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Original Article

Association of Vitamin D Deficiency with Recurrent Respiratory Tract Infections in Pediatric Age Group

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ABSTRACT

Background: Vitamin D deficiency is now declared a global health problem. The low level of serum Vitamin D contributes to a number of illnesses. Vitamin D deficiency has a well-established link with the recurrent respiratory tract infections in all age groups, especially pediatric and elderly age group. However, the inverse relation between vitamin D treatment and frequency of Respiratory tract infection is still uncertain. **Objective:** To determine the association of the vitamin D deficiency and its treatment with the frequency of recurrent respiratory tract infections in pediatric age group (1 to 14 years). **Method:** In this prospective Cohort Study, we assessed the response of 139 selected children to the vitamin D supplementation and resultant change in the frequency of respiratory tract infections, over a period of 6 months, from February 01, 2021 to July 30, 2021 at Children Hospital & Institute of Child Health, Faisalabad. **Results:** After calculating sample size, 139 Vitamin D Deficient children of age 5 years to 14 years were selected for this study. In this prospective cohort, the frequency of the RTIs in these children is documented on the basis of total 6, monthly hospital visits to evaluate the association of RTIs with serum Vitamin D levels. The frequencies of Nasal Obstruction (p=<0.02), Sinusitis (<0.01), Tonsilitis (p=<0.001), Pharyngitis (p=<0.02) remarkably declined after correcting serum vitamin D levels. **Conclusion:** Recurrent RTIs in school going children have multiple physical, psychological, and social effects on the affected children. Repetitive infections not only result in weak immune system, financial burden, and impaired school performance/attendance, but also stunted growth due to persistent septic burden in growing age. In agreement with multiple studies, our study also concludes that Vitamin D Deficiency is significantly associated with the frequency of recurrent episodes of RTIs.

KEYWORDS: 25-OH Vitamin D3, Vitamin D deficiency, Pediatrics, Respiratory Tract Infection, Vitamin D3 supplementations

INTRODUCTION

Respiratory health problems in children are one of the major causes of their hospital visits, accounting for second most common cause of morbidity and mortality in pediatric age group, globally [1]. RTI has higher rates of hospitalizations in children under 5 years of age [2]. With repeated RTI episodes, children from the age 5 to 14 years become vulnerable to social, psychological, and behavioral impairments [1-3]. Vitamin D is well-known for its classical hormonal activities that include regulation of bone mineral components and serum calcium regulation. Moreover, with the discovery of Vitamin D receptors VDR on the surface of macrophages and natural killer cells indicate that Vitamin D has immunomodulatory effects on the innate and acquired immune systems [4, 5]. Supposedly, the Vitamin D deficient children with history of recurrent infections should be benefitted by the Vitamin D supplementation. However, there is limited knowledge regarding the efficacy of Vitamin D supplementation in the treatment and prevention of recurrent respiratory tract infections in pediatric age group [6].

Respiratory tract infections (RTI) are sub-classified according to duration and anatomy. According to duration of RTI, it could be Acute (less than 2 weeks) or Chronic (more than 2 weeks) [7].According to anatomical landmarks, RTI is categorized into Upper and Lower Respiratory Tract infections. Upper RTI is when airway infection is anywhere starting from nostrils to vocal cords, including Paranasal sinuses, Eustachian tube, and middle ear. Lower RTI covers the infections from trachea onwards, up till alveoli [7, 8]. Acute RTI is usually viral, occurs occasionally/ seasonal, and self-limiting (resolves on its own with little to no treatment). Whereas chronic RTI is often associated with multiple hospital visits with recurrent infections followed by long-term complications [9,10].

Vitamin D is a fat soluble vitamin, synthesized in the skin on sun exposure. The ultraviolet radiations in the sunlight photolyze the pre-existing 7-DHC (Dehydrocholesterol) in the skin and synthesize Pro-vitamin D3, and later convert it into Pre-vitamin D3 or Cholecalciferol. The cholecalciferol goes into two step hydroxylation process in liver and kidney under influence of 25-hydroxylase and 1 alpha hydroxylase respectively. The liver produces 25-hydroxy-cholecalciferol, an inactive form of Vitamin D3, which gets converted into active form in the kidneys, 1,25-Hydroxycholecalciferol, after second and final hydroxylation process [11-13].

The other source of getting Vitamin D is diet. There are numerous animal and plant sources of vitamin D with variable bioavailability. Plants are the source of Vitamin D2 which needs further processing in the body to transform into an activated D3 form. Overall, plant source proves to be an inadequate supply of Vitamin D [14]. However, diet is not the only factor that controls serum vitamin D levels. The possible factors that contribute to the vitamin D deficiency in human body are:

1. **Insufficient Vitamin D synthesis in skin: due to**

- Dark complexion
- Age (infants, elders)
- High BMI (obese)
- Physical blockage to the sunlight (heavy clothing, sunscreen application, etc.)
- Weather (e.g., cloudy, rainy weather, or extreme summer and winter season with limited sun exposure).
- Location (e.g., high latitude, low altitude)

2. **Dietary Insufficiency**

- Malnutrition (including eating disorders)
- Malabsorption Syndromes (Intestinal pathologies, Pancreatic and Hepatobiliary) insufficiency)
- Vegetarians
- Post Gut Resection Surgery (Short Bowel Syndrome)

3. **Postnatal Factors**

- Low birth weight
- Maternal Vitamin D deficiency
- Delayed weaning

4. **Genetic/Metabolic Disorders**

- Chronic Liver Disease (CLD)/ Chronic Kidney Disease (CKD)
- Hyperparathyroidism, Diabetes Mellitus
- Congenital resistance to Vitamin D
- Growth hormone deficiency or insufficiency

5. **Drugs**

- Antiepileptics (e.g., Phenytoin, Phenobarbiturates, Topiramate, Carbamazepine)
- Steroids (e.g., Glucocorticoids)
- Anti-retroviral agents (for the treatment of HIV)
- Antifungal drugs (e.g., Ketoconazole)

The aim of this study is to observe the effects of Vitamin D supplementation on the frequency of respiratory tract infections. In the past studies, it was noted that different variables affected the end results when it comes to assessing the relationship between vitamin D deficiency and Recurrent RTI [4-8]. In this study, we tried our best to keep the variables constant to get the un-biased results. We took a selective group of children under observation with the history of recurrent RTIs and gave them Vitamin D supplementation for 6 months and assessed whether the frequency of RTIs changed or did not change.

For this study, the children were selected on the basis of the following inclusion and exclusion criteria:

INCLUSION CRITERIA

- School going children of age 5 years to 14 years were included in the study as they were more prone to experience recurrent RTI episodes and had well-established dietary habits
- Patients whose attendants were willing to participate in the study
- Patients whose serum Vitamin D level was less than 10ng/dl and were not diagnosed with Vitamin D Deficiency at the time of recruitment for this study
- Patients who were not taking Vitamin D supplementation earlier
- Patients who were experiencing recurrent episodes of respiratory tract infections

EXCLUSION CRITERIA

- Patients whose attendants were not willing to participate in the study and did not show compliance with the regular follow-up visits
- Patients having serum Vitamin D3 level more than 10ng/dl (Vitamin D3 insufficiency or normal levels)
- Children with BMI value above or below the normal range
- Patients who were already diagnosed with vitamin D deficiency and were taking supplements
- Patients with a co-morbidity or pathology that was contributing to the recurrent respiratory infections or vitamin D deficiency. (In that case Vitamin D Deficiency as a cause of RTI could not be established)

MATERIALS AND METHODS

The Ethical Approval from the Ethical Review Board (ERB) of Children Hospital and Institute of Child Health Faisalabad was obtained prior to the data collection of this study. Informed Verbal Consent from the attendants was obtained by explaining them the purpose of this study and their contribution in it. The cooperation of attendants included the assurance of regular follow-up checks for proper documentation. Those who denied participation in the study were neither forced nor included in this study. With the permission of authorities and guardians of selected patients (considering the inclusion and exclusion criteria) data collection was started. CH & ICH Faisalabad is a tertiary care hospital and caters a large number of population, including referrals from other districts. So, the exact population was categorized as unknown. The calculated sample size for unknown population was 139. The other considerable parameters were Confidence level 95%, Margin of error 5%, and Population proportion 10%.

Blood samples were collected from the participants, twice during this study to evaluate Serum 25 (OH) D levels before and after giving vitamin D supplementations. Their anthropometric measurements were taken prior to their selection. In this study. Height is calculated in centimeters (cm), Weight is calculated in Kilograms (kg), and Body Mass Index (BMI) is calculated in kilogram per meter square (kg/m^2). Only those who had all these three parameters within the normal ranges were included in the study. During the process of data collection, the patient’s identity, personal and medical information was kept confidential. It was ensured before hand that this study would not cause any harm to the rights and general welfare of the included subjects, by any means.

Statistical Package for Social Sciences Version 20 (SPSS-20) was used to perform the statistical analysis. The Quantitative data e.g., age, gender, weight, height, and BMI were analyzed by using mean, SD, and z-score. These demographic and anthropometric parameters document the general built and well-being of the patients. All the patients were monitored for their BMI to exclude the chances of fluctuations in serum vitamin D levels because of it. Attendants were guided to closely monitor the diet, weight, and physical wellbeing of their children as the data would have become irrelevant if their BMI fluctuated from the normal range.

The study was conducted from February 2021 to July 2021, which excluded the potential influence of winter season. The group of subjects was selected on the basis of same ethnicity and race, living at the same latitude and altitude, belonging to the same/moderate socioeconomic status to ensure the authenticity of the results, keeping the variables in check and excluding the potential factors for vitamin D deficiencies.

RESULTS

Anthropometric Characteristics of the Participant Children (n=139)

In this prospective cohort study, 139 participants of calculated sample size were observed over the period of 6 months. The participants were stratified into 10 age groups, from 5 years to 14 years. The calculated anthropometric measurements were compared with the standardized values established by World Health Organization (WHO). BMI of all the pediatric age groups had z-score <2, which indicates that the children included in this study were having anthropometric parameters within normal ranges. Table 1 illustrates the Mean and Standard Deviation (SD) of height, weight, and BMI of each age group.

Age (Years)	Frequency (n)	Percentage	Height (cm)		Weight (Kg)		Body Mass Index (BMI)	
			Mean	Standard Deviation (SD)	Mean	Standard Deviation (SD)	Mean	Standard Deviation (SD)
5	7	5%	109.90	6.82	18.90	3.74	13.80	1.18
6	15	11%	116.10	6.96	20.80	4.31	14.11	2.10
7	12	9%	121.70	7.22	22.70	2.68	14.24	1.26
8	9	6%	126.40	7.42	25.40	7.29	14.61	1.10
9	18	13%	128.39	7.66	28.20	3.58	15.03	2.80
10	12	9%	131.76	7.72	31.50	4.51	16.11	2.82
11	18	13%	136.48	7.94	33.60	7.82	16.34	2.92
12	21	15%	142.34	6.12	87.00	14.60	18.24	4.05
13	9	6%	149.95	6.58	39.00	7.16	18.76	3.70
14	18	13%	152.29	4.85	42.00	5.52	18.58	3.40

Table 1. Anthropometric Measurements in terms of Height (cm), Weight (Kg), and BMI (Kg/m^2) of age groups 5-14 years

Distribution of Serum Vitamin D Levels Among the Children (Before Vitamin D Supplementation)

As described earlier in the inclusion criteria, only the Vitamin D Deficient candidates were included in the study, having serum Vitamin D levels less than 25 ng/dl (nanogram per deciliter). Table 2 categorizes the Serum Vitamin D levels in three groups before starting the trial/giving them oral Vitamin D supplementation: 25-20 ng/dl, 15-20 ng/dl, and 10-15 ng/dl. Most of the children (62.58%) fall into the range of 20-25 ng/dl with p-value less than 0.001. p-value less than 0.05 is considered significant.

Vitamin D status ng/dl (Before getting Supplementation)	Frequency (n)	Proportions (%)	95% Confidence Interval (CI)	p-value
20-25	87	62.58	1.04-11.5	<0.001
15-20	48	34.53	1.23-9.55	<0.001
10-15	4	2.87	1.21-7.32	<0.001

Table 2. Serum Vitamin D distribution among 139 participants before giving them oral Vitamin D Supplementation.

Distribution of Serum Vitamin D Levels Among the Children (After Vitamin D Supplementation)

Once it was established that all the selected candidates in this study were having Vitamin D Deficiency (<25 ng/dl) their oral supplementation was started. By the end of the 6 months of proper follow-up, Table 3 demonstrates the distribution of serum vitamin D levels in 3 categories: Vitamin D deficiency (<25 ng/dl), Vitamin D insufficiency (25-40 ng/dl), and normal Vitamin D levels (>40 ng/dl). After 6 months of supplementation, children with Vitamin D deficiency, insufficiency, and normal levels were, n=8 (5.75%), n=25 (17.98%), and n=106 (76.25%), respectively.

Vitamin D status ng/dl (After getting Supplementation)	Frequency (n)	Proportions (%)	95% Confidence Interval (CI)	p-value
10-15	0	0	0	0
15-20	0	0	0	0
20-25	8	5.75	0.72-0.99	0.01
25-40	25	17.98	0.82-1.90	<0.001
40-60	57	41	1.05-1.97	<0.001
>60	49	35.25	0.98-2.10	<0.001

Table 3. Distribution of Serum Vitamin D levels by the end of 6 months of oral supplementation of vitamin D.

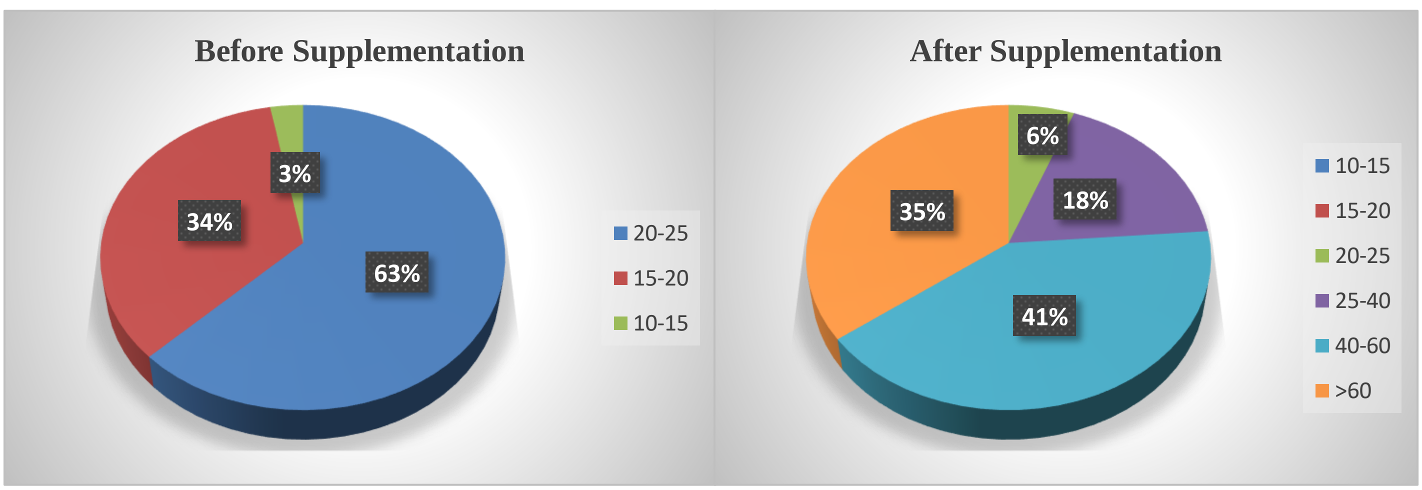

Figure 1.Pie Charts showing Comparative analysis between the Vitamin D distribution among candidates before and after 6 months of oral Vitamin D supplementation.

Changes in the Frequency of RTI Episodes with Improving Vitamin D Levels

The common respiratory tract infections that were considered in this study included Seasonal Influenza, Nasal Obstruction, Sinusitis, Tonsilitis, Pharyngitis, Bronchitis, and Pneumonia. The frequencies of these RTIs were documented on every month's follow-up visits. The RTIs with significant p-value (<0.05) showed remarkable decrease in their frequencies after 6 months of Vitamin D supplementation, including Nasal Obstruction (p=<0.02; frequency decreased from 33% to 19%), Sinusitis (p=<0.01; frequency decreased from 19% to 6%), Tonsilitis (p=<0.001; frequency decreased from 28% to 14%), and Pharyngitis (p=<0.02; frequency decreased from 44% to 30%).

Types of common RTIs	History of frequency of RTIs in subsequent opd visits						
	1st visit (February)	2nd visit (March)	3rd visit (April)	4th visit (May)	5th visit (June)	6th visit (July)	p-value
Seasonal Influenza	5	8	7	_	2	5	2.34
Nasal Obstruction	46	42	38	25	19	26	<0.02
Sinusitis	26	23	22	17	10	9	<0.01
Tonsilitis	39	34	31	29	25	20	<0.001
Pharyngitis	61	64	58	53	48	42	<0.02
Bronchitis	10	2	7	3	1	1	0.07
Pneumonia	4	3	6	2	_	1	1.35

Table 4. Showing the changes in the frequency of selected Respiratory Tract Infections (RTIs) in relation to every following monthly visits with on-going oral Vitamin D supplementation.

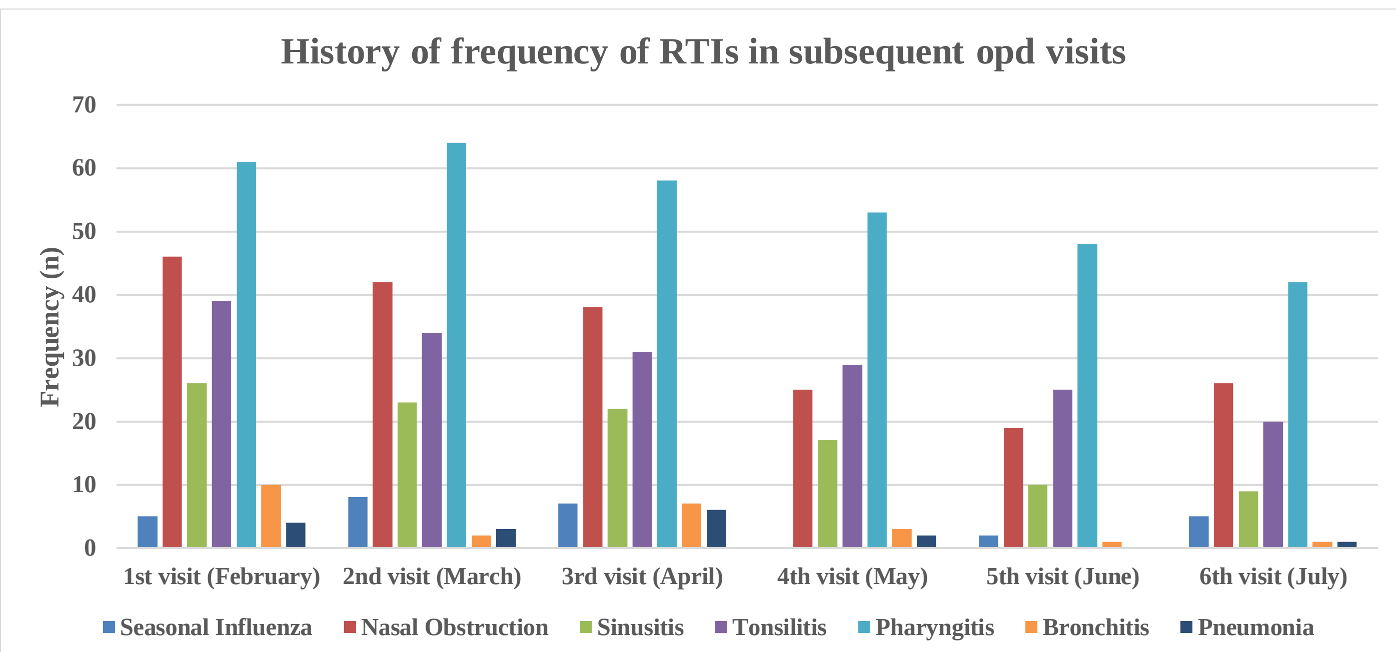

Figure 2. Bar chart showing Comparative analysis between the subsequent change in the frequency of the RTIs every month.

DISCUSSION

This study aimed to explore the correlation between vitamin D deficiency and the frequency of various respiratory tract infections. It also provided information regarding the change in the frequencies of RTIs with the gradual resolution of vitamin D deficiency with regular oral supplementation.For this study, the subjects were selected without the discrimination of gender, ethnicity, geological location, height, weight, or BMI. It was ensured that all the participants of this study were vitamin D deficient and were not taking supplements for it. Vitamin D deficiency is prevalent in our society and the most common causesare indoor activities and/or limited sun exposure. Moreover, the reduced consumption of Vitamin D fortified dietary products may also contribute to its deficiency. The participants of this study did not have any pathological causes for their vitamin D deficiency.

As a result of our study, we concluded a significant association between the frequencies of nasal obstruction, sinusitis, tonsilitis, and pharyngitis with vitamin D deficiency and its recovery. In the case of vitamin D deficiency, these RTIs were more common among the subjects. However, their incidences decreased by almost 50% with the recovery of their serum vitamin D status.

The relationship between Serum Vitamin D levels and respiratory tract infections is a matter of debate. Multiple studies show contradictory results. On one hand, some studies suggest that Vitamin D is associated with the regulation of phagocytic activities and maturation of various immune cells. So, when the vitamin D level in serum drops, it makes the body vulnerable to viral and bacterial infections. Likewise, the lymphoid tissues get hypertrophied resulting in tonsillitis and adenoiditis with adenotonsillar hypertrophy (ATH) [15, 16]. In that case, the persistent vitamin D deficiency can potentially result in several complications including Obstructive Sleep Apnea Syndrome (OSAS), Otitis Media with Effusion (OME), Chronic Sinusitis, Nasal polyposis, and/or Benign Paroxysmal Vertigo (BPV).

On the other hand, results of some studies show that the increased frequency of inflammatory insults to the body makes the body more receptive for Vitamin D and thus increases its serum levels [16-18]. Also, most of the recent studies found no relation between serum Vitamin D levels and infectious/ inflammatory diseases [17, 18].

The main causes of these discrepancies in results are concluded to be ethnic, socioeconomic, geographic, nutritional, and cultural differences. However, in this study we tried to avoid all these variables to get the unbiased results. The results of our study are consistent with the recent evidence that Vitamin D helps in strengthening innate immune system by inducing neutrophils and macrophages in the respiratory linings to release Cathelicidin, an endogenous anti-microbial peptide [19]. It is also established now, that Vitamin D enhances the production of Reactive Oxygen Species and promotes autophagy that protects against not only the RTIs but also a number of chronic illnesses like autoimmune disease, asthma, diabetes, cancer, cardiovascular diseases etc. [20]

It is known to all that the recurrent infections substantially affect the general health and linear growth in young children. Respiratory tract infections are one of them. The RTIs, especially those which involve inflammation of the throat, are associated with decreased oral intake, malnutrition, making the child more susceptible to the long-term detrimental effects. Fighting such infections results in enormous nutritional/ catabolic losses, exponential increase in the nutrients and metabolites requirements, and redirected transport of nutrients to the lymphoid tissues instead of bones and muscles. All these factors considerably affect the growth and development of young children [21, 22]. The possible influencing factors are poor hygiene, low socioeconomic status, second hand smoke, atopy, and family history which can enhance adherence of pathogens to the inflamed respiratory mucosa [23-25].

The serum vitamin D has a significant impact on the general health and well-being of respiratory mucosa. It helps in wound healing and repair, natural host defenses, normal immune cell functioning and fighting against inflammation. It is also known to control the atopic reactions or respiratory tract sensitizations/hyper-responsiveness [26].

This preliminary study highlights the significance of serum vitamin D levels in growing age. Along with multiple, known benefits of Vitamin D in the optimal growth and development of the young children, it also strengthens the immune system. In children with recurrent RTIs, especially nasal obstructions, sinusitis, pharyngitis and tonsillitis, Vitamin D supplementation can play a vital role in the disease prevention and control [27-30].

CONCLUSION

Vitamin D deficiency is a widespread problem among young children and so are the recurrent RTIs. This study elaborates the frequency of RTIs in a selected group before and then after giving them oral Vitamin D supplementation. The results show inverse relation between the serum levels of vitamin D and the monthly episodes of RTIs. For more significant results and to establish guidelines regarding the management of recurrent RTI with vitamin D supplementation in pediatric age group, extensive studies are required. This study aims to get the attention of health authorities and higher education committee to explore this correlation on a broader platform and plan general public awareness programs for the awareness on getting adequate sunlight exposure, risks of vitamin D deficiency, and/or screening of vitamin D levels in suspected children of growing age.

CONCENT FOR PUBLICATION

All authors unanimously agreed to publish this article.

DISCLOSURE

The authors declare no conflicts of interest for this work.

CONTRIBUTION

Misha Anam Conceptualization of the Project, Data Collectionand Principal Investigator, **Noor Ul Ain** Conceptualization of the Project, Manuscript Writing , **Sughra Mahnoor Mangrio** Statistical Analysis, Drafting & Revision , **Maira Maheen** Literature Research, Manuscript Writing, **Zara Zahid** Literature Research, Statistical Analysis, **Omar Sameh Mohamed Elsebai Talkhan** Literature Research, Drafting & Revision , **Soumya Bhattacharya** Literature Research, Drafting & Revision , **Lim Jun Yi** Literature Research, Statistical Analysis.

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