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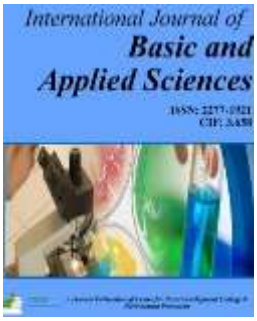

Full Length Research Paper

Association between Vitamin D and Urinary Tract Infection in the Primary School Egyptian Children: A Case-Control Study

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ABSTRACT

Background: *Urinary tract infection (UTI) is common in children with significant complications. The understanding of pathophysiological mechanisms and preventive measure are crucial. Vitamin D expected to play a significant role in UTI. However, results are not conclusive.* ***The aim of the work:*** *This study aimed to investigate the relationship between serum vitamin D levels and UTI in the primary school age children.* ***Patients and Methods:*** *A total of 49 of primary school children with UTI (study group) and another 49 age and sex matched healthy children were included as a control group. All were evaluated by history taking, clinical examination and laboratory investigations. Urine analysis, culture and sensitivity were performed. The vitamin-D was considered normal if it is ≥ 30ng/ml, insufficient if more than 20 and less than 30ng/ml and deficient if levels < 20ng/ml.* ***Results:*** *Patients and controls were comparable regarding child's age, gender and weight for age. However, children with UTI had significantly higher C-reactive protein (CRP), white blood cells count, and erythrocyte sedimentation rate, and a significant reduction of serum vitamin D (19.02 ± 8.51 vs 30.12 ± 9.09 ng/dl, respectively). In addition, there was significant reduction of the number of children with sufficient vitamin-D in the study than the control group (34.7% vs 67.3% respectively). Insufficient vitamin D concentrations were significantly associated with higher levels of CRP, WBCs and lower platelets. Furthermore, there was significant positive correlation between vitamin D levels and RBCs. In addition, there was negative correlation between vitamin D levels and each of WBCs and CRP.* ***Conclusion:*** *Low values of vitamin D levels are associated with UTI in primary school children. Vitamin D supplementation is advocated for vulnerable groups.*

Introduction

Urinary tract infection (UTI) is commonest in children [(1)]. Infection is usually due to *Escherichia coli* (about 80–90% of cases). The predominance of *E. Coli* is attributed to its ability to invade the endothelium of the urinary tract [(2)]. Risk factors for increased UTI include, but not limited to, genetic factors, chronic constipation, type-1 diabetes mellitus, and immune deficiency [(3)].

Vitamin D is one of the pleiotropic hormones that plays a significant role in general and bone health, calcium homeostasis, and the integrity of the immune and cardiovascular system [(4-6)]. In previous decades, there was a considerable attention to the potential effects of vitamin D on the health. Vitamin D and its receptor (Vitamin D receptor; VDR) activity and expression play an important role in protection against infections through immune-mediated responses [(7,8)]. Vitamin D usually produced in the skin through exposure to sunlight (ultraviolet radiation), which stimulates expression of antibacterial peptides (e.g., β-defensin and cathelicidin) from macrophages and monocytes [(9)]. Thus, it is expected that, vitamin D deficiency could play a role in the susceptibility for infection and there is growing evidence to support this role [(10,11)]. For example, reduced vitamin D was reported in children with pneumonia, tonsillitis and sepsis [(12-14)].

In urinary tract infection, there is a contradictory result about the association of vitamin with UTI. Some (e.g., Georgieva *et al.* [(15)]) have showed that serum vitamin D levels were reduced in cases with UTI than healthy children. Others (e.g., Mahyar *et al.* [(16)]) reported that, higher vitamin D levels are associated with higher risk of UTI.

The aim of the work

This study was conducted to investigate the potential relationship between serum vitamin D levels and urinary tract infection in the primary school age children.

Patients and methods

This was a prospective case-control study. It was conducted in the Department of Pediatrics, Al-Azhar Faculty of Medicine (Damietta), between June 2018 and June 2020. A total of 49 of primary school children who had a UTI with no risk factors for it were included. Another 49 age and sex matched healthy children were included as a control group. The inclusion criteria for study group were the presence of clinical signs indicating UTI (e.g., fever, abdominal pain, dysuria, etc..), pyuria, confirmed diagnosis by positive urinary culture, no vitamin supplementation during the last year, no associated malnutrition or obesity, and no other renal disorders. On the other side, child with concomitant disease (e.g., septicemia, diabetes mellitus or any immune deficiency, or who had rickets were excluded). In addition, children with any congenital anomalies of the urinary tract, neurogenic bladder or chronic renal failure were also excluded. For control group, any child with acute or chronic systemic disease, who had vitamin D supplementation during last year, with nutrition disorder such as obesity or growth retardation were excluded. These strict exclusion criteria were set to remove all confounding factors which could affect the vitamin D levels.

Urine sample for analysis were obtained by the midstream clean catch method. Then, samples were inoculated on blood agar and MacConkey agar dishes at a 35–37°C and examined at 24–48 h after culturing to determine a colony count and identify pathogenic bacteria. Pyuria was identified if the spun urine had ≥ 5 white blood cells (WBCs) per high-power field on a spun urine. Positive urine cultures were defined as more than 10^5 CFU/ml of a single pathogen in a midstream urine sample **(17)**.

This study was approved by the institutional review board (IRB) of Damietta Faculty of Medicine, Al-Azhar University, Egypt (#IRB00012367-19-08-004), and an informed consent had been assigned by the legal guardian. Each child had been clinically evaluated in a systematic manner. The assessment started by inquiry about child demographics (e.g., age and gender) and symptoms of UTI. Then, general clinical examination was performed by the measurement of child weight, and height. Then patient was categorized into normal or abnormal (e.g., underweight) for gestational age. Any clinical signs recorded during clinical examination were documented. A urine analysis was performed and mid-stream sample was cultured. Blood sample was obtained by venipuncture, centrifuged and serum was used to determine serum creatinine, blood urea nitrogen (BUN), C-reactive protein, and determination of vitamin D levels. Finally, complete blood count was performed by automatic analyzer. Serum 25(OH)D 3 was measured by chemiluminescence immunoassay with a Cobas e 601 module of the Cobas 6000 series autoanalyzer (Roche Diagnostics, Germany) according to methods described by the manufacturer, while serum creatinine, BUN and CRP levels were determined by the spectrophotometric method using the Cobas 6000 series autoanalyzer (Roche Diagnostics, Germany). The vitamin-D was considered normal if it is ≥ 30ng/ml, insufficient if levels were more than 20 and less than 30ng/ml and deficient if levels < 20ng/ml.

Statistical analysis: All analyses were performed by the Statistical Package of Social Science, version 18.0 (SPSS Inc., Chicago, Illinois., USA). Numerical variables were presented as mean ± standard deviation (SD), and groups were compared by the independent two samples "*t*" test. Categorical variables were presented by their relative frequencies (number) and percentages compared using the Chi square test. Correlation was assessed by calculation of Pearson's correlation coefficient

Results

In the current study, patients and controls were comparable (with no significant difference) regarding child's age, gender and weight for age. However, children with UTI (the study group) had significantly higher CRP, white blood cells count, and erythrocyte sedimentation rate. However, there was significant reduction of serum vitamin D in the study than the control groups (19.02±8.51 vs 30.12±9.09 ng/dl, respectively). In addition, there was significant reduction of the number of children with sufficient vitamin-D in the study than the control group (34.7% vs 67.3% respectively) (Table 1). In the study group, insufficient vitamin D concentrations were significantly associated with higher levels of C-reactive protein, reduced red blood cells, higher white blood cells and lower platelets. However, child age, gender, weight for age and ESR showed non-significant differences between children with UTI and insufficient when compared to those with UTI and sufficient vitamin D levels (Table 2). Results of the current work revealed significant positive correlation between vitamin D levels from one side and each of RBCs and platelets from the other side. In addition, there was negative correlation between vitamin D levels and each of WBCs and CRP (Table 3).

Table (1): Comparison between study and control groups regarding studied variables

Variables		Study (n=49)	Control (n=49)	Test	P value
Age (years)	Mean±SD	8.63±1.23	8.45±1.30	0.71	0.48
	Min.-Max.	7-12	7-12		
Gender (n,%)	Male	16(32.7%)	20(40.8%)	0.70	0.40
	Female	33(67.3%)	29(59.2%)		
Weight for Age	Normal	44(89.8%)	46(93.9%)	0.54	0.46
	Underweight	5(10.2%)	3(6.1%)		
CRP (mg/dl)	Mean±SD	10.73±3.57	2.77±1.03	***6.23***	***<0.001****
RBCs X10^6/ml	Mean±SD	4.04±0.43	4.38±0.60	***3.15***	***0.002****
WBCs X10^3/ml	Mean±SD	14.30±3.11	5.43±0.82	***14.97***	***<0.001****
Platelets X10^3/ml	Mean±SD	276.51±42.83	266.30±29.31	1.37	0.17
ESR	Mean±SD	30.40±5.30	7.75±2.36	***19.28***	***<0.001****
Vitamin D (n/dl)	Mean±SD	19.02±8.51	30.12±9.09	***27.28***	***<0.001****

Vitamin D Category	Sufficient	17(34.7%)	33(67.3%)	***10.45***	***0.002****
	Insufficient	32(65.3%)	16(32.7%)		

Table (2): Variables related to vitamin D insufficiency in the study group

Variables		Insufficient (n=32)	Sufficient (n=17)	Test	P value
Age (years)	Mean±SD	8.59±1.13	8.70±1.44		
Gender (n,%)	Male	8(25.0%)	8(47.1%)	2.45	0.12
	Female	24(75.0%)	9(52.9%)		
Weight for Age	Normal	27(84.4%)	17(100.0%)	2.95	0.14
	Underweight	5(15.6%)	0 (0.0%)		
CRP (mg/dl)	Mean±SD	12.13±3.00	8.12±3.12	***4.38***	***<0.001****
RBCs X10^6/ml	Mean±SD	3.82±0.16	4.47±0.45	***7.35***	***<0.001****
WBCs X10^3/ml	Mean±SD	14.92±2.72	13.13±3.52	***1.98***	***0.05****
Platelets X10^3/ml	Mean±SD	266.65±35.36	295.05±50.21	***2.30***	***0.026****
ESR	Mean±SD	30.12±5.25	30.94±5.52	0.51	0.61
Vitamin D (n/dl)	Mean±SD	12.93±1.43	30.47±0.51	***48.52***	***<0.001****

Table (3): Correlation between vitamin D and other variables in the study group

	Vitamin D	
	r	p
Age	0.044	0.763
RBCs	0.719**	<0.001
WBCs	-0.284*	0.048
Platelets	0.292*	0.042
CRP	-0.503**	<0.001
ESR	0.068	0.642

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Discussion

The current work revealed that, primary school age children with UTI had significantly lower levels of vitamin D with significant increase of inflammatory markers (e.g., CRP, WBCs and ESR). In addition, there was significant correlation between vitamin D and each of RBCs, WBCs, and CRP. The correlation with inflammatory markers was negative and it was positive (proportional) with red blood cells. These results confirm the association between vitamin D deficiency and UTI, which could be expressed through inflammatory and immune mediators. In addition, hypocalcemia associated with hypo-vitaminosis D could had a role in UTI as it reduces the functions of lymphocytes and neutrophils [(18)]. Vitamin D immunomodulatory effects are produced by increased vitamin D receptors on immune cells. In addition, it increased the macrophages' oxidative ability and influences the production of cytokine, phosphatase and hydrogen peroxide. The macrophages motility and activity are increased by vitamin D. The active form of vitamin D is converted by macrophages, and it regulates the antibacterial peptides gene expression that is important for the immune defense mechanisms [(19)]. Besides, vitamin D increases bacterial clearance [(20)].

Results of the current work are in line with Mahmoudzadeh *et al*. [(21)] who reported that, the infants with UTI and the control group were comparable regarding their age and gender. However, vitamin D levels were lower in UTI than control group (14.5 ng/mL vs 27 ng/mL, $p < 0.001$). In addition, the prevalence of vitamin D levels lower than 20 ng/dl was higher in the children with UTI than in the healthy controls (68% vs 18%) ($p < 0.001$). In addition, in cases, there was a negative correlation between serum vitamin D and white blood cell count, age, body temperature, platelet count, ESR and CRP. However, the correlation between vitamin D and age did not be discovered in the current study and could be due to different sample size. Shalaby *et al*. [(22)] from Egypt, also reported a significant reduction of vitamin D in children, aged 2 months to 6 years with UTI than the healthy controls. This explained by reduced production of antibacterial peptides and production of modulating cytokines. Another study from Turkey reported that, children aged 2–18 years showed that vitamin D deficiency was a risk factor for UTI [(1)]. Ovunc Hacihamdioglu *et al*. [(23)] from Turkey included 38 healthy children and 36 with UTI demonstrated that children with vitamin D deficiency were incapable to enhance the production of their urine cathelicidin during infection. The increased production of urine cathelicidin could prevent UTI. Our results are also in line with Yang *et al*. [(24)] studied the effect of vitamin D deficiency on the risk of UTIs in infants, 1–12 months old. They reported that, vitamin D levels in infants with UTI were significantly lower than in the control group.

In the current work, there was female sex predominance. These results are in line with Sherkatolabbasieh *et al*. [(20)] and Shalaby *et al*. [(22)] who reported that, UTI affects 1% of boys and up to 5% of girls. In pediatrics, the UTI have acute and chronic complications. But it had a benign course in adults. Thus, prevention is crucial. In addition, Katikaneni *et al*. [(25)] reported increased number of infants and toddlers with vitamin D deficiency in UTI than in the control groups. However, Mahyar *et al*. in 2018 [(16)] is in contrast to most studies. They included infants and children aged 1 month to 12 years with UTI and

matched healthy controls. The results showed that vitamin D levels in children with UTI were significantly higher than in the control (20.4 versus 16.9 ng/ml, respectively, P = 0.01). Furthermore, Noorbakhsh *et al*. [26] included 25 patients under 5 years of age with UTI and 40 healthy controls and reported no significant differences between the study and control groups regarding vitamin D levels. This could be explained by small number of cases than in the current study.

The main limitation of the current work is the lack of second vitamin D measurement after treatment of UTI. However, we could conclude that, reduced vitamin D levels are associated with UTI in primary school children. Thus, vitamin D supplementation is advocated for vulnerable groups and future studies on a large number of patients with inclusion of different age groups are warranted.

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Author contribution: Authors contributed equally in the current work.

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