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Research Article

Assessment of Vitamin D Levels in Children with Chronic Suppurative Otitis Media

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Abstract
Objective: to detect vitamin D level in children with chronic suppurative otitis media (CSOM) in comparison to normal control group. **Materials and Methods:** Prospective comparative case control study was conducted on 85 children aged from 3 to 16 years at Otorhinolaryngology department, Minia University Hospital divided into 2 groups: **Group A (case group)** Forty-five cases with CSOM and **Group B (control group)** including Forty healthy children with normal Tympanic membrane (TM). Serum samples were used to assay the level of 25(OH) vitamin D. Vitamin D deficiency was considered as 25(OH)D <20 ng/ml. **Results:** Eighty-five children, divided into forty-five cases suffering from CSOM (15 males and 30 females) **(Case group)** and forty children (20 males and 20 females) with normal tympanic membrane **(Control group)**. The mean vitamin D level in case group was 27.4 ± 22.1 while in control group was 35.6 ± 15.9. In case group Vitamin D deficiency was detected in 24 cases (53.3%), insufficient in 5 cases (11.1%), and sufficient in 16 cases (35.6%) while in control group, Vitamin D deficiency was detected in 5 cases only (12.5%), insufficient in 10 cases (25%), and sufficient in 25 cases (62.5%) with significant difference of vitamin D deficiency between case and control group. **Conclusion:** Vitamin D level in children with CSOM was found to be significantly lower than that in control group with normal TM, so assessment of vitamin D level is very important in children with CSOM to decrease recurrent acute exacerbation and prevent complications.

Keywords: chronic suppurative otitis media (CSOM), Vitamin D, children, deficiency

Introduction
Usually caused by gram-negative bacteria, chronic suppurative otitis media (CSOM) is an inflammation of the mucoperiosteal lining of the middle ear cleft that lasts longer than three months. It often appears clinically as deafness and discharge and is a persistent disease with an insidious onset, may cause severe devastation and irreversible sequelae [(1)]

In reducing the frequency and severity of bacterial and viral infections, serum 25[OH]Vitamin D (25[OH]VD) may have a significant immunomodulatory effect. Additionally, a number of research suggested that children with low serum 25(OH) VD levels are more susceptible to respiratory viral illnesses. Theoretically, vitamin D deficiency could raise the incidence of recurrent acute otitis media, and vitamin D supplementation might be associated with a reduction in the frequency of new episodes in kids with otitis media (OM). [(2)]

Vitamin D acts as an anti-inflammatory by lowering interleukin and interferon gamma activity, which in turn lowers inflammation. Vitamin D deficiencies have been linked to middle ear infections and respiratory tract infections in numerous studies. All immune system cells, notably those in the B and T cells, monocytes and macrophages have receptors for vitamin D. The peptide-cathelicid action is increased by vitamin D. This peptide functions as an antibacterial. Vitamin D also affects calprotectin and S100 regulator, two additional antibacterial factors. The strength of monocytes and macrophages is multiplied as a result of rising vitamin D levels, which all work together to strengthen the immune system. [(3)]

Children with acute recurrent otitis media should have their serum vitamin D levels checked, and for those with low levels, vitamin D supplementation in addition to standard treatment options may help to improve the condition. Low levels of vitamin D may be one of the risk factors for chronic or fungal sinusitis, according to research by Mulligan et al., 2012 on the relationship between vitamin D deficiency and chronic sinusitis.[(4)] [(5)]

In addition to its other roles, vitamin D influences the body's ability to fight inflammation by regulating the generation of immune cells and cytokines, both of which are essential in the pathophysiology of many immune-related diseases. Numerous immune cells express the vitamin D receptor (VDR) and the enzyme CYP27B1, which suggests that vitamin D controls immune function. A mechanistic study found that vitamin D regulates inflammatory pathways linked to the development of cancer, including cytokines, prostaglandins, nuclear factor kappa B pathway, MKP5, MAP kinase phosphatase 5, and immune cells. Numerous studies have demonstrated that vitamin D can prevent the development of tumours by affecting the inflammatory process. The most prevalent pediatric disease and the main reason for pediatric visits is otitis media (OM), a middle ear infection. By reducing the generation of interleukins and interferon-gamma, vitamin D lowers inflammation. Treatment for upper respiratory tract infections like OM may include the use of vitamin D in addition to conventional therapies.[(6)]

Materials and Methods

Prospective comparative case control study was conducted on 85 children aged from 3 to 16 years old at Otorhinolaryngology department, Minia University Hospital from February 2022 to October 2022.

This study was approved by the ethics committee of faculty of medicine Minia University **(Approval No. 230: 2022).**The parentss of each patient signed an informed consent form when was enrolled in the study and patients' medical records and personal information were kept confidential.

Children were divided into two groups:

<u>Group A (case group):</u>

Forty-five cases with chronic suppurative otitis media (CSOM) either unilateral or bilateral with history of recurrent ear discharge more than 3 months duration, otoscopic examination reveals central tympanic membrane perforation.

<u>Group B (control group):</u>

Forty apparently healthy children with normal Tympanic membrane (TM) with no perforation as proved with otoscopic examination chosen from children underwent circumcision or inguinal hernia repair operations in department of pediatric surgery that confirmed with ENT examination as they do not have any sign of CSOM or upper respiratory tract (URT) infection.

Exclusion Criteria:

- Patients who had a known chronic or systemic disease affecting the level of vitamin D as rickets, renal impairment, liver failure or malignancies.
- Diabetes mellitus.
- Vitamin D consumption: patients with history of vitamin D supplementation especially during the last week.

<u>Assay of serum vitamin D</u>

Blood samples were drawn in the morning between 8 AM and 11 AM. After centrifugation at room temperature for 20 minutes, aliquots of the serum samples were frozen consecutively and stored at -20°C until analyzed.

Serum samples were used to assay the level of 25(OH)D. Test procedure for the determination of 25 (OH) vitamin D in human serum by ELISA kit (DRG International Inc., Mountain Avenue, Springfield, USA) is a solid-phase enzyme-linked immunosorbent assay (ELISA), based on the principle of competitive binding.

vitamin D deficiency was recognized as 25(OH)D of up to 20 ng/ml. Vitamin D insufficiency was also determined as 21–29 ng/ml. The recommended preferred level for vitamin D is at least 30 ng/ml (considered as sufficient level).

Statistical analysis:

- The analysis of the data was carried out using the IBM SPSS version 20.0 statistical package software (IBM; Armonk, New York, USA).
- Normality of the data was tested using the Kolmogorov-Smirnov test.
- Data were expressed as median (IQR) for non-parametric quantitative data, in addition to both number and percentage for qualitative data.
- Mann Whitney test or non-parametric quantitative data between the two groups.
- The Chi-square test was used to compare categorical variables.
- A p-value less than 0.05 was considered significant.

Results

Eighty-five children aged from 3 to 16 years were included in this study, divided into forty-five cases suffering from CSOM (15 males and 30 females) either unilateral CSOM in 33 cases (73.3%) or bilateral CSOM in 12 cases (26.7%) **(Case group)** and forty children (20 males and 20 females) with normal tympanic membrane with no previous history of ear discharge or ear operations **(Control group)**

The mean age of case group was 9.9 ± 3.6 while that of the control group was 8.6 ± 3.6 with no significant difference regarding age or gender distribution between both groups as shown in table 1, figure 1, and figure 2

Serum 25-OH Vitamin D level was measured in all participants. The mean vitamin D level in case group was 27.4 ± 22.1 while in control group was 35.6 ± 15.9.

In case group Vitamin D deficiency was detected in 24 cases (53.3%), insufficient in 5 cases (11.1%), and sufficient in 16 cases (35.6%) while in ***control group***, Vitamin D deficiency was detected in 5 cases only (12.5%), insufficient in 10 cases (25%), and sufficient in 25 cases (62.5%) with significant difference of vitamin D deficiency between case and control group as observed in table 2, table 3 and figure 5

Vitamin D deficiency in studied groups (Both cases and control) was detected in 29 participants (24 in case group and 5 in control group) with mean age 9.9 ± 3.6 in 12 males (41.4%) and 17 females (58.6%), while vitamin D was not deficient in 56 participants (21 in case group and 35 in control group) with mean age 8.9 ± 3.6 in 23 males (41.1%) and 33 females (58.9%) with no significant age and gender distribution difference between participants with vitamin D deficiency or not deficiency in both case and control groups as illustrated in table 4, figure 6 and figure 7

Also, there was no significant difference between cases with deficient vit D (N=24) and control with deficient vit D (N= 5) regarding age and gender distribution as shown in table 5

In case group, when comparing cases with Deficient vit D (N= 24) with other cases with not deficient vit D (N=21) we found that the mean age of cases with deficient vit D (N= 24) was 9.7 ± 3.6 divided into 15 cases with unilateral CSOM (62.5%) and 9 cases with bilateral CSOM (37.5%) in 8 males (33.3%) and 16 females (66.7%).

However, in cases with not deficient vit D (N= 21), the mean age of cases with not deficient vit D (N= 21) was 10.4 ± 3.4 divided into 18 cases with unilateral CSOM (85.7%) and 3 cases with bilateral CSOM (14.3%) in 7 males (33.3%) and 14 females (66.7%).

No significant difference regarding age, gender distribution or types of CSOM in case group according to Vit. D level (deficient or not) as clearly obvious in table 6, figures 8, 9, 10.

Table (II): Comparison of different Vitamin D levels between case and control groups and types of CSOM:

		Cases N= 45	Control N= 40	p value
CSOM: **Unilateral** **Bilateral**	**N %**	 33 (73.3%) 12 (26.7%)	----------	----------
Vitamin D level	**Mean ± SD** **Median** **IQR**	27.4 ± 22.1 18.3 (10.7 – 52.6)	35.6 ± 15.9 35.0 (25.3 – 47.7)	**0.019***
Vitamin D: **Deficiency** **Insufficiency** **Sufficiency**	**N %**	 24 (53.3%) 5 (11.1%) 16 (35.6%)	 5 (12.5%) 10 (25.0%) 25 (62.5%)	**<0.0001***

- Mann-Whitney test for non- parametric quantitative data between the two groups.
- Chi-square test for qualitative data between the two groups.
- *: significant level at p value <0.05

Table (III): Comparison between vitamin D deficiency in case and control group

		Cases N= 45	Control N= 40	p value
Vitamin D: **Deficient** **Not**	**N %**	 24 (53.3%) 21 (46.7%)	 5 (12.5%) 35 (87.5%)	**<0.0001***

- Chi-square test for qualitative data between the two groups.
- *: significant level at p value <0.05

Table (IV): Vitamin D deficiency in studied groups (cases and control)

		Studied groups N= 85		p value
		Deficient vit D **N= 29**	**Not deficient** **N= 56**	
Age	**Mean ± SD** **Range** **Median** **IQR**	9.9 ± 3.6 (3.0 – 16.0) 10.0 (7.5 – 12.5)	8.9 ± 3.6 (3.5 – 16.0) 9.5 (5.3 – 12.0)	0.221
Gender **Male** **Female**	**N %**	 12 (41.4%) 17 (58.6%)	 23 (41.1%) 33 (58.9%)	0.978

- Mann-Whitney test for non- parametric quantitative data between the two groups.
- Chi-square test for qualitative data between the two groups.
- *: significant level at p value <0.05

Table (V): Age and Gender distribution between cases and control group of Vit. D deficiency

		Cases with Deficient vit D N= 24	Control with Deficient vit D N= 5	p value
Age	Mean ± SD Median IQR	9.7 ± 3.6 10.0 (7.0 – 12.8)	11.6 ± 2.9 12.0 (9.0 – 14.0)	0.283
Gender Male Female	N %	8 (33.3%) 16 (66.7%)	4 (80.0%) 1 (20.0%)	0.058

- Mann-Whitney test for non- parametric quantitative data between the two groups.
- Chi-square or Fisher's exact test for qualitative data between the two groups.
- *: significant level at p value <0.05

Table (VI): Vitamin D deficiency and not deficiency: Cases only

		Cases N= 45		p value
		Deficient vit D N= 24	Not deficient N= 21	
Age	Mean ± SD Median IQR	9.7 ± 3.6 10.0 (7.0 – 12.8)	10.4 ± 3.4 11.0 (8.0 – 12.5)	0.523
Gender Male Female	N %	8 (33.3%) 16 (66.7%)	7 (33.3%) 14 (66.7%)	<0.99
CSOM: Unilateral Bilateral	N %	15 (62.5%) 9 (37.5%)	18 (85.7%) 3 (14.3%)	0.079

- Mann-Whitney test for non- parametric quantitative data between the two groups.
- Chi-square or Fisher's exact test for qualitative data between the two groups.
- *: significant level at p value <0.05

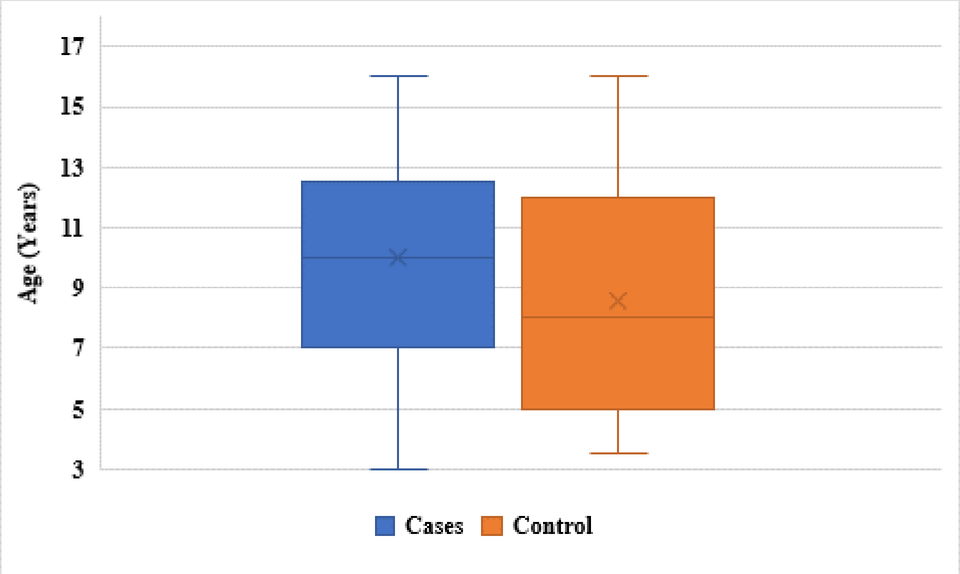

Figure (1): Box plot for age comparison between cases and control groups

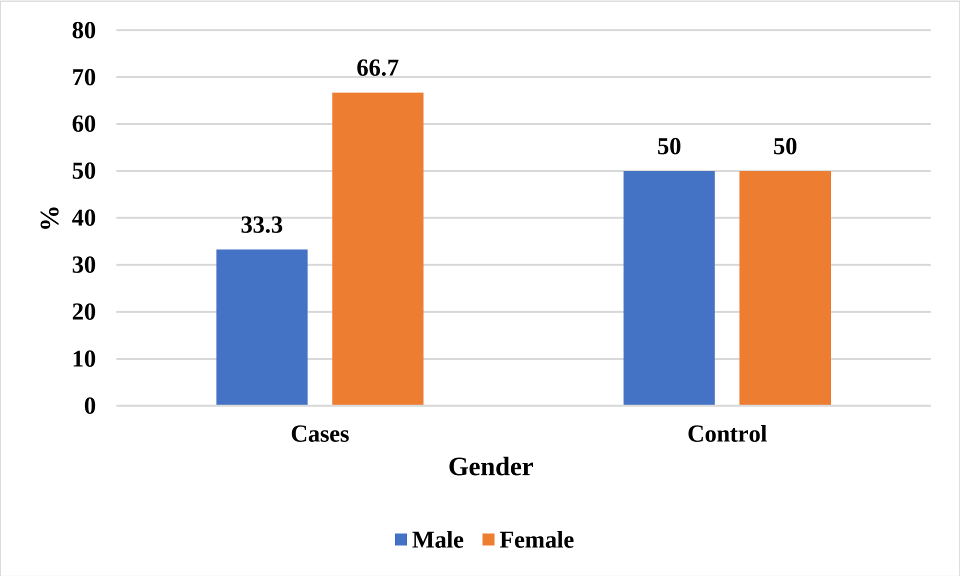

Figure (2): Gender distribution of cases and control groups

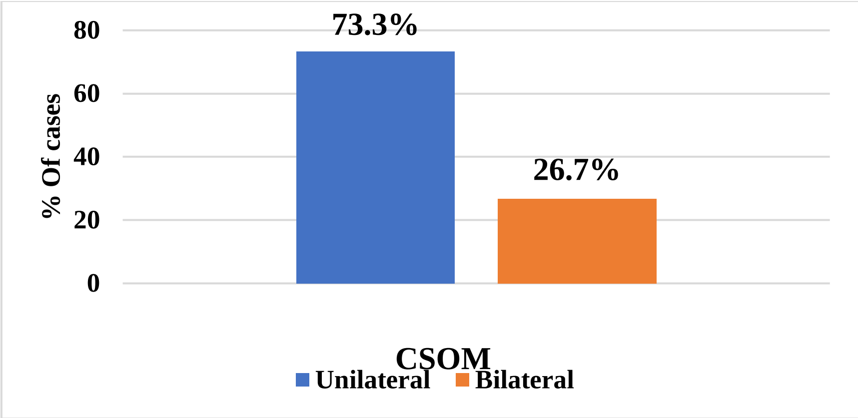

Figure (3): CSOM types of Cases

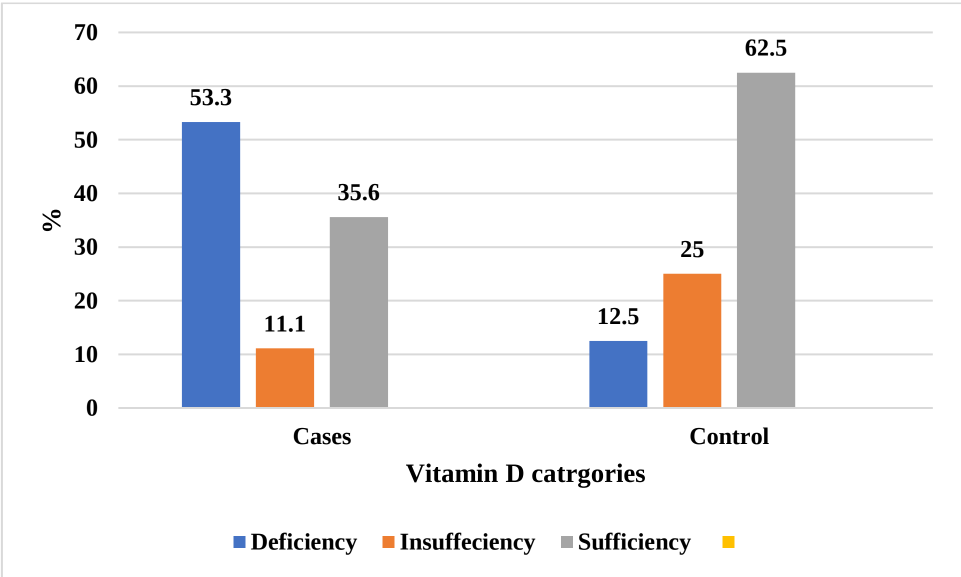

Figure (4): Vitamin D level categories comparison between cases and control

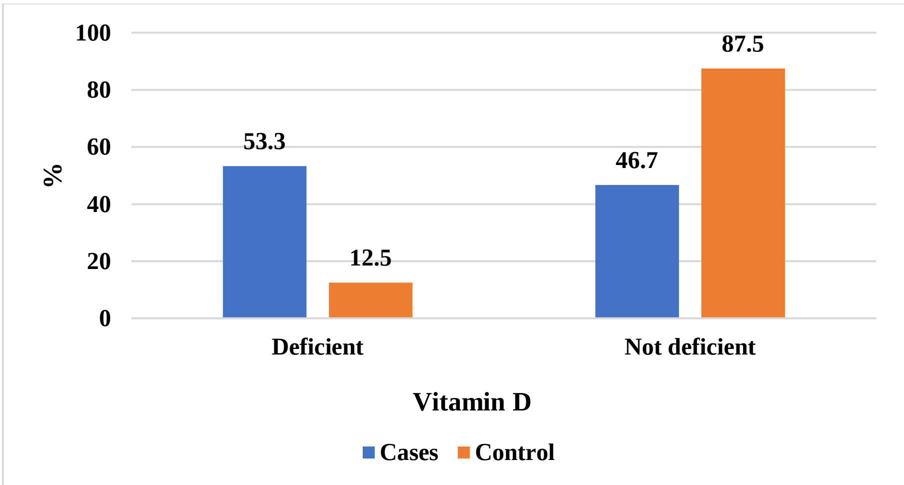

Figure (5): Comparison between cases and control group in % of individuals with deficient Vitamin D.

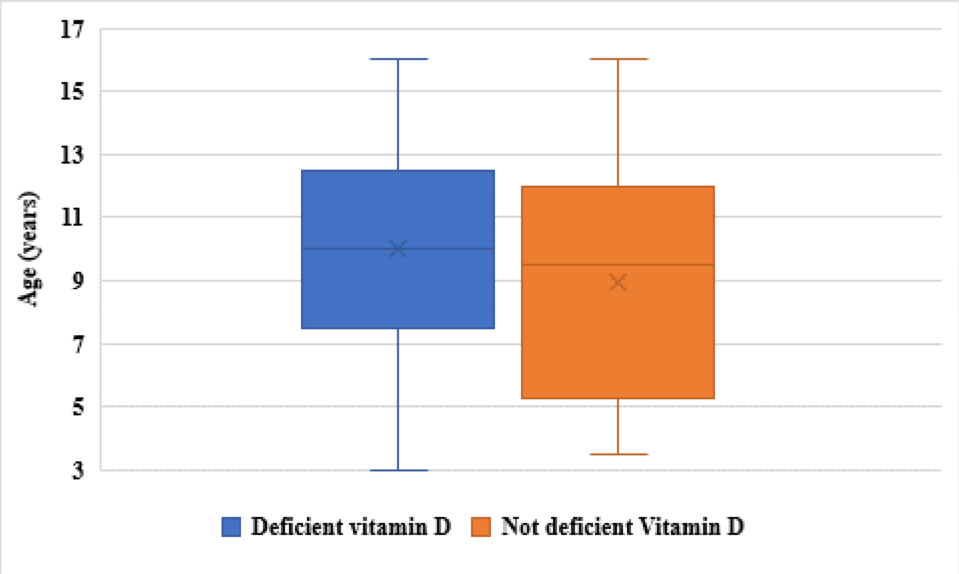

Figure (6): Box plot of age comparison between deficient and not deficient vitamin D within the two studied groups

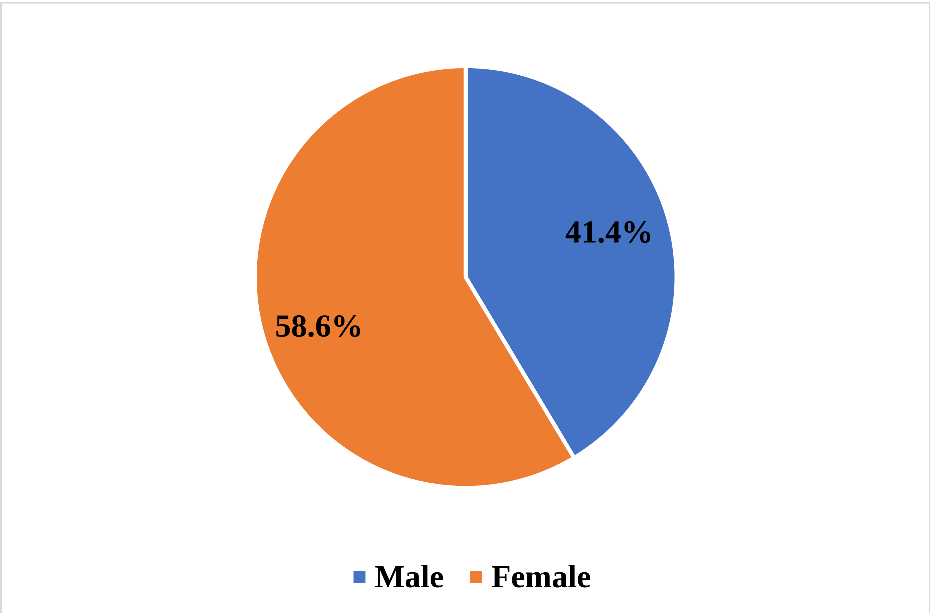

Figure (7): Gender distribution of deficient vitamin D individuals within the two studied groups

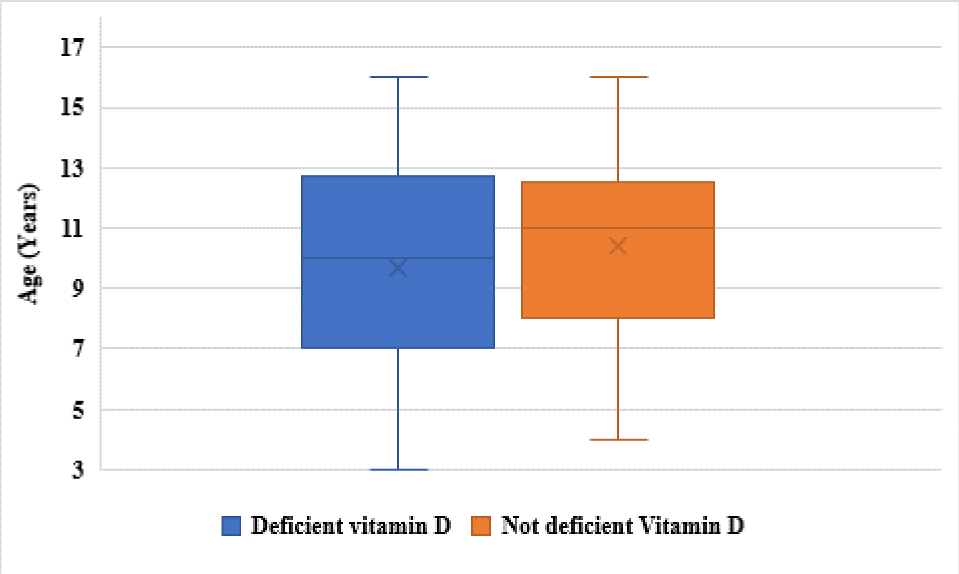

Figure (8): Box plot of age comparison between deficient and not deficient vitamin D within cases group.

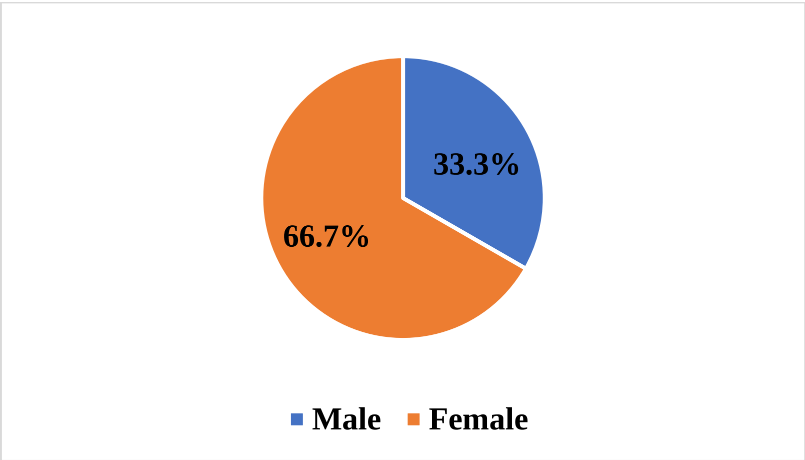

Figure (9): Gender distribution of deficient vitamin D individuals within the cases group.

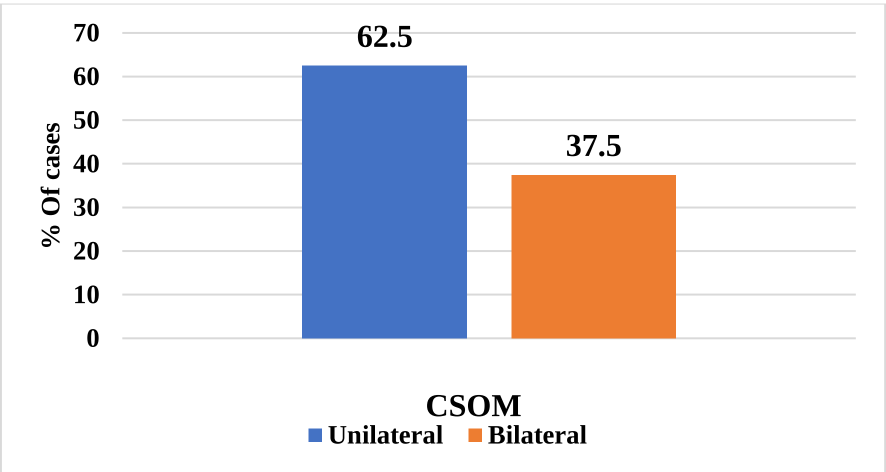

Figure (10): CSOM types within deficient vitamin D Cases

Discussion

The World Health Organization (WHO) recommended the need for appropriate screening programmes of school children for early detection of ear diseases and decreased hearing in order to prevent psycho social consequences. If the prevalence of chronic suppurative otitis media among paediatric age group is more than 4%, ear diseases must be considered as public health problems.[7]

Multiple research work have been conducted to correlate vitamin D and human diseases, especially in otolaryngology, as vitamin D insufficiency is thought to be a cause and risk factor for a number of ear diseases. Patients who frequently visit outpatient otolaryngology clinics often have vitamin D deficiencies.[8]

Vitamin D insufficiency has been linked to the onset and recurrence of BPPV[9], Meniere's disease [10]. Also, according to other researches, vitamin D insufficiency was correlated with middle ear diseases as otosclerosis and tympanosclerosis [6].

Current study reveals that there is significant difference between children with CSOM and control heathy children regarding vitamin D deficiency and also, we noticed that patients with CSOM and vitamin D deficiency were subjected to recurrent acute exacerbation and ear discharge following recurrent URT infections that correlates with study conducted by Cayir et al., 2014 who compared serum levels of vitamin D between 108 healthy children and 84 children with recurrent OM. Between the two groups, they discovered a statistically significant correlation. They also discovered that supplementing treatment with vitamin D decreased the recurrence of OM. Also, they showed that a deficiency of vitamin D may increase the incidence of OM and other infections of upper respiratory tract [11].

116 children with AOM participated in a randomised control trial that Marchisio et al., 2014 [12] carried out. 58 kids received supplements containing 1000 IU vitamin D per day, whereas the remaining participants received a placebo. They discovered that children who got vitamin D supplements had decreased rates of AOM. Also, participants had a considerably decreased probability of developing AOM when their blood vitamin D levels > 30 ng/ml, demonstrating the critical function that vitamin D plays in preventing recurrent cases of otitis media and that correlates with current study as we found that patients with CSOM had lower level of vitamin D in comparison to control and that reflect the critical role of vitamin D in prevention of recurrent otitis media and subsequently development of CSOM.

In 16,063 people over the age of 20years, assessment of vitamin D serum levels by Park et al.,[13] was done and they found a weighted prevalence of COM of 3.8%. Significant evidence suggests that the emergence of COM was linked to high levels of vitamin D, and this association was significant ($P < 0.01$) in contrast to our study, but the age group is different, and they did not identify which type of otitis media in addition to different locality.

Although CSOM typically affects malnourished children in underdeveloped nations, there hasn't been much research on how nutritional inadequacies contribute to its severity or its aetiology.

Elemraid, et al., (2011) compared the nutritional status of Yemeni children with CSOM to that of healthy controls in order to find dietary correlates related to the occurrence and severity of this infection. As a result, CSOM was discovered to be a significant health problem in these Yemeni kids. Vitamin D deficiency and iron replenishment were linked to the severity of CSOM disease, despite the fact that these relationships were significantly reduced in the age-adjusted analysis[14] and that correlates with current study in that children with vitamin D deficiency are more susceptible to development of CSOM and repeated acute infections.

Both AOM and COM have been linked to lower plasma vitamin D levels when compared to controls, according to research by Salamah, et al., 2022 ($P = 0.02$) and ($P = 0.04$), respectively.[6]

Li et al., 2016 conducted systematic review and meta-analysis that revealed that OM was linked to reduced vitamin D levels [2]

A comparative systematic evaluation of the data linking particular nutritional deficiencies, including vitamin D, with middle-ear diseases and infections found no human-specific research linking vitamin D shortage or status with chronic suppurative otitis media (CSOM). Furthermore, 5 studies reported data from the 89 papers discovered through the systematic search of 16,689 people who were included in the meta-analysis, observing that plasma vitamin D level may play a significant role in the progression of AOM [6]. As a result, we advise further research on a wider spectrum for the accurate identification of the relationship between plasma vitamin D level and the onset and progression of CSOM. Additionally, monitoring children's plasma vitamin D levels as part of routine examinations may be crucial to protecting them from CSOM and its complications.

Conclusion

Vitamin D level in children with CSOM was found to be significantly lower than that in control with normal TM, however further studies on larger scale are needed to confirm this relation and assessment of vitamin D level is very important in children with CSOM to decrease recurrent acute exacerbation and prevent complications.

- No conflict of interest .
- Fund: funded by personal efforts of the authors.

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