

Association of Subclinical Vitamin D Deficiency with Severe Acute Lower Respiratory Tract Infections in Children

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Abstract: Background: Acute lower respiratory infection (ALRI), primarily pneumonia, is a common cause of morbidity and mortality in children younger than 5 y of age, particularly in developing countries. **Aim:** The aim of this study is to determine whether subclinical vitamin D deficiency in children from 2 months up to 5 years of age is a risk factor for severe acute lower respiratory tract infections (ALRTI). **Patient and methods:** This was a cross sectional descriptive study *was carried out on 100 children divided into two groups: Group 1(n=70):* patients with severe lower respiratory tract infections (**LRTIs**) mostly bronchopneumonia and acute bronchiolitis. **Group 2(n=30): control group** of apparently healthy children with matched age and sex with patient groups presenting by minimal/compliant in outpatient clinics. All cases were taken from out and inpatient pediatric department and intermediate care unit of Bab- ELshearia university hospital, AL-Azhar faculty of medicine after approval of pediatric department and university ethical committee, during the period from November 2015 to May 2016. **Results:** Serum vitamin D level was lower in patients (46.24 ± 25.84) than control (64.02 ± 23.79) with significant difference ($p=0.002$). **Conclusion:** Subclinical vitamin D deficiency in children younger than 5 years old has significant risk factors for severe ALRI in Egyptian children.

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1. Introduction

Acute Lower Respiratory Tract Infections (ALRTIs) in children less than five years old are the leading cause of childhood morbidity and mortality in the world and represent almost 60% of infant infectious disease hospitalizations. (Harris et al., 2011).

Vitamin D, an essential steroid hormone, is primarily synthesized in the skin and liver from sun exposure, but it can also be obtained through dietary intake or supplements (Holick, 2007). Vitamin D requires two consecutive hydroxylations at position C25 and C1 α to become fully active and exerts its effects through the vitamin D receptor (VDR), which is widely distributed (Cianferotti and Marcocci, 2012).

Vitamin D influences several immune pathways, with the net effect of boosting mucosal defences while simultaneously dampening excessive inflammation (Pfeffer and Hawrylowicz, 2012). Vitamin D facilitates direct anti-microbial effects of the innate immune system and attenuates an overwhelming inflammatory response by modulating the crosstalk between cells of the innate immune system and T cells (Jolliffe et al., 2013).

Vitamin D3 is a prohormone mostly derived from 7-dehydrocholesterol by ultraviolet irradiation of

the skin. Vitamin D is rarely found in food as vitamin D3 (from animal sources) or vitamin D2 (from vegetal sources) and therefore it cannot be defined merely as a nutrient (Cianferotti and Marcocci, 2012).

For this reason, no.

Therefore, definition of subclinical vitamin D deficiency or vitamin D insufficiency, based on serum 25(OH) D levels, may differ according to the target effect. As far as classical effects are concerned, there is no consensus on the minimum serum 25(OH) D concentration (50 or 75 nmol/L, i.e. 20 or 30 ng/ml), which would guarantee a normal mineral and bone homeostasis (Cianferotti and Marcocci, 2012).

2. Patients and Methods

Study design:

This study was a cross sectional descriptive study.

Study Setting:

All cases were taken from out and inpatient pediatric department and intermediate care unit of Bab- ELshearia university hospital, AL-Azhar faculty of medicine after approval of pediatric department and university ethical committee, during the period from November 2015 to May 2016.

Study population:

The study was carried out on 100 children divided into two groups:

Group 1 (n=70):

Patients with severe lower respiratory tract infections (**LRTIs**) mostly bronchopneumonia and acute bronchiolitis.

Group 2 (n=30):

Control group of apparently healthy children with matched age and sex with patient groups presenting by minimal complaint in outpatient clinics.

The selection of patients was based on criteria of inclusion and exclusion.

Inclusion criteria:

- Patients age between 2months-5 years.
- Children with severe acute lower respiratory tract infection. (The **WHO** criteria for non-severe pneumonia included: a history of cough and/or difficult breathing of less than 3 weeks duration, with (a) increased respiratory rate (Rate \geq 60/min if age <2 months, \geq 50/ min if age 2–12 months and \geq 40/ min if age 12–60 months); (b) lower chest wall in drawing (severe pneumonia); or (c) cyanosis and/or inability to feed or drink (very severe pneumonia). (*Scott et al., 2012*).

Exclusion criteria:

- Rachitic children.

Methods:

All cases and control groups were subjected to the following:

3. Results

Table (1): Demographic characteristics of the studied groups.

	Groups		Tests	
	Cases	Control	X ² /t	P-value
Sex				
Female	27(38.6%)	15(50.0%)	1.126	0.289
Male	43(61.4%)	15(50.0%)		
Age				
Range	2-60	2-57	0.576	0.566
Mean±SD	12.06±8.24	13.13±9.15		
Weight(kg)				
Range	3-16	4-14	3.03	0.016*
Mean±SD	7.12±2.71	8.62±3.03		
Height/length cm				
Range	50-100	40-90	0.877	0.382
Mean±SD	67.80±9.99	69.77±10.98		
Head circumference(cm)				
Range	34-50	38-49	2.312	0.023*
Mean±SD	41.78±3.14	43.37±3.18		

P > 0.05: Non significant (NS) P < 0.05: Significant (S) P < 0.01: Highly significant (HS)

This table shows statistical significant difference between both groups as regard to weight, head circumference and no statistical significant difference regarding to sex, age and height/length.

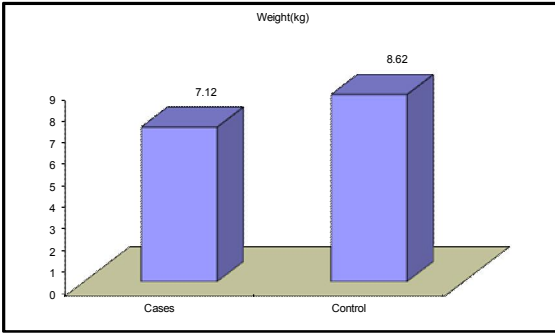


Figure (1): Mean of weight (kg) in control and patient groups.

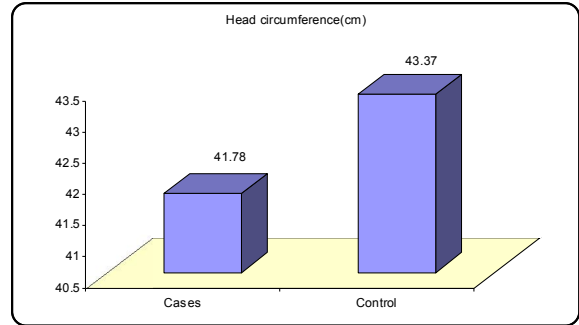


Figure (2): Mean of head circumference (cm) in control and patient groups.

Table (1): Comparison between control and patient groups regarding vital signs.

Groups						T-test	
	Range	Mean	±	SD	t	P-value	
Heart rate (beat / minute)							
Cases	68 - 170	147.53	±	15.06	9.434	<0.001*	
Control	110 - 130	120.67	±	5.95			
Respiratory rate (cycle / minute)							
Cases	43 - 95	58.76	±	7.98	16.484	<0.001*	
Control	23 - 45	32.20	±	5.72			
Temperature (° C)							
Cases	37.4 - 39.5	38.275	±	0.12	0.769	0.444	
Control	36.6 - 37.8	37.08	±	0.25			

Table shows high statistical significant difference between the two groups as regard heart rate (beat / minute) and respiratory rate (cycle / minute). While there was no statistical significant difference in temperature (° C) between the two groups.

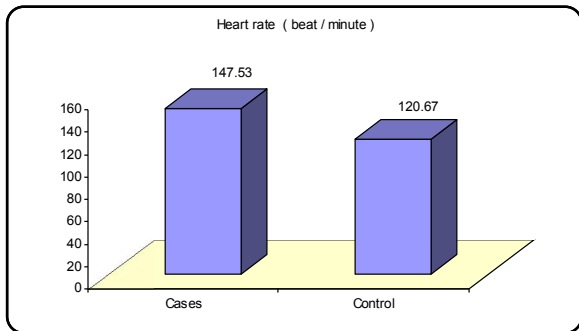


Figure (3): Mean of heart rate (beat / minute) in control and patient groups.

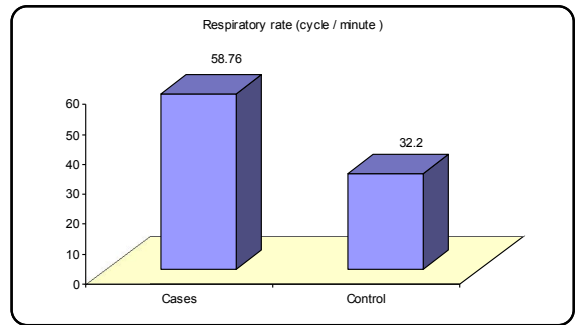


Figure (4): Mean of respiratory rate (cycle / minute) in control and patient groups.

Table (3): Comparison of mean ± SD serum level (ng/ml) of 25-OH VitaminD in patient and patientgroups.

Groups	Vitamin D level					T-test	
	Range	Mean	±	SD	t	P-value	
Cases	4.4 - 123	46.24	±	25.84	3.227	0.002*	
Control	10.3 - 98.8	64.02	±	23.79			

This table shows statistical significant difference between the two groups as regard serum level (ng/ml) 25-OH Vitamin D.

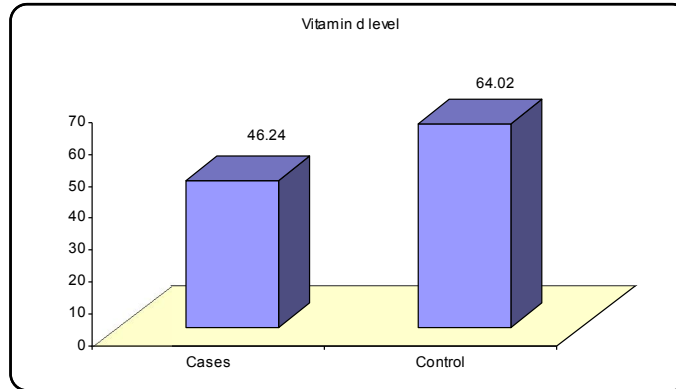


Figure (5): Mean serum level (ng/ml) of 25-OH Vitamin D in control and patient groups.

Table (4): Comparison between number and percentage of exposure to sun in patient group regarding clinical symptoms.

	Exposure to sun				Chi-square	
	No		Yes		X ²	P-value
	N	%	N	%		
Runny nose	3	100.0	0	0.0	0.462	0.496
Fever	23	100.0	0	0.0	5.054	0.025*
Cough	32	100.0	0	0.0	8.697	0.003*
Difficult of breathing	61	87.1	9	12.9		

Table shows statistical significant difference in patient groups as regard cough and fever. While there was no statistical significant as regard runny nose.

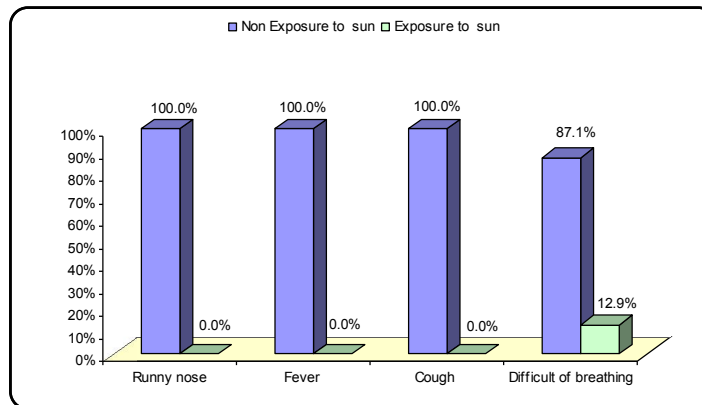


Figure (6): Percentage of exposure to sun in patient group regarding clinical symptoms.

Table (5): Comparison between number and percentage of Vitamin D serum levels (ng/ml) in patient groups as regard picture of complaint.

	Vitamin D level (ng/ml)						Chi-square	
	Severe deficiency (<10 ng/ml)		Insufficiency (10-30 ng/ml (Adequacy (>30 ng/ml)		X ²	P-value
	N	%	N	%	N	%		
Runny nose	0	0.0	0	0.0	3	100.0	1.343	0.511
Fever	6	26.1	4	17.4	13	56.5	13.410	<0.001*
Cough	6	18.8	12	37.5	14	43.8	20.033	<0.001*
Difficult of breathing	6	8.6	15	21.4	49	70.0		

This table shows high statistical significant difference in patient groups as regard cough and fever in relation to serum 25-OH Vitamin D level. While there was no statistical significant difference as regard runny nose with serum 25-OH Vitamin D level (ng/ml).

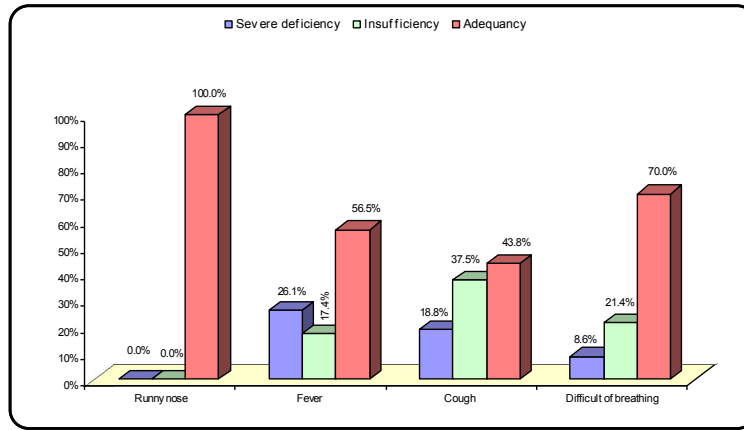


Figure (7): Percentage of picture of complaint with serum Vitamin D level (ng/ml) in patient group.

Table (6): Comparison between number and percentage of serum level Vitamin D (ng/ml) in both patient and control groups.

Vitamin D level	Groups					
	Cases		Control		Total	
	N	%	N	%	N	%
<10 (Severe deficiency)	10	14.3%	0	0.0%	6	6.0
10-30 (Insufficiency)	26	37.1%	9	30.0%	18	18.0
>30 (Adequacy)	34	48.6%	21	70.0%	76	76.0
Total	70	100.0	30	100.0	100	100.0
Chi-square	X ²		6.345			
	P-value		0.042*			

This table shows statistical significant difference of number and percentage of Vitamin D level in both patient and control groups, where increased number of patients with severe deficient and insufficient level of Vitamin D and increased number of control with adequate level of Vitamin D.

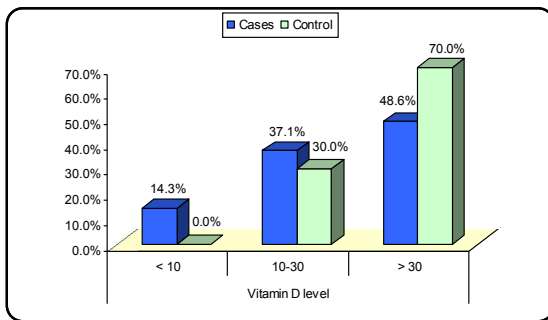


Figure (8): Comparison of number and percentage of serum levels (ng/ml) Vitamin D level in both patient and control groups.

4. Discussion:

This study was designed to evaluate 25 hydroxy vitamin D serum level and its relation to ALRT infection in children.

Our study was conducted on 100 patients: 70 children with severe ALRTI as patient group and 30 children with minimal complaint as control group.

Male patients was more than females without reaching significance. *Falagas et al., 2007* also report that RTI is common in male children. Sex difference in incidence and severity may be due to alteration of immune system caused by sex hormones (*Falagas et al., 2007*). These findings also may be explained by genetic factors, anatomic, lifestyle, behavioral, and socioeconomic differences between males and females *Ellis (1988)*.

Mean age of patient is (12.06±8.24) months which is in agreement with *Ujunwa and Ezeonu 2014*.

Weight is one of the anthropometric measures that reflecting good general condition. We report significant difference (p= 0.016) between patients (7.12±2.71) and control (8.62±3.03), where children who suffer from malnutrition were more susceptible to

severe lower respiratory tract infection which was in agreement with *Smith et al., 1991*.

Both heart rate and respiratory rate was significantly higher in patients than control ($p < 0.001$) in both while temperature was higher in patients. The heart rate and respiratory rate are an important indicator for inflammatory response at the time of infection which was in agreement with *Thompson et al., 2009* who found statistical significance as regarding all abovementioned vital signs suggesting that vital signs can be used to differentiate children with serious infections from those with less serious infections.

Different types of feeding among both patients and control either exclusive breast feeding, artificial feeding or combined showed no significant difference ($p=0.826, 0.359, 0.656$) respectively with relatively higher percent of control than patients in both Exc. breast feeding and combined group (*44.3% patients - 46.7% control and 38.6% patients - 43.3% control*) respectively, where breast feeding is one of the most important elements of good health.

Breast feeding either exclusive or combined associated with relative higher level of vitamin D than artificial feeding in both patients and control

These results are contrary with *Wayse et al., 2004* finding who report significant difference between ALRTI Indian patients with Exc. breast feeding and control. Lower number of control in our study may be the cause of non-significance.

Sun exposure was common in control than cases (9 cases and 19 control) with significant difference ($p < 0.001$) which is in agreement with *Wayse et al., 2004* who reported significant difference ($p = 0.006$) between severe ALRTI patient and control.

Inappropriate level of vitamin D in patients with limited sun exposure may be due to cultural practice, prolonged breast feeding without vitamin D supplementation, limited outdoor activity, a lack of government regulation for increased burden of infectious diseases (*Fuleihen, 2009*).

Also sun exposure has significant reduction of ALRTI symptoms specially cough and fever which confirm findings of *Wayse et al., 2004* as regarding protective effect of sun exposure by increasing serum of vitamin D.

In our study serum vitamin D associated with severe ALRI ($p = 0.002$), due to the immunological and the anti-infective role of Vitamin D against severe ALRI which is in agreement with *Wayse et al., 2004* who found similar association ($p < 0.001$) indicating that vitamin D is one of the protective factors against severe ALRI and *Belderbos et al., (2011)* who found that low levels of 25(OH) D is relative risk of respiratory infection. Also *Muhe et al., 1997*

conclusion support a role of vitamin D in protection against infectious diseases.

Symptoms of ALRTI showed significant reduction with higher vitamin D level specially cough and fever as shown in (table 18) where the patient who had severe deficiency < 10 ng/ml presented by all severe symptoms and less severity of symptoms increase when the serum vitamin D became insufficiency or adequacy so these results confirming findings of protective effect of Vitamin D.

Conclusion

Children with ALRTI had significantly lower serum levels of vitamin D ($P=0.002$). Growth parameters were significantly affected in children with respiratory tract infections (low weight and head circumference).

ALRTI was predominantly presented in male without reaching significance. Heart rate and respiratory rate on of the most important signs in diagnosis of ALRTI.

Breast feeding either exclusive or combined showed protective effect in comparison to artificial feeding.

Exposure to sun is one of the sources of vitamin D and help in protection against ALRTI.

Vitamin D level showed protective effect against symptoms of ALRTI specially cough and fever.

Recommendation

- Encouragement of sunlight exposure of young children is one of the protective methods through increasing serum level of vitamin D.
- Vitamin D-rich supplements may be beneficial in decreasing burden of respiratory tract infection.
- Reinforcement of breastfeeding in the population to maximize child protection against respiratory tract infection.

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