Original article

Vitamin D supplementation and the risk of infections in fullterm infants: Correlations with the maternal serum vitamin D

Background: *Recently, epidemiologic and genetic studies suggest a vital and complex role of vitamin D on immune system function and regulation. Vitamin D insufficiency has been linked with susceptibility to infection and autoimmune diseases. The relationship between vitamin D deficiency and risk of infections in early life is still under investigations . **Objective:** To examine the effect of vitamin D supplementation in the first 6-months of life on the immunity and risk of infections during the first year in infants . **Methods:** A prospective controlled study included 99 full term infants divided into two groups: group I included 48 infants supplemented with daily 400 I.U vitamin D for 6-months and group II included 51 infants not supplemented with vitamin D. Investigations needed for diagnosis of respiratory, gastrointestinal tract, and urinary tract infections were addressed every visit until the infants' first birth day. Two mls of maternal blood were withdrawn for 25-hydroxy vitamin D assessment using radioimmunoassay . **Results:** The incidence of infections totally were less common in infants supplemented with daily vitamin D than those not supplemented (p value = 0.01). There were significant negative correlations between the incidence of respiratory and gastrointestinal infections and maternal vitamin D levels (p value = 0.001, r= -0.65, versus p value = 0.001, r= -0.61 respectively).There were significant negative correlations between the incidence of both respiratory and gastrointestinal infections and gestational ages, weights of infants, normal vaginal delivery, or rural residence. There were significant positive correlations between the incidence of both respiratory and gastrointestinal infections and maternal age, multigravida, neonatal dark skin and paternal smoking . **Conclusions:** The findings support the importance of vitamin D supplementation for the first 6-months of life as well as maintaining normal maternal serum vitamin D levels during pregnancy for its importance for the skeletal system and innate immunity in infants.*

Keywords: Vitamin D, Respiratory, GIT, Urinary tract, infections, Immunity

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INTRODUCTION

The role of vitamin D in the regulation of calcium and bone metabolism is well established. Recently, more physiologic functions for vitamin D have been reported. Epidemiologic and genetic studies as well as research using animal models suggest a vital and complex role of vitamin D in immune system function and regulation.[1,2] Vitamin D exerts many of its effects through contact with vitamin D receptors, which have been found in a variety of cells, including lung cells and many cells of the immune system.[3] The finding that most tissues and cells in the body have vitamin D receptors and that many of them possess the enzymatic apparatus to synthesize the active form 1,25-dihydroxyvitamin D from the primary vitamin D, 25-hydroxyvitamin D, has provided new insight into the role of this vitamin deficiency in pathogenesis of several diseases. Vitamin D insufficiency has been linked with susceptibility to infection, particularly respiratory infections,[4] asthma,[5] autoimmune diseases[6] and the development of a variety of cancers.[7] Human milk reflects the vitamin D status of the mother and often contains inadequate levels of 25-hydroxyvitamin D for infant nutrition. In 2008, the American Academy of Pediatrics (AAP) recommended 400 IU of vitamin D supplementation of all infants.[8] The relationship between vitamin D deficiency and the risk of childhood infections is still under investigations particularly during the first year of life.

The study examines the effect of vitamin D supplementation in the first 6-months of life on the rate of infections during the first year of life especially respiratory, GIT and urinary tract infections in full term infants. The relationship between the incidence of these infections and the maternal serum vitamin D levels at birth were meant to be evaluated.

METHODS

This study included 99 full term infants attending the neonatal outpatient clinic, pediatric department, Minia University Hospital during the period from January 2010 to February 2012. They were divided into two groups: group I included 48 full term infants supplemented with daily 400 I.U vitamin D for the first 6-months of life after birth and group II included 51 full term infants not supplemented with vitamin D. History taking, clinical examination and other investigations needed for diagnosis of respiratory tract infections (otitis media, pharyngitis, tonsillitis/laryngitis, bronchitis, bronchiolitis and pneumonia), GIT infections (gastro-enteritis) and urinary tract infections (lower and upper UTI) were addressed every visit (monthly or earlier if needed) until the first birth day for this infant. Only 99 out of 114 infants completed the study after one year and 15 infants dropped from the study due to either irregular visits to our clinic, refusal of their parents or care takers to follow up, incubation during the first month due to any cause or missed cases.

Inclusion criteria: All infants were full term infants (37-42 weeks), exclusively breast fed for the first 6-months, of non-complicated pregnancy, regularly visiting the neonatal follow-up clinic.

Exclusion criteria: pre-term infants <37 weeks, infants of complicated pregnancies like DM or pre-eclampsia, infants of mothers receiving medications for any cause, infants of asthmatic (or atopic) mothers or fathers, infants with known history of hereditary or familial immune deficiency disorders and infants receiving artificial milk either supplementary or alternatively to breast milk and infants incubated for any cause .

Methodology: All infants were exposed every visit to careful history taking (fever, cough, cold, ear discharge, respiratory distress, refusing feeding, vomiting, diarrhea, abdominal distention, burning micturition, dysuria, change color of urine, and oliguria). Thorough clinical examination (vital signs, anthropometric measures, lymphadenopathy, skin rash, edema, skin infections, complete chest examination including air entry, abnormal additional sounds like crepitations and wheezes and local abdominal examination including organomegaly, abnormal abdominal masses, and ascites) was done for all enrolled infants.

For the laboratory investigations 2 mls of venous blood were withdrawn under complete aseptic conditions for sepsis screen including complete blood count, CRP estimation, and blood culture. Urine, stool or CSF cultures as well as, liver and renal function tests were performed when needed. X-ray chest, abdominal ultrasonography and chest, abdomen or brain CT if needed according to the case possible diagnosis.[9] Two mls of maternal blood were withdrawn for 25-hydroxy vitamin D assessment using radioimmunoassay method.[10,11] The samples withdrawn within 24-hours after birth before discharge from the hospital. Vitamin D level values were used as a continuous variable and were categorized in descriptive analyses as desirable (or sufficient) when scores were at least 75 to 100 nmol/l, insufficient between 50 and 75 nmol/l and deficient when < 50 nmol/l, as previously reported.[12] Informed consent was obtained for their participation, including blood collection and longitudinal follow-up of their offspring. The study protocol was approved by the faculty of medicine, Minia University .

Statistical Analysis:

Values are presented as mean ± SD, range, or as the number of subjects and proportions. The Student t test was used for group comparisons of normally distributed variables, and the Mann-Whitney U test and Wilcoxon signed-rank test were used for comparisons of variables with skewed distribution. The chi square test was used to compare proportions. Correlation coefficients were used to describe associations between variables, and multiple regression analysis was used to detect any relationships between the variables. The following variables were considered in multivariate models of the relationship between the incidence of infections and gestation age, birth weight, gender, maternal or paternal smoking during pregnancy, maternal skin, residence, mood of delivery and maternal age. P <0.05 was considered significant. Analyses were performed using the SPSS software package (SPSS V 8.0 for Windows).

RESULTS

Analysis of demographic characteristics of the studied groups revealed that there were nonsignificant differences between patients and controls as regard age, sex, weight and residence (table 1). Table 2 shows the clinical and radiological presentations of the patient group.

Cough and rhonchi were the most presenting symptoms and signs respectively. Table 3 shows the laboratory data of studied groups. No statistical significance was obtained between the two groups as regard white blood cell count, hemoglobin level and platelet count.

Our study showed a highly significant decrease in 25OHD, LL-37 and a highly significant increase in Hs-CRP in children with asthma than in control group (table 4). The lowest levels of 25OHD, LL-37 and highest level of Hs-CRP were found in patients with moderate persistent and severe persistent asthma (table 5). There was a highly significant positive correlation between 25OHD and LL37 in patients, control groups and a significant negative correlation between both 25OHD and LL37 and Hs-CRP in patients group (table 6). High WBC count (specially neutrophils and lymphocytes) and Hs-CRP level and low levels of hemoglobin, 25OHD, LL 37 in patients' group were considered risk factors of asthma (table 7).

Table 1. Demographic and laboratory data of studied groups

Parameter		**group I (n=48)**	**group II (n=51)**	**P-value**
Gestational age (weeks)	**Range** **Mean ± SD**	37.0- 42.0 39.1±2.5	37.0-42.0 39.9±2.4	0.31
Gender	**Males** **Females**	24(50%) 24(50%)	30(58.8%) 21(41.2%)	0.4
Weight (kg)	**Range** **Mean ± SD**	2.9-4.2 3.5±0.4	2.8-4.1 3.4±0.4	0.1
Mode of delivery	**NVD** **CS**	19(39.6%) 29(60.4%)	23(45.1%) 28(54.9%)	0.6
Maternal age (years)	**Range** **Mean ± SD**	18-39 26.1±6.9	18-39 25.8±6.6	0.8
Gravity	**Primigravida** **Multigravida**	5(10.4%) 43(89.6%)	7(13.7%) 44(86.3%)	0.7
Maternal skin	**Dark-skinned** **Light-skinned**	19(39.6%) 29(60.4%)	23(45.1%) 28(54.9%)	0.6
Maternal residence	**Rural** **Urban**	24(50%) 24(50%)	21(41.2%) 30(58.8%)	0.5
Smoking (maternal or paternal)	**Yes** **No**	21(43.8%) 27(56.2%)	23(45.1%) 28(54.9%)	0.7
Hb (gm/dl)	**Range** **Mean ± SD**	12-17 14.2±1.6	11-17 13.9±1.6	0.3
Platelets ($\times 10^3/\mu l$)	**Range** **Mean ± SD**	40-520 313.2±128.1	120-520 296.1±120.4	0.4
WBCs ($\times 10^3/\mu l$)	**Range** **Mean ± SD**	3.5-17 11.5±4.2	3-17 11.1±4.2	0.6
Maternal vitamin D (nmol/l)	**Range** **Mean ± SD**	16-102 50.4±21.1	16-104 48.5±21.9	0.3

**Significant, ** highly significant, BMI= body mass index*

Table 2. Comparison between the number of respiratory, GIT and urinary tract infections in the studied groups

Parameter		group I (n=48)	group II (n=51)	P-value
Total respiratory tract infections	Range Mean ± SD	0-11 3.7±2.7	0-11 5.9±2.9	0.001**
Otitis media	Range Mean ± SD	0-3 0.9±0.8	0-3 1.5±1.04	0.003**
Pharyngitis/tonsillitis	Range Mean ± SD	0-3 1.3±0.9	0-3 1.4±0.9	0.06
Bronchitis	Range Mean ± SD	0-2 0.6±0.7	0-2 0.8±0.7	0.06
Bronchiolitis	Range Mean ± SD	0-2 0.6±0.7	0-3 1.4±0.9	0.001**
Pneumonia	Range Mean ± SD	0-1 0.1±0.3	0-1 0.5±0.4	0.001**
GIT infections	Range Mean ± SD	0-3 0.7±0.9	0-3 1.1±0.8	0.01*
Total urinary tract infections (UTI)	Range Mean ± SD	0-4 1.5±1.5	0-4 1.8±1.4	0.3
Upper UTI	Range Mean ± SD	0-2 0.6±0.6	0-2 0.7±0.5	*0.5*
Lower UTI	Range Mean ± SD	0-3 0.9±0.8	0-3 1.1±1.06	0.2
Other infections#	Range Mean ± SD	0-3 1.5±1.5	0-4 1.8±1.4	0.3

**Significant, ** highly significant*

 # Other infections= fever with rash, CNS, skeletal and soft tissue, sepsis, typhoid or other not common infections

Table 3. Correlations between the frequency of respiratory, GIT, and urinary tract infections and other studied parameters

Parameters	Respiratory infections		GIT infections		UTI infections	
	P	R	P	R	P	r
Gestational age (weeks)	0.001**	-0.70	0.01*	-0.85	0.09	-0.26
Male gender	0.11	0.31	0.21	0.25	0.9	0.26
Wt (Kg)	0.01*	-0.62	0.01*	-0.65	0.04*	-0.26
NVD	0.001**	-0.35	0.001**	-0.32	0.001**	-0.34
Maternal age (years)	0.01*	0.46	0.01**	0.52	0.01*	0.24
Multigravida	0.02*	0.23	0.03*	0.43	0.1	0.2
Mat. Dark skin	0.01*	0.55	0.01*	0.36	0.1	0.1
Mat Rural residence	0.01*	-0.53	0.01*	-0.30	0.2	-0.34
Mat. smoking	0.001**	-0.70	0.01*	-0.85	0.009**	-0.26
Hb (gm/dl)	0.9	0.27	0.9	-0.45	0.08	-0.26
Platelets *(×10³/µl)*	0.6	0.17	0.8	-0.32	0.06	-0.16
WBCs *(×10³/µl)*	0.01*	-0.51	0.01*	-0.24	0.09	0.26
Maternal vitamin D (nmol/l)	0.001^{**}	-0.65	0.001^{**}	-0.61	0.06	-0.29

**Significant, ** highly significant, BMI= body mass index,* NVD= normal vaginal delivery

Table 4. Correlations between the frequency of respiratory, GIT, and urinary tract infections and maternal vitamin D level in the studied groups

Variables	Group I (no.=48)		Group II (no.=51)		Total (no.=99)	
	r	(p)	r	(p)	r	(p)
Respiratory infection	-0.62	0.001^{**}	-0.72	0.001^{**}	-0.65	0.001^{**}
Gastroenteritis	-0.62	0.001^{**}	-0.59	0.002^{**}	-0.61	0.001^{**}
UTI	-0.20	0.1	-0.37	0.07	-0.29	0.06

**Significant, ** highly significant*

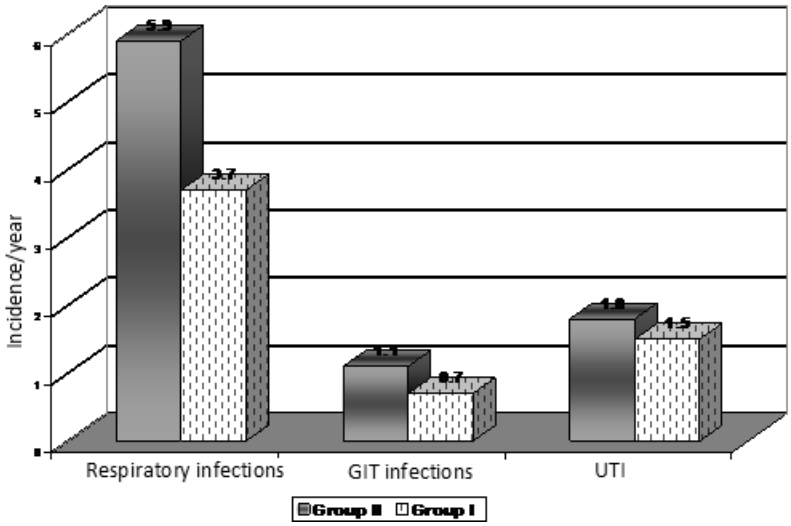

Figure 1. Comparison between the incidence of respiratory, gastrointestinal (GIT) and urinary tract infections (UTI) in studied groups.

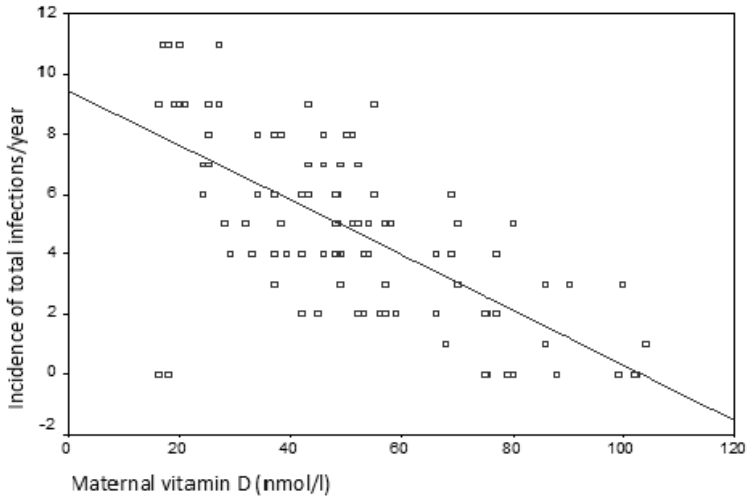

Figure 2. Correlation between the maternal vitamin D levels and the incidence of total infections in the studied groups.

DISCUSSION

In this study, the incidence of infections totally as well as the number of patients suffering from recurrent attacks of infections were significantly lower in infants supplemented with daily 400 IU vitamin D for 6-months after birth than those not supplemented (p-value=0.001). These results reflect the role of vitamin D in immunity as reported by other studies.[13, 14]

Respiratory tract infections especially otitis media, bronchiolitis and pneumonia were less common in infants supplemented with vitamin D and this is in agreement with other studies on vitamin D deficiency that revealed increased incidence of upper[15] and lower[16] respiratory tract infections. Airway epithelial cells have been found to express high levels of 1α-hydroxylase, converting 25-hydroxyvitamin D to its active form, leading to the increased production of both cathelicidin and the Toll-like receptor coreceptor CD14, important in the recognition of Gram-positive and -negative bacteria.[1-3] It enhances the differentiation and recruitment of macrophages, which may lead to an increased ability to fight infection.

Devereux et al, 2007[17] reported that vitamin D deficiency increased the risk of wheezy chest during the first year of life and they attributed this to the immuneregulatory effect of vitamin D in preventing respiratory tract infections that lead to wheezy chest. Many studies reported that vitamin D deficiency is more common in asthmatic children[18,19] which may be due to two mechanisms;

the immune prophylactic effect of vitamin D against respiratory infections which may be triggering factors for precipitation of asthma and to the direct immune regulatory effect of vitamin D that control asthma.

In the current study, the incidence of gastro-enteritis was more common in infants not supplemented with vitamin D which reflects the immune prophylactic effect against GIT infections. This immune prophylactic function of vitamin D may be due to its effect on T-helper cells. Vitamin D acts on dendritic cells, which play a central role in the activation of T-cell-mediated immune responses. As a result, a tolerogenic phenotype is induced with decreased expression of MHC class II and costimulatory ligands, decreased secretion of the immunostimulatory cytokine IL-12 and increased IL-10, an anti-inflammatory cytokine with potent inhibitory effects on Th1 and Th2 responses.[20] Also, vitamin D inhibits IFN-γ synthesis. It also increases serum levels of TGF-β1, a complex cytokine with a role in the peripheral induction of Foxp3+ Treg immunosuppression and in wound healing and repair.[21, 22]

There were no significant differences concerning urinary tract infections (upper and lower) between the two groups (p value = 0.3). This may be attributed to two reasons; the small number of subjects suffering from UTIs in this study and the mechanisms of urinary tract infection which depend mainly on ascending infections or weakness in the local defense mechanisms of the urinary tract.

In our series, there was a significant negative correlation between the incidence of total infections and the maternal serum vitamin D in both groups and this reflects the effect of maternal vitamin D on the immune functions of infants during the first year of life. These results were in agreement with the study of Haggerty,[23] who reported that there were positive correlations between the maternal serum levels of vitamin D during the last trimester and with the neonatal levels of vitamin D as well as the incidence of infections in the neonatal period.

In the current study, the incidence of respiratory and GIT infections were negatively correlated with gestational age and weight of infants. This may be due to the immaturity of the immune system in these infants.[24]

The incidence of infections especially in the respiratory tract were more common in infants living in urban areas and infants with dark skin; factors that increase the incidence of vitamin D deficiency due to less sun exposure.[25] Exposure to smoking either maternal or paternal increased the risk of respiratory, GIT and urinary infections in both groups. This is in agreement with many studies that reported the passive effect of smoking on the immune functions of the mother herself and her offspring.[26]

In the current study, 57% of enrolled mothers were vitamin D deficient with vitamin D serum levels less than 50 nmol/l, while 32 % of levels were insufficient (50 and 75 nmol/l). In spite of living in a sunny country; a problem that needs to be studied and solved with maternal vitamin D supplementation during pregnancy. The results were comparable with other reports[27]. This high frequency of women suffering from vitamin D deficiency may be due to increased time spent indoors, skin coverage with clothing, greenhouse effect and bad dietetic habits decreasing vitamin D absorption.[28]

No correlations were found between the maternal vitamin D levels and maternal gravity, maternal age, infant gender or any of the hematological data of infants of both groups.

Our study has several limitations: First, the sample size is limited which does not allow for solid conclusions. We did not collect data on maternal intake of vitamin D nor do we have data on maternal serum 25(OH)D concentrations all through the pregnancy course. Both of which would have given a more complete estimate of prenatal vitamin D status. Also, we had no enough data about the causative organisms either viral or bacterial of respiratory, GIT or urinary tract infections as we mainly depended on the clinical diagnoses. We also did not analyze the culture results and did not perform any cultures for viral diseases. Lastly the neonatal levels of vitamin D were not measured (for financial reasons) and this would have been more helpful for direct correlations to other studied parameters.

In conclusion, vitamin D supplementation (400 IU daily) for 6-months after birth is associated with lower frequency of both respiratory and GIT infections, but had no effect on the incidence of urinary tract infections during the first year of life. There were significant negative correlations between the maternal vitamin D levels and the incidence of infections during the first year of life. The findings support the importance of vitamin D supplementation during the first 6-months of life in full term infants who are exclusively breast fed as well as maintaining normal maternal serum vitamin D levels during pregnancy, not only for its importance for the skeletal system but also for potential immune functions.

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