serum 25 (OH)D levels and a level < 15ng/mL was accepted as vitamin D deficiency.[11] Subgroup analysis was performed based on baseline characteristics, physical examination findings and treatment outcomes.

Our treatment protocol for OME consists of family education and close follow up for 3 months. We suggest oral antibiotics and intranasal glucorticoids in the treatment of OME. We suggest ventilation tube insertion if patients have persistent glue-like effusion in the middle ear, persistent retraction or persistent OME-associated hearing loss after the 3-month trial period of educational and medical therapy.

Statistical analysis was performed using SPSS version 21 (IBM, Armonk, NY). Descriptive statistics were performed by independent t-tests and the Mann-Whitney U-test for mean comparisons of variables with two groupings. For variables with

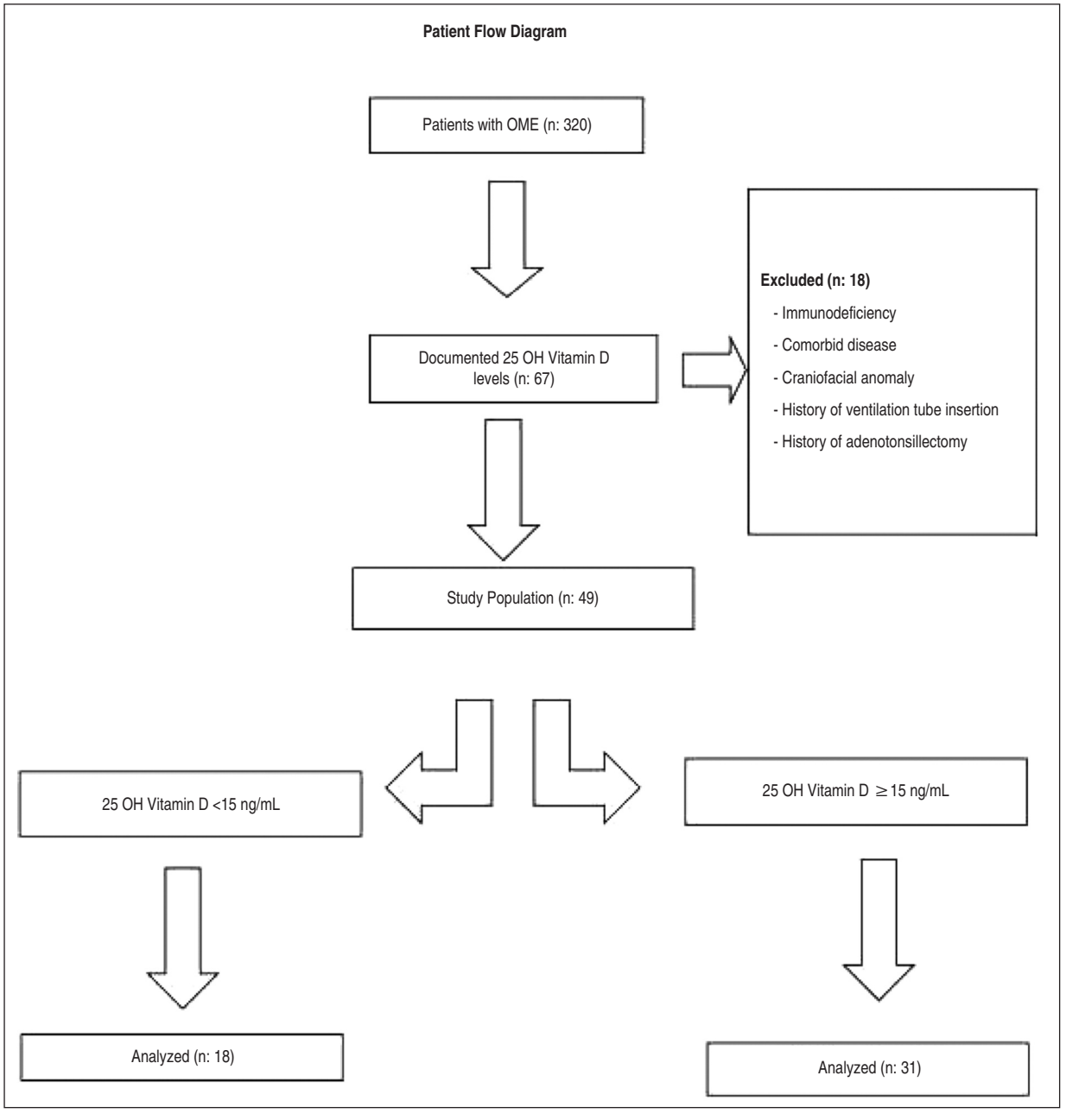

FIGURE 1: Flow diagram of patients selection.

groupings of three or more, a one-way ANOVA test was utilized. Chi squared and Fisher's exact test were used to analyze categorical variables. All tests were two-tailed, and results were considered significant for $p \leq 0.05$.

RESULTS

The charts of 320 patients with OME were reviewed and 67 of these patients had 25(OH)D levels available. 18 out of these 67 patients were excluded from the study because they met one or more of the exclusion criteria noted in the methods section of this manuscipt. The study population consisted of 30 boys (61.2 %) and 19 girls (38.8%) with mean age of 5.85 ± 2.74 years. The most common indication of 25(OH)D analysis was recurrent URI (65.3%) followed by routine child examination (34.7%). The mean sibling age difference was

1.89±0.84 years and 17 of those patients' family (34.7%) had a history of smoking. The mean 25OHVitaminD level was 16.87. Table 1 summarizes the demographics of the overall population. 18 of 49 patients had 25OHVitaminD deficiency and these were categorized into Group 1. Group 2 included patients with 25OHVitaminD level ³ 15 and a total of 31 patients fell into this category. Table 2 summarizes the subgroup analysis. The mean durations of treatment were 6.83 weeks and 3.80 weeks in Group 1 and Group 2 respectively (p: 0.010). 8 of 18 patients in Group 1 underwent ventilation tube insertion while 4 of 31 patients in Group 2 underwent ventilation tube insertion. The rates of ventilation tube insertion were 44.4% and 12.9 % in Group 1 and Group 2 respectively (p: 0.018). There was no statistically significant difference between the subgroups in terms of age, sex, primary symptom, duration of primary symptom, history of previous treatments, history of smoking at home, or type of house heating. The mean sibling age difference was 2.22 years in the Group 1 and 1.70 years in the Group 2 (p:0.040). There was no statistically significant difference between the subgroups in terms of laboratory work except PTH levels. The mean PTH levels were 73.87 and 42.12 in Group 1 and Group 2 respectively (p=0.003).

TABLE 1: Demographics of overall population.

		n	%
Sex	Male	30	61.2
	Female	19	38.8
Age (year)	Mean	5.85	
	SD	2.74	
Siblings	Mean	1.89	
	SD	0.84	
Type of House Heating	Stove	17	34.7
	Central Heating	24	49.0
	Others	8	16.3
Smoking at Home	Yes	17	34.7
	No	32	65.3
Comorbid Disease	Yes	5	10.2
	No	44	89.8
Primary Symptom	Hearing Loss	37	75.5
	Otalgia	3	6.1
	Routine Exam	3	6.1
	Other	6	12.2
Duration of Primary Symptom	Mean	6.01	
	SD	9.73	
History of Previous Treatments	Yes	33	67.3
	No	16	32.7
Duration of Current Treatment (week)	Mean	4.91	
	SD	4.02	
Ventilation tube Insertion	Yes	12	24.5
	No	37	75.5

SD: Strandart deviation.

DISCUSSION

Toll-like-receptors (TLRs) are stimulated and cathelicidin is expressed if an infection occurs in the epidermis.[12] Macrophages contribute to the localization of infection by releasing cytokines from T lymphocytes and immunoglobulins from active B lymphocytes.[3,13,14] Monocytes and macrophages play a key role in activation of an innate immunity against the invasive characteristics of many infections organisms.[3,13,15] The increased chemotactic and phagocytic effects of monocytes and macrophages have been reported in an enriched activated vitamin D environment. Active vitamin D stimulates the synthesis of antimicrobial peptides, defensins and cathelicidin from natural killer cells and respiratory tract epithelial cells.[3,12] In addition, upregulated calprotectin and S100 protein levels have been documented as an effect of active vitamin D.[13] These proteins are very important for an effective humoral immune system. There is a positive correlation between Vitamin D and immunity. In the event of vitamin D deficiency immune response is impaired and leukocyte chemotaxis is affected, leading to an increased rate of infections.[5,13] The first prototype infection associated with Vitamin D deficiency is tuberculosis, which has been studied over the years and a powerful correlation has been documented.[16,17] These other infections organisms are also frequently seen in vitamin D deficiency: *Streptococcus pneumoniae, Hemophilius influenza* and *Moraxella catarrhalis*, Group A streptococcus.

OME is one of the most commonly seen inflammatory processes in children which can lead to hearing loss, decreased school performance and

TABLE 2: Subgroup analysis.

		Group 1 (n:18)	Group 2 (n:31)	p
Sex	Male	8	22	0.063
	Female	10	9	
Age (year)	Mean	6.59	5.44	0.167
Siblings	Mean	2.22	1.70	**0.040**
Type of House Heating	Stove	7	10	0.324
	Central Heating	9	15	
	Others	3	5	
Smoking at Home	Yes	5	12	0.324
Primary Symptom	Hearing Loss	14	23	0.911
	Otalgia	1	2	
	Routine Exam	0	3	
	Other	3	3	
History of Previous Treatments		12	21	0.590
Duration of Primary Symptom		7.44	5.16	0.434
Duration of Current Treatment		6.83	3.80	**0.010**
Ventilation tube Insertion	Yes	8	4	**0.018**
	No	10	27	
WBC		9.73	10.44	0.440
Hgb		12.42	12.13	0.379
MPV		9.96	9.51	0.185
Platelet		339.38	362.12	0.324
CRP		5.90	4.98	0.742
Ferritin		42.66	42.93	0.983
UIBC (unsaturated iron binding capacity)		293.58	309.46	0.408
TSH		2.80	2.27	0.114
T4		1.14	4.96	0.465
B12		511.72	548.93	0.523
PTH		73.87	42.12	**0.003**
25OHD3		11.31	21.02	**0.001**
Ca		9.66	9.89	0.113
P		4.74	4.76	0.783
Mg		2.06	2.05	0.839
ALP		203.58	221.01	0.331

impaired social development. The incidence of OME incidence has a seasonal variance. Viral and bacterial respiratory tract infections increase the risk of OME and this is one factor that increases the incidence of OME in winter. The infectious agents that cause OME commonly originate from colonizing bacteria from nasopharynx, the most important of these being *Streptococcus pneumoniae, Hemophilius influenza* and *Moraxella catarrhalis*. Additionally, viral agents, such as rhinovirus, adenovirus and influenza play an important role in the pathophysiology of OME. A decreased cathelicidin synthesis was documented in the bronchial epithelial cells in patients having frequent respiratory tract infections.[15] The synthesis of immune-modulating proteins such as defensins, cathelicidin, calprotectin and S100 are Vitamin D dependent and this may explain the increased incidence of URI in patients with Vitamin D deficiency. Some authors advocate that Vitamin D may be effective in the treatment of respiratory tract infections.[18-22]

Our study indicates an increased duration of treatment in patients with Vitamin D deficiency. This 1.79-fold increased duration of treatment may lead to the increased cost of treatment and decreased quality of life during treatment. Djurhuus at al. recently reported that approximately 3 in 10 children born in 2010 (Denmark) will undergo at least one ventilation tube insertion before their fifth birthday.[23] The overall rate of ventilation tube insertion was 24.4% in our study population, which correlates with published rates in the literature. However, the rate of ventilation tube insertion was significantly greater in patients with Vitamin D deficiency (44.4 %). The increased rate of ventilation tube insertion carries the risk of complications and increased cost of treatment. The most common complications of ventilation tube insertion are otorrhea, perforation of the tympanic membrane and tympanosclerosis.[24] The risk of these complications may indirectly increase in patients with vitamin D deficiency.

Socioeconomic differences such as low income, smoking at home, type of house heating, siblings and male sex may also play important role in OME.[25] 46 patients of the study population (93.8 %) had at least one sibling. 30 of 49 of the studied patients (61.2%) were male and 17 out of 49 patients (34.7%) had history of smoking at home by parents. These were identified as the most common risk factors of our study population. There was no statistical significance among the subgroups in terms of to sex, age, type of house heating, or smoking at home. The number of siblings was significantly increased in patients with Group 1. This increased number of siblings might be related to low socioeconomic status since people with low socioeconomic status tend to have more children.[25] The mean PTH level was significantly increased in patients with Vitamin D deficiency which is a compensation mechanism.

The main limitation of the current study is a retrospective setting. The indications of vitamin D analysis were not randomized so the study population is restricted. These both factors prevent us to generalize our results.

CONCLUSION

There is a significant association between 25OH VitaminD deficiency and treatment outcomes of OME. The mean duration of treatment and the rate of ventilation tube insertion were significantly increased in patients with vitamin D deficiency. These preliminary findings suggest the need for further studies to delineate more clearly the role of Vitamin D supplementation in patients with OME.

Acknowledgment

All authors thank to Dr. Amar Gupta for his English reduction.

REFERENCES

1. Hewison M. An update on vitamin D and human immunity. Clin Endocrinol (Oxf) 2012;76(3):315-25.
2. Edfeldt K, Liu PT, Chun R, Fabri M, Schenk M, Wheelwright M, et al. T-cell cytokines differentially control human monocyte antimicrobial responses by regulating vitamin D metabolism. Proc Natl Acad Sci U S A 2010;107(2):22593-8.
3. Bikle D. Nonclassic actions of vitamin D. J Clin Endocrinol Metab 2009;94(1):26-34.
4. Hughes DA, Norton R. Vitamin D and respiratory health. Clin Exp Immunol 2009;158(1):20-5.
5. Walker VP, Modlin RL. The vitamin D connection to pediatric infections and immune function. Pediatr Res 2009;65(5 Pt 2):106R-13R.
6. Cayir A, Turan MI, Ozkan O, Cayir Y. Vitamin D levels in children diagnosed with acute otitis media. J Pak Med Assoc 2014;64(11): 1274-7.
7. Bylander-Groth A, Stenström C. Eustachian tube function and otitis media in children. Ear Nose Throat J 1998;77(9):762-4.
8. Lee HJ, Park SK, Choi KY, Park SE, Chun YM, Kim KS, et al. Korean clinical practice guidelines: otitis media in children. J Korean Med Sci 2012;27(8):835-48.
9. Kirbas A, Kirbas S, Anlar O, Turkyilmaz AK, Cure MC, Efe H. Investigation of the relationship between vitamin D and bone mineral density in newly diagnosed multiple sclerosis. Acta Neurol Belg 2013;113(1):43-7.
10. Mithal A, Wahl DA, Bonjour JP, Burckhardt P, Dawson-Hughes B, Eisman JA, et al; IOF Committee of Scientific Advisors (CSA) Nutrition Working Group. Global vitamin D status and determinants of hypovitaminosis D. Osteoporos Int 2009;20(11):1807-20.
11. Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. Pediatrics 2008;122(2):398-417.
12. Selvaraj P. Vitamin D, vitamin D receptor, and cathelicidin in the treatment of tuberculosis. Vitam Horm 2011;86:307-25.
13. Szodoray P, Nakken B, Gaal J, Jonsson R, Szegedi A, Zold E, et al. The complex role of vitamin D in autoimmune diseases. Scand J Immunol 2008;68(3):261-9.

14. Adorini L, Penna G, Giarratana N, Roncari A, Amuchastegui S, Daniel KC, et al. Dendritic cells as key targets for immunomodulation by Vitamin D receptor ligands. J Steroid Biochem Mol Biol 2004;89-90(1-5):437-41.
15. Yim S, Dhawan P, Ragunath C, Christakos S, Diamond G. Induction of cathelicidin in normal and CF bronchial epithelial cells by 1,25-dihydroxyvitamin D(3). J Cyst Fibros 2007;6(6): 403-10.
16. Dini C, Bianchi A. The potential role of vitamin D for prevention and treatment of tuberculosis and infectious diseases. Ann Ist Super Sanita 2012;48(3):319-27.
17. Ralph AP. Vitamin D supplementation in patients with tuberculosis. Am Fam Physician 2010;82(6):577-83.
18. Cannell JJ, Vieth R, Umhau JC, Holick MF, Grant WB, Madronich S, et al. Epidemic influenza and vitamin D. Epidemiol Infect 2006;134(6):1129-40.
19. Morcos MM, Gabr AA, Samuel S, Kamel M, el Baz M, el Beshry M, et al. Vitamin D administration to tuberculous children and its value. Boll Chim Farm 1998;137(5):157-64.
20. Cantorna MT, Zhao J, Yang L. Vitamin D, invariant natural killer T-cells and experimental autoimmune disease. Proc Nutr Soc 2012;71(1):62-6.
21. Marom T, Marchisio P, Tamir SO, Torretta S, Gavriel H, Esposito S. Complementary and alternative medicine treatment options for otitis media: a systematic review. Medicine (Baltimore) 2016;95(6):e2695.
22. Levi JR, Brody RM, McKee-Cole K, Pribitkin E, O'Reilly R. Complementary and alternative medicine for pediatric otitis media. Int J Pediatr Otorhinolaryngol 2013;77(6):926-31.
23. Djurhuus BD, Skytthe A, Christensen K, Faber CE. Increasing rate of middle ear ventilation tube insertion in children in Denmark. Int J Pediatr Otorhinolaryngol 2014;78(9):1541-4.
24. Browning GG, Rovers MM, Williamson I, Lous J, Burton MJ. Grommets (ventilation tubes) for hearing loss associated with otitis media with effusion in children. Cochrane Database Syst Rev 2010;6(10):CD001801.
25. Lubianca Neto JF, Hemb L, Silva DB. Systematic literature review of modifiable risk factors for recurrent acute otitis media in childhood. J Pediat (Rio J) 2006;82(2):87-96.