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Vitamin – D Deficiency and Relation to Recurrent Respiratory Tract Infection in children less than 5 years

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I. Introduction:

The role of diet in the development of rickets was determined by Edward Mellany between 1918-1920[1]. In 1921, ELMER Mc Collum identified an anti-rachitic substance found in certain fats could prevent rickets[2]. Because the newly discovered substance was the fourth Vitamin identified, it was called Vitamin D. Vitamin D is a group of fat soluble pro-hormones, the two major forms of which are vitamin D_2 (or ergocalciferol) and vitamin D_3(or cholecalciferol) In India sub clinical vitamin D deficiency is wide spread in all age groups[3,4]. Dietary intakes of both calcium and vitamin D are very low in majority of population except in high socioeconomic groups.[5] Vitamin D is involved in the regulation of 1000 human genes. Since few foods contain vitamin D, sunlight exposure is the primary determinant of vitamin D status in humans[6]. Vitamin D is found naturally in very few foods. Foods containing Vitamin D include some fatty fish (mackerel, salmon, sardines), and fish liver oils, egg yolk. Other sources of Vitamin D include fortified foods particularly dairy products and some cereals. .The metabolite formed in the skin and the vitamin D absorbed in the gut must be hydroxylated in the liver to form 25-hydroxyvitamin D [25(OH) D] and then hydroxylated in the kidney to active form 1α, 25-dihydroxyvitamin D [1, $25(OH)_2D$][7]. The main function of vitamin D in the body is to regulate calcium and phosphorous homeostasis, a process essential for bone mineralization[8]. Most of the physiological effects of vitamin D in the body are mediated by its active form 1, 25(OH) vitamin D[9]. It acts through a transcription factor – vitamin D receptor (VDR) which present in the nuclei of target cells.10

Risk Factors for Deficiency

Exclusively breast-fed infants: Infants who are exclusively breast-fed and do not receive vitamin D supplementation are at high risk of vitamin D deficiency, particularly if they have dark skin and /or receive little sun exposure[11].

Obesity: Obesity increases the risk of vitamin D deficiency[12]

Use of sun screen with a sun protective factor pf 8 inhibits more than 95% of vitamin D in the skin[12]

Inflammatory bowel disease, fat malabsorption syndromes , liver and kidney disorders results in impaired absorption and conversion due to its active form.

Manifestations of Vitamin D Deficiency

Vitamin D deficiency causes several bone diseases Osteomalacia,Osteoporosis including Rickets, where the earliest sign of sub clinical vitamin D deficiency is craniotabes, abnormal softening of the skull[13.]

Vitamin D malnutrition increases the susceptibility to several chronic diseases such as high blood pressure[12], cancer12, multiple sclerosis, depression[14], peripheral arterial disease[15] and several auto immune diseases including type 1 diabetes.[12.], chronic muscle pain and weakness in both children and adults.[16.] Vitamin D deficiency also increases the risk of respiratory tract infections such as Influenza[17] and Tuberculosis.[18, 19]

To determine vitamin D status, the serum concentration of 25(OH) D, the major circulating form of the hormone, must be measured[20].

Role of Vitamin D in Immunomodulation

The role of Vitamin D as a therapeutic immunomodulator has only recently returned to the centre of research arena due to increasing awareness of global Vitamin D deficiency epidemic[21.] . VDR ligands also affect maturation, differentiation, and migration of dendritic cells and inhibit the DC-dependent T cell activation, resulting in over all state of immune suppression[22]

It has potential antimicrobial actions against different organisms such as bacteria, viruses and fungi[23]

Upper Respiratory Tract Infections

Upper respiratory tract infections (URTI) including nasopharyngitis, pharyngitis, tonsillitis and otitis media constitute 87.5% of the total episodes of respiratory infections. Acute lower respiratory tract infection (ALRI) is the most important global cause of childhood death. Micronutrient deficiencies may increase the risk of ALRI[24]

Currently accepted standards for defining vitamin D status in children and adolescents as follows:
Vitamin D sufficiency: 25(OH) D > or =20 ng/ml (> or =50 nmol/l),
Vitamin D insufficiency: 25(OH) D between 15-20 ng/ml (37.5-50 nmol/l),
Vitamin D deficiency: 25(OH) D between 5-15 ng/ml (12.5-37.5 nmol/l) and
Severe deficiency: 25(OH) D < 5 ng/ml (<12.5 nmol/l).Individuals with 25(OH) D levels above 100 ng/ml have been arbitrarily designated as having vitamin D excess and above 150 ng/ml is considered as intoxicated[25]. Time off school or parental time off work was significantly associated with parental worry and disruption[26].The vast majority of acute upper respiratory tract infections are caused by viruses, does not require antimicrobial agent unless it is complicated by acute otitis media with effusion, tonsillitis, sinusitis, and lower respiratory tract infection. The most common bacterial agents causing sinusitis are S. pneumoniae, H. influenzae, M. catarrhalis, S. aureus and S. pyogenes. Acute About 15% of the episodes may be due to Group A beta hemolytic streptococcus (GABS) [27].

Lower Respiratory Tract Infections Two-thirds of childhood deaths due to lower respiratory infections occur in infancy due to croup (laryngotracheobronchitis), bronchitis, and bronchiolitis. Pulmonary infections are common in boys more than girls [28].

Recurrent Respiratory Tract Infection

Pediatric respiratory tract infections are one of the most common reasons for physician visits and hospitalization, and are associated with significant morbidity and mortality. Respiratory infections (RI), mainly involving the upper airways, are common in children and their recurrence constitutes a demanding and difficult diagnostic challenge for the pediatricians to discriminate between those with simply-managed cause for their symptoms such as recurrent viral infections or asthma, from the children with more serious underlying pathology such as bronchiectasis or immune dysfunction.

Definition

Recurrent infectious rhinitis is usually defined as more than five episodes per year and recurrent pharyngitis or tonsillitis more than three episodes within 12 months [29, 30, 31]
Though the causes are multiple, it can be grouped into one of the following categories[32]
i) RRI in normal child
ii) RRI in atopic child
iii) RRI in a child with chronic disease
iv) RRI in immune-deficient childIt is evident, that only a few appropriate tests are enough helpful to discriminate between a "well-being" child and a patient with immune dysfunction (Woroniecka & Ballow, 2000).
It has been proposed that to diagnose RRI at least one of the following criteria has to be
Present (Gruppo di Studio di Immunologia della Societá Italiana di Pediatria, 1988):
≥ 6 respiratory infections per annum,
≥ 1 respiratory infections per month involving the upper airways from September to April,
≥ 3 respiratory infections per annum involving the lower airways.

II. Aims And Objectives

Aim

To study the association of vitamin D deficiency with recurrent respiratory tract infections in children less than 5 years

Objectives

1. To assess Vitamin D levels in recurrent respiratory tract infections
2. To explore the association between Vitamin D deficiency and recurrent respiratory tract infections

III. Material And Methods

Source Of Data

All the children admitted in the Department of Paediatrics and also who attend the paediatric OPD, Kamineni Hospita, L.B.Nagar, Hyderabad with inclusion criteria are included in the study.

Cases Inclusion Criteria

1. Children between >1 month to 5 years of age
2. Children with symptoms of recurrent respiratory tract infections, defined as

- To diagnose RRTI, at least one of the following criteria needs to be met (Gruppo di Studio di Immunologia della Societá Italiana di Pediatria, 1988)

≥ 6 respiratory infections per annum
≥ 1 respiratory infection per month involving the upper airways from September to April
≥ 3 respiratory infections per annum involving the lower airways

Cases Exclusion Criteria

1. Children less than 1 month of age and greater than 5 years of age
2. Children with congenital heart disease
3. Receipt of Vitamin D supplementation within last 4 weeks.

Controls Inclusion Criteria

Children of same age group attending the hospital for other reasons.
Controls can be defined as:
a) No care giver reported history of fast or difficult breathing or lower chest wall in drawing (using a local term) of >1 day duration, or a diagnosis of 'pneumonia' at a health centre, during the past 1 month
b) No signs of tachypnoea or lower chest wall in drawing at the time of study recruitment or assessment

Controls Exclusion Criteria

1. Children less than 1 month of age and greater than 5 years of age
2. Children with congenital heart disease
3. Receipt of Vitamin D supplementation within last 4 weeks.

Design Of Study

Prospective non-randomised 2 group design-group-1 – RRTI present and group-2-RRTI absent and measure Vitamin D levels.

sample size

All patients (IP and OP) with and without recurrent respiratory tract infections who fulfill the inclusion criteria during the study period. Previous studies reported prevalence of vitamin D deficiency in children with respiratory tract infection in the range of 40-80% against a prevalence of approximately 20% in children without respiratory tract infections (controls). This study is designed to detect a difference of atleast 40% in the prevalence of vitamin deficiency between cases and controls. In order to detect this difference at 5% level of significance an 90% power of the test the minimum sample required is 36 per group. In order to reach a set of 72 evaluate children (cases and controls) we targeted 90 patients after factoring anticipated dropouts and patients who will not consent to participate

Duration Of Study Period

One year period

Methodology: All patients aged 1 month to 5 years with and without recurrent respiratory tract infections attending the outpatient department or admitted as inpatient in the Department of Pediatrics, Kamineni Hospitals, Hyderabad will be tested for serum Vitamin D levels by standard serological test using ELISA method.
Informed consent will be taken from the parents.
Information is obtained from the parents as per the proforma and anthropometry is measured.
About 3 ml of blood is collected and sent for serum 25 (OH) vitamin D analysis

IV. Statistical Analysis

The data is entered and analysed in MS Excel 2007. The categorical variables are summarized by proportions and the continuous variables by mean and SD. Differences between groups, if any are analysed by Chi square test or Fisher exact test for categorical variables, Independent samples t-test for continuous variables, using OpenEpi (online version). Odds ratio was used to assess the association between exposures and outcomes. The data is graphically summarized by bar charts

V. Results

A total of 90 children were considered for study during my study period. Out of total 90 cases, 50 children with recurrent respiratory tract Infections were taken as Group I, while 40 children without recurrent respiratory tract Infections (RRTI) were taken as Group II

Demographic Characteristics of the Studied Groups-Number of male children-33(66%),females-17(34%) in groupI(RRTI),and in group II(NoRRTI) males were 21(52.5%), females 19(47.5%),and in both groups children were from urban areas. P value > 0.05: not significant. Analysis of demographic characteristics

of the studied groups revealed that there were no significant differences between patients and controls with regard to age, sex and residence.

Table 1: Vitamin D levels Vs RRTI

Vitamin D levels(ng/ml)	Group I (RRTI) n=50	Group II (no RRTI) n=40	Total	OR (95% CI)	P value
Deficiency<20	43(86%)	14(35%)	57(63%)	11.41 (3.69-37.17)**	<0.001**
Normal=/>20	7(14%)	26(65%)	33(37%)		
Total	50(100%)	40(100%)	90(100%)		

OR: odds ratio, CI: confidence interval, **: highly significant, *: not significant

In Group I (RRTI), 86% (43) children had Vitamin D deficiency whereas in Group II (no RRTI), 35%(14) had Vitamin D deficiency Having Vitamin D deficiency increases the odds of RRTI by 11 times (the risk is increased by 11 times)

Table: 2 Vitamin D Mean (SD) among studied groups

Vitamin D nmol /l	Group I (RRTI) n=50	Group II (no RRTI) n=40	T	P-value
Mean(SD)	41.7(15.1)	64.6(34.2)	4.25	0.0001
Range	20-100	20-140		

P-value < 0.01: Highly significant

The mean value of Vitamin D for Group I (RRTI) was 41.7 compared to Group II 64.6(no RRTI). There is a highly significant positive correlation between Vitamin D and RRTI group

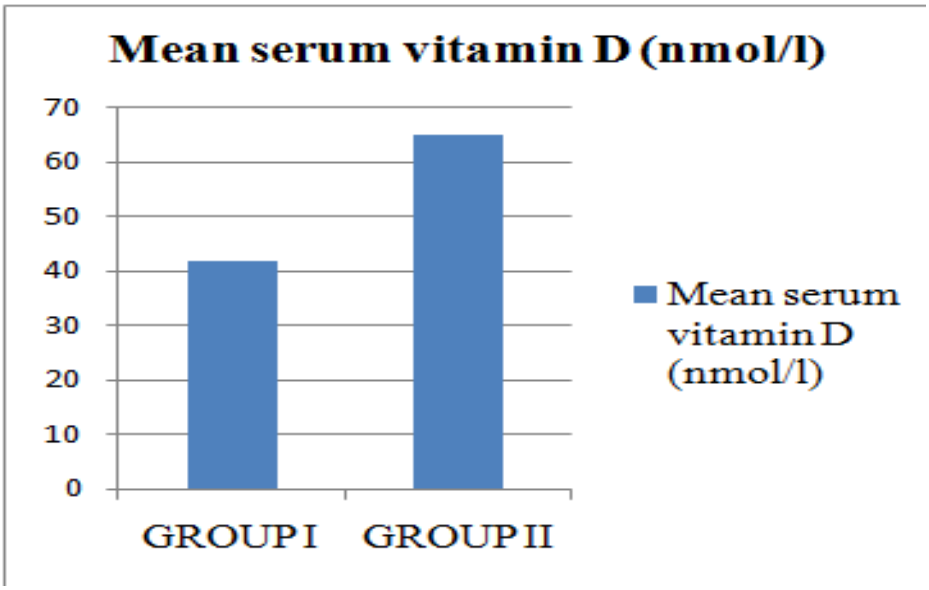


Fig: Mean Vitamin D levels in Group I (RRTI) and Group II (no RRTI)

Table 3: Gender v/s Vitamin D among the Studied Groups

Gender	Group I (RRTI) (n=50)			Group II (No RRTI) (n=40)		
	Vitamin D Deficient	Vitamin D Normal	Total	Vitamin D Deficient	Vitamin D Normal	Total
Male	28(65%)	5(71%)	33(66%)	9(64%)	12(46%)	21(52.5%)
Female	15(35%)	2(29%)	17(34%)	5(36%)	14(54%)	19(47.5%)
Total	43(100%)	7(100%)	50(100 %)	14(100%)	26(100%)	40(100%)

OR (95% CI)	0.75 (0.1-5.3)*	2.1 (0.46-10.18)*
P value	0.91*#	0.28*

OR: odds ratio, CI: confidence interval, **: highly significant, *: not significant, #: Yates correction

There was no difference in male female ratio in Group I (RRTI) as well as Group II (no RRTI). Males were 65% in Group I and 64% in Group II and females percentage was 35% and 36% respectively. This value is statistically not significant.

Fig: 4 Gender v/s Vitamin D among the Studied Groups

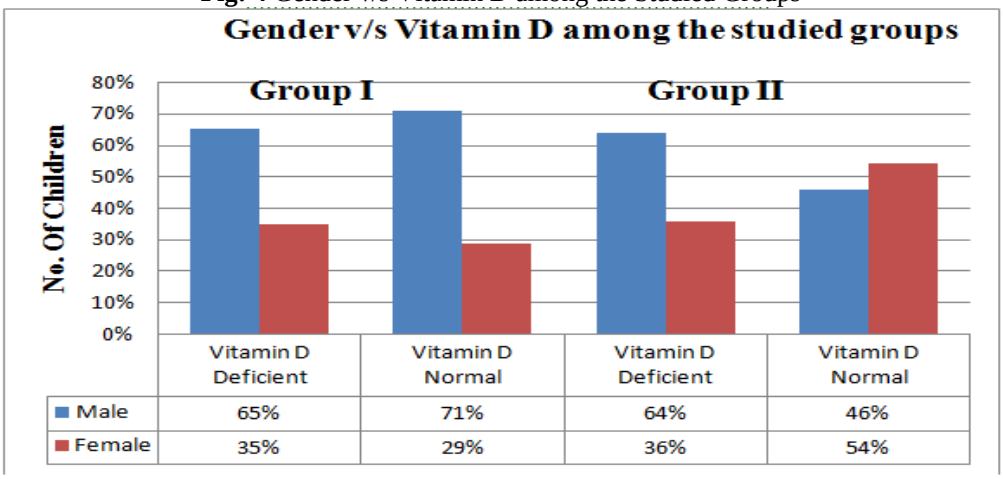


Table 5: Age v/s Vitamin D among the Studied Groups

Age in months	Group I (RRTI) (n=50)			Group II (No RRTI) (n=40)		
	Vitamin D Deficient	Vitamin D Normal	Total	Vitamin D Deficient	Vitamin D Normal	Total
1-12	8(18.5%)	2(29%)	10(20%)	1(7%)	5(18%)	6(15%)
13-24	11(26%)	1(14%)	12(24%)	9(65%)	7(30%)	16(40%)
25-36	4(9%)	1(14%)	5(10%)	2(14%)	6(23%)	10(25%)
37-48	12(28%)	1(14%)	13(26%)	1(7%)	3(11%)	3(7%)
49-60	8(18.5%)	2(29%)	10(20%)	1(7%)	5(18%)	5(13%)
Total	43(100%)	7(100%)	50(100%)	14(100%)	26(100%)	40(100%)
χ^2 Df	1.49* 4			5.48* 4		
P value	0.82*			0.24*		

χ^2 : Chisquare value, df: degree of freedom, **: highly significant, *: not significant

In Group I (RRTI), Vitamin D deficiency was seen more in 28% and 26% in 37-48 months and 13-24 months respectively. Whereas in Group II (no RRTI), Vitamin D deficiency was seen maximum in 13-24 months (65%) followed by 25-36 months (14% only). There is no significant association was found between age and vitamin D deficiency between the groups.

Fig: 5 Age v/s Vitamin D among the Studied Groups

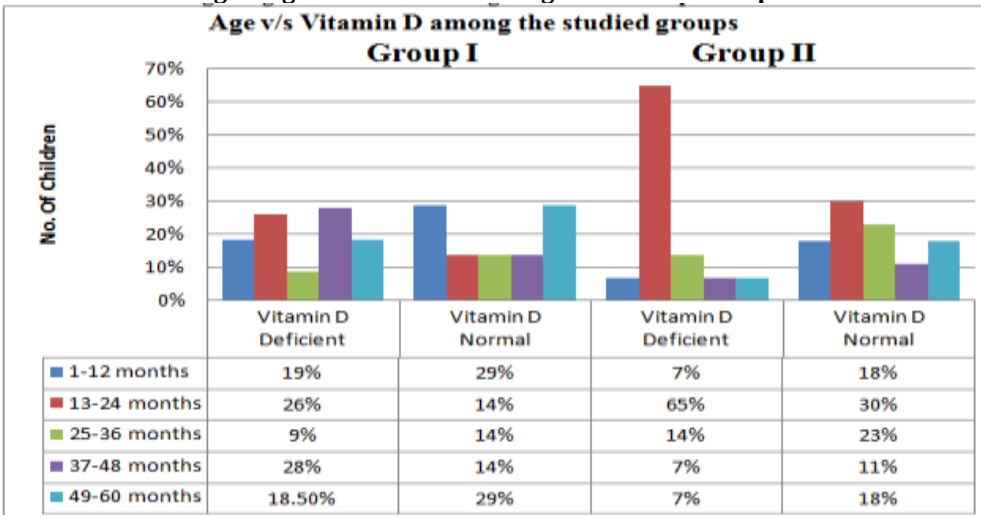


Table 6: Exclusive breast feeding v/s Vitamin D among the Studied Groups

Exclusive breast feeding for 6 months	**Group I (RRTI) (n=50)**			**Group II (No RRTI) (n=40)**		
	Vitamin D Deficient	**Vitamin D Normal**	**Total**	**Vitamin D Deficient**	**Vitamin D Normal**	**Total**
Given	20(47%)	4(57%)	24(48%)	1(7%)	21(81%)	22(52.5 %)
Not given	23(53%)	3(43%)	26(52%)	13(93%)	5(19%)	18(47.5 %)
Total	43(100%)	7(100%)	50(100%)	14(100%)	26(100%)	40(100%)
OR (95% CI)	0.65 (0.1-4.4)*			0.02 (0.0004-0.19)**		
P value	0.91*#			<0.001**#		

OR: odds ratio, CI: confidence interval, **: highly significant, *: not significant, #: Yates correction

In Group I(RRTI), Vitamin D was deficient in 53% of children who had not received exclusive breast feeding for 6 months whereas in Group II(no RRTI) 93% were Vitamin D deficient in non-exclusive breast feeding.

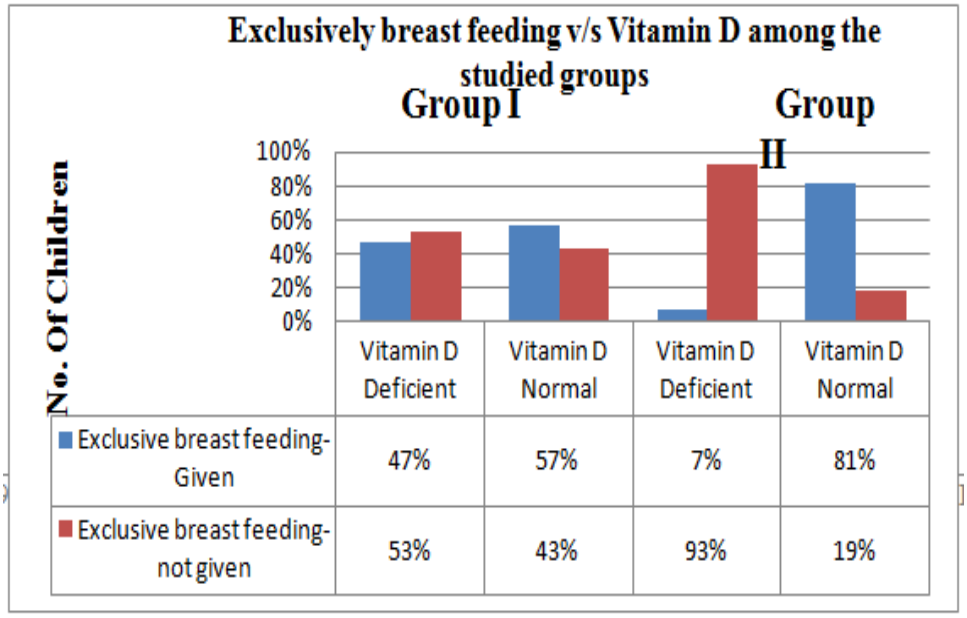


Fig: 6 Exclusive breast feeding v/s Vitamin D among the Studied Groups

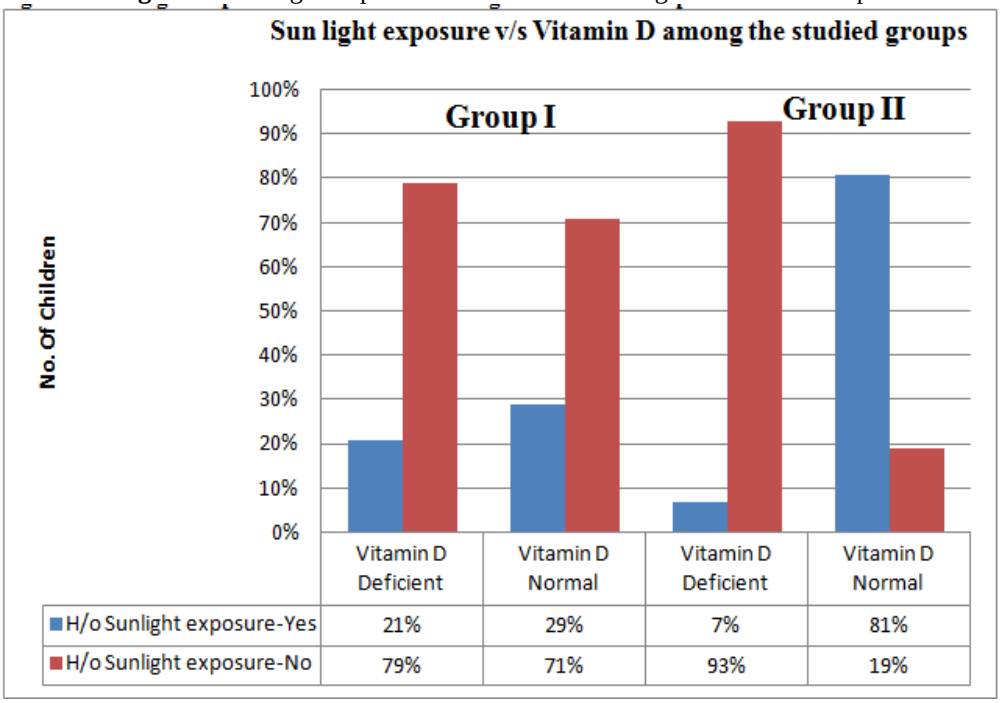
Table 7: H/o Sunlight Exposure v/s Vitamin D among the Studied Groups

H/o Sunlight exposure (between 10 am to 3 pm)	Group I (RRTI) (n=50)			Group II (No RRTI Group) (n=40)		
	Vitamin D Deficient	Vitamin D Normal	Total	Vitamin D Deficient	Vitamin D Normal	Total
Yes	9(21%)	2(29%)	11(22%)	1(7%)	21(81%)	22(55%)
No	34(79%)	5(71%)	39(78%)	13(93%)	5(19%)	18(45%)
Total	43(100%)	7(100%)	50(100%)	14(100%)	26(100%)	40(100%)
OR (95% CI)	0.66 (0.1-8.1)*			0.02 (0.0004-0.2)**		
P value	0.96*#			<0.001**#		

OR: odds ratio, CI: confidence interval, **: highly significant, *: not significant, #: Yates correction

79% of Group I (RRTI) and 93% of Group II(no RRTI) who were not exposed to sunlight had Vitamin D deficiency.

Fig: 7 H/o Sunlight Exposure v/s Vitamin D among the Studied Groups



VI. Discussion:

The association between Vitamin D levels and susceptibility to recurrent respiratory tract infections was studied in children between1 month to 5 years. Serum 25-hydroxy Vitamin D levels were measured in children with recurrent respiratory tract infections as well as in healthy, similar age group without history of respiratory tract infections.

In our study, there were non significant differences between Group I (RRTI) and Group II (no RRTI) regarding age, gender and site of residence to explain the low levels of Vitamin D in the group I(RRTI). Similarly studies done by Albanna *et.al* ,, by Wayse *et.al*[4] (P-value=0.09) showed no significant difference between cases and controls regarding socio demographic variables.

Table no 8: Percentage of Vitamin D deficiency in respiratory tract infections

Studies	n	GROUP I (RRTI)	GROUP II (no RRTI)	P-value
In our study	90	86%	35%	<0.001
Wayse *et.al*[43]	150	80%	31%	<0.001
Roth *et.al* 2010[24]	50	84%	60%	0.01
Albanna *et.al*[6]2010	80	77.5%	20%	<0.001
Karatekin 2009	40	92%	80%	0.01

The main finding of our study was that serum 25-hydroxy Vitamin D concentrations in the Group I(RRTI) was significantly lower than those in the Group II(no RRTI). In Group I (RRTI), 86% had Vitamin D deficiency where as in Group II (no RRTI) 35% which is comparable to Wayse *et.al* (80% and 31%), Roth et.al (84% and 60%), Albanna et.al (77.5% and 20%) and little higher percentage of deficiency was found in Karatekin i.e. 92% in group I and 80% in group II.

VII. Mean Vitamin D Levels

Table no 9: Mean Vitamin D levels in various studies in respiratory tract infections in nmol/l

Studies	n	GROUP I (RRTI) Mean	GROUP II (no RRTI) Mean	P- value
In our study	90	41.7	64.6	<0.001
Wayse et.al[43]	150	22.8	38.4	<0.001
Albanna et.al[6]2010	80	37.6	87.25	<0.001
Karatekin[59] 2009	40	22.8	40.8	0.011
Roth et.al 2010[24]	50	29.1	39.1	0.015

Mean value of Vitamin D was low 41.7 in Group I (RRTI) compared to 64.6 in Group II (no RRTI) which is comparable with Wayse *et.al*[43](22.8 and 38.4), Karatekin[59] (22.8 and 40.8), Albanna *et.al*[6] (37.6 and 87.25%),) and Roth *et.al*[24] (29.1 and 39.1). There is a significant correlation was found between Vitamin D deficiency and RRTI group (P-value= <0.001)

Exclusive Breast Feeding

Table no 11: Vitamin D deficiency with RRTI Vs Exclusive breast feeding

Study	n	Number of breast fed	% of Vitamin D deficiency in breast fed
In our Study	90	50	47%
Nighat haider *et.al*[55]	137	137	85.3%

Vitamin D deficiency was seen (47%) in exclusively breastfed infants for 6 months. No significant association was found between exclusive breast feeding and Vitamin D deficiency in recurrent respiratory tract infections (P-value = 0.91). However, in another study done by Nighat haider *et.al*[55], Vitamin D deficiency was more common in breast fed infants i.e. 85%

VIII. Sun Exposure

Table no 12: Vitamin D deficiency with RRTI Vs Sun exposure

Studies	n	Sun exposed	Not exposed to sun
In our study	90	21%	79%
Nighat haider *et.al*[55]	137	55.1%	98.3%

79% of Vitamin D deficiency was seen in children who were not exposed to sunlight and only in 21% cases Vitamin D was deficient even with adequate sun exposure (P-value=0.96) which is comparable to a study done by Nighat haider *et.al*[55], which showed Vitamin D deficiency is more common in children who were not exposed to sunlight(98.3%)

IX. Conclusions

1.This study showed that 86% of children with respiratory tract infections had vitamin D deficiency.
2.Vitamin D deficiency and no. of respiratory tract infections are more in male children than female children.
3.The mean vitamin D levels in group I(RRTI) was 41.7nmol/l compared to 64.6nmol/l in groupII (no RRTI).
4.Vitamin D deficiency and no. of respiratory tract infections are more in the 37-48 months age group followed by 13-24 months age group.
5.VitaminD levels were low in children who were exclusively breast fed for 6months(47%).
6.Vitamin D levels were low in children who had poor exposure to sunlight.(79%).
7.There was no significant association between vitaminD levels and age, sex ,distribution, exclusive breast fed infants and sun exposure in recurrent respiratory tract infections.

Recommendations

1. There is a need for prospective randomized trials in this field to establish cause effect relation between Vitamin D and RRTI.
2. Education regarding the importance and timing of sun exposure should be done (half an hour a day for 5-6 days /week between 10am to 3pm.).

3. As most of the children are deficient in serum VitaminD levels, routine VitaminD supplementation may be recommended**.**

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