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Association of vitamin D deficiency and urinary infection in newborn

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ABSTRACT

Aim: To establish the relationship between urinary tract infection (UTI) in newborns and vitamin D deficiency.
Material and methods: The study group consisted of 60 newborns followed in the neonatal intensive care unit due to UTI. The controls were 60 healthy newborns with similar distribution of gestational week. Vitamin D levels <15 ng/mL were defined as low.
Results: The median serum 25(OH) D concentrations in the study group were lower than the control group (10,2 ng/mL and 16 ng/mL, respectively) (p=0,0001). In the study group, the multivariate logistic regression analysis showed that a serum level of 25(OH) D<15ng/ml [odds ratio 7, 95%, confidence interval 1.72-28.33; p=0.006] may be a risk factor for UTI in newborns.
Conclusion: Low level of 25(OH) D might be associated with an increased risk of UTI in term newborns.

Key words: 25-hydroxyvitamin D, urinary tract infection, newborn.

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Introduction

Urinary tract infection (UTI), which is a common disease in childhood [1], presents with different clinical findings in the neonatal period. UTI symptoms in the newborn are not very common. It may present with many non-specific findings like jaundice, fever, failure to thrive and vomiting. Early recognition of this infection is very important for the prevention of sequelae like hypertension and kidney injury. The urinary tract infection frequency is approximately 15% in term newborns admitted to the hospital [2]. Diagnosis of urinary tract infection in term infants is often postnatal 2-3 weeks. UTI symptoms in the neonatal period are neither very obvious nor specific. In order to make a diagnosis, the physician must be suspicious of this condition. In the neonatal period, clinical findings such as fever or hypothermia, malnutrition, vomiting, diarrhea, prolonged neonatal jaundice, irritability, lethargy, acidosis, abdominal distention, inability to gain weight, restlessness, crying while urinating and convulsions may be observed. UTI is most commonly caused by Gram-negative bacilli. Escherichia, Klebsiella, Enterobacterium, Proteus, the members of the Enterobacteriaceae family, are the causative agents of urinary tract infections. The most common of these, E.coli takes the first place with a frequency of 75-90% [3].

Also the most important effect of vitamin D one calcium and bone metabolism, it has been associated with infections. Leukocytes as well as monocytes and macrophages function through activation of Toll -like receptors (TLRs) found in cells of organs such as the epidermis, lung, intestine, and bladder. TLR has transmembrane recognition of pathogenic microorganisms and stimulation of this

receptor by the pathogen stimulates innate immunity in the host. Antimicrobial peptides (defensin, cathelicidin) and reactive oxygen products are stimulated, which in turn cause the death of microorganisms. Among these antimicrobial peptides, cathelicidin is very important. Active vitamin D stimulates the synthesis of antimicrobial peptide-cathelicidin from epithelial, myeloid series cells as well as "natural killer" cells and epithelial cells [4,5,6].

A previous study has also shown that during urinary infection of E.coli, a significant increase in the antimicrobial peptide cathelecidin determined after the supplementation of vitamin D in human urinary bladder cells [7]. Recently, Vitamin D deficiency has been associated with many other infections in pediatric population [8].

When the literature was scanned for investigating vitamin D deficiency and urinary tract infections in newborns, we could not find any literature about this topic.

In this study, we investigated whether there is a relationship between urinary tract infection and vitamin D deficiency in newborns.

Materials and methods

This study has been conducted in Sami Ulus Teaching and Research Hospital, Ankara, Turkey, during November 2021-March 2022. The study was approved by Local Ethics Committee.

The newborns attended to the newborn clinics with complaints of, poor feeding, failure to thrive, prolonged jaundice and taken urine culture by suprapubic aspiration or urinary catheterization methods. Culture positive accepted when 10^4 CFU/ mL of a single pathogen detected in urinary catheterization, or any number of colonies of an organism taken by suprapubic aspiration were taken to study group.

60 newborns were included throughout the study. Controls were healthy newborns who admitted to outpatients' department for postnatal follow up and needed blood samples to be taken in somehow. Cases with a gestational week < 37 weeks, intrauterine developmental deficiency, major congenital abnormality, babies feeding with were excluded. We further excluded patients if more than one organism detected in cultures. Patients with congenital anomalies of the kidney or urinary tract were also excluded.

Demographic characteristics of the neonates as gestasyonel week, birth weight and gender were recorded. Leukocyte, C-reactive protein (CRP) levels, types of microorganisms isolated in urine cultures were also enrolled in the study. The number of leukocytes above 20.000/mm^3 at the first recourse and CRP value above 0.5 mg/dl was considered significant.

2 mL of total blood taken to measure Vitamin D levels were obtained and serums stored at -20°C for analyses. APPLIED 3200 Biosystem (DPC Cirrus Inc., Diagnostic Products Corporation Los Angeles, CA 90045 USA) device, used to assess vitamin D levels. Plasma 25(OH)D concentration ≤15ng/mL was accepted as deficiency based on the recommendations of the American Pediatric Academy [9].

Statistical analyses: SPSS ver. 16.0 (SPSS Inc., Chicago, IL, USA) used to evaluate the data. All analyses were performed with Pearson's chi-square test, Mann-Whitney U. Multiple linear regression analysis was used to identify the risk of UTI with independent risk factors.

Results

Study group included 44 males and 16 female neonates, while the control group included 38 males and 22 females. The mean gestational week of the study group was 38.9± 0.84weeks, and 38.76±0.72 in the control group. Mean postnatal age was not significantly different between the study and the control groups (12.2±4.6days and 10.3±5.2days respectively; *p*: 0.72). When the demographic data of the neonates are analyzed, the two groups were similar in gestational week, birth weight, age and gender (Table 1).

E.coli was the most frequently detected microorganism in UTI patients (%87), Klebsiella and Staphylococcus epidermidis were the most common microorganisms after E.coli, respectively.

Table 1. Anthropometric characteristics and levels of 25(OH) D in the study and control groups.

Parameters	**Study Group n: 60**	**Control Group n: 60**	***p***
Birth weight(g) *	3325±510	3305±303	0.51
Length (cm) *	49.5±1.33	49.3±1.34	0.39
Head circumference (cm) *	33.6±1.1	34.5±1.2	0.21
Gestational age (week) *	38.9±0.84	38.76±0.72	0.89
25(OH)D levels of neonates (ng/ml)	10.2 (6,7-13,7)	16 (12-18)	**0.0001**

*Mean ± SD

Median level of 25(OH)D vitamin in the neonates was 10.2L (IQR 6,7-13,7) in the study group and 16ng/mL (IQR= 12-18) in the control group (p=0.0001). An assessment of the vitamin D levels of the neonates showed that a total of 84 patients had vitamin D levels below 15 ng/mL; 64 of the patients were in the study group and 20 were in the control group. Adequate Vitamin D levels, in other words levels above 20 ng/mL, were noted in twelve patients in the control group and in only two patients in the study group.

The multivariate logistic regression analysis showed that a serum level of 25(OH) D<15ng/ml [odds ratio (OR)7, 95%, confidence interval (CI) 1.72-28.33; p=0.006] was found to increase the risk of UTI development.

Discussion

Vitamin D is a hormone that is necessary for proper skeletal maintence. In recent years, the scientific world has focused on the effect of vitamin D on infections and the immune system [10]. Its role in the arrangement of the immune system increased with the discovery of the presence vitamin D receptors (VDRs), in neutrophils, monocytes, macrophages and in almost all immune system cells [11]. Natural immunity is associated with the production of Antimicrobial peptides (AMPs); like ß-defensins, cathelicidins which has ability to kill viruses, bacteria and fungi [12] and vitamin D through 1,25(OH)2D3/VDR complex, is effective in the production of AMPs locally against infections (13). Human cathelicidin peptide contains active vitamin D response element (VDRE) in the promoter region (14) and it has been shown that $1,25(OH)_2D3$ increases LL-37 levels in neutrophils (15). Antimicrobial activity of these peptides against multiple Gram-positive and Gram negative human pathogens were known [16].

Vitamin D defiency has been related with respiratory tract infection [17] wheezing and bacterial vaginosis [18] therewithal. A previous study has been proven that there is a relationship between low levels of vitamin vitamin D and urinary tract infection [19].

One of these studies has also been observed that women receiving vitamin D supplementation can produce more cathelicidin in the bladder epithelium [7]. A recent case control study found a relationship with vitamin D deficiency and UTI in children [20]. As a result of the meta-analysis vitamin D insufficiency had a markedly increased risk of having UTI [21]. Another study from Turkey, Tekin et al. [1] showed that children with serum levels of 25(OH)D<20ng/ml are 3.5 times more likely to develop UTI than those with normal

levels, Aslan et al. [22] reported that some of the VDR gene polymorphisms (FokI,BsmI, ApaI, and TaqI) studied in children with UTI, the risk of upper and lower UTI was markedly increased for FokI Ff and ff genotypes compared with FF genotype,so with the knowledge that vitamin D modulates the immune response against infections,VDR gene polymorphisms may be important for susceptibility to UTI. A study from Sweden [23] showed in a mouse model that vitamin D deficient mice have more bacteria in their bladder and further that vitamin D receptor was upregulated in the urinary bladder when encountering E. coli infection.

In the light of these information, we wanted to examine whether low vitamin D levels cause a tendency to urinary tract infection in newborns. In the present study, 25(OH)D levels in the neonates who have been followed with UTI were found to be lower than the levels in healthy neonates and showed that vitamin D deficiency in neonates was independently associated with UTI.

The strength of our study is that there is no difference in demographic data between the study and control groups and evaluation made in the same season.

In conclusion, low 25(OH)D vitamin levels may be a risk factor for UTI in the neonates. For this hypothesis randomized controlled trials are needed.

We think that identifying vitamin D supplements individually for each baby and also in mothers and providing the necessary support at the appropriate time can improve the vitamin D levels and reduce the risk of UTI in the neonates.

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