ORIGINAL ARTICLE

The serum vitamin D levels in children with urinary tract infection: a case–control study

M. Sadeghzadeh[1], **P. Khoshnevisasl**[2], **N. Motamed**[3] **and L. Faghfouri**[4]

1 Zanjan Metabolic Disease Research Center, 2 Zanjan Social Determinants of Health Research Center, Department of Pediatrics, 3 Dept. of Community Medicine and 4 Dept. of Pediatrics, Ayatollah Moussavi Hospital, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran

Abstract

Urinary tract infection (UTI) is one of the most common infections in infants and children. The aim of this study is to evaluate the association between vitamin D levels and urinary tract infections in children. This case-control study was performed on 80 children aged 1–12 years with urinary tract infection referred to the pediatric clinic of Mousavi Hospital in Zanjan, Iran. For each patient in the case group, an individual of the same age and sex was selected in the control group. Vitamin D was measured by the ELISA method. Statistical analysis was performed by SPSS V22 software. In this study, 80 children were divided into two groups of 40 cases (UTI) and control. Serum levels of vitamin D in the case group were significantly lower than in the control group [OR (95%CI) = 3.316 (1.286–8.550),(p = 0.013)]. In females, serum levels of vitamin D in cases were significantly lower than for controls [OR (95%CI) = (5.417 (1.685–17.417), P-value = 0.005)]. No significant relationship was found between serum levels of vitamin D in cases and controls regarding male gender, age and weight. Conclusions: This study showed that vitamin D deficiency has a significant relationship with the prevalence of UTI in children. Vitamin D deficiency and female gender are more frequent risk factors for UTI.

Keywords: Cathelicidin, children, urinary tract infection, UTI, vitamin D
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Corresponding author: P. Khoshnevisasl, Department of Pediatrics, Ayatollah Moussavi Hospital, Zanjan, Iran
E-mails: sadeghzadeh@zums.ac.ir **(M. Sadeghzadeh),** khoshnevis@zums.ac.ir **(P. Khoshnevisasl),** nima.motamed@zums.ac.ir **(N. Motamed),** Ladan_fa32@yahoo.com **(L. Faghfouri)**

Introduction

Urinary tract infection (UTI) is one of the most common infections in infants and children [1]. UTI may have acute and chronic complications in children compared to adults, which usually has a benign course [2]. It occurs in 1% of boys and up to 5% of girls and is more frequent than bacterial meningitis, otitis media and pneumonia [3]. A large number of children with symptomatic urinary tract infections are in the first decade of life and are prone to kidney scars and subsequent possible complications such as growth retardation, arterial hypertension, proteinuria and finally, chronic renal failure. The severity of a urinary tract infection is determined by a variety of factors, including the pathogen and the host's immune response [4]. Up to 90% of UTI is caused by Escherichia.coli [3].

Vitamins and micronutrients may play an important role in supporting the human body's defense system, and their homeostasis plays an essential role in controlling infections. In the Middle East and Asia, micronutrients and vitamin deficiencies, especially vitamins A and D deficiencies, are very common in children due to inadequate intake and loss of these substances during periods of recurrent infections [5]. Vitamin D essentially controls calcium hemostasis, and its deficiency is seen all over the world. The role of vitamin D in controlling infections and autoimmune diseases is mentioned in many studies [6–9]. Although the association of vitamin D deficiency and recurrent UTI in premenopausal women is reported, recent studies revealed the association of UTI and vitamin D levels less than20 ng/mL in children. A study suggested that the susceptibility of

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children to UTI can be explained by the vitamin D receptor gene polymorphism. It was proposed that the effect of vitamin D deficiency on the immune system can explain the risk of infection in those patients [6].

Due to the important role of vitamin D in the prevention of UTI, we decided to investigate the association between vitamin D levels and urinary tract infections in children.

Material and methods

This case-control prospective study was conducted at Mousavi Hospital in Zanjan, Iran, during autumn and winter 2019. Eighty children aged 1–12 years were enrolled in this study and were equally divided into case and control groups. The case group was selected by simple random sampling from patients referred to the clinic and pediatric ward of Mousavi Hospital. For each patient in the case group, the control of the same age and sex was selected from healthy outpatient children who came for routine medical control, had no evidence of UTI, volunteered to participate in this study and had a personal desire to perform laboratory tests. The inclusion criteria for case group include: (1) age 1–12 years (2) diagnosis of first symptomatic, non-complicated UTI based on urine culture (3) not receiving vitamin D supplement in therapeutic dose in the last 6 months. The exclusion criteria in both groups include: (1) presence of anatomical disorder, (2) history of vesicourethral reflux or nephrogenic disorders, (3) neurological defects, including cerebral palsy and spina bifida and (4) cognitive and intelligence disorders. In patients younger than 3 years, urine samples were collected by the Urine Bag method, and in older than 3 years, they were collected by a midstream clean-catch method. Positive culture with colony counts of more than 10^5 colony-forming units/mL was considered as urinary tract infection. Vitamin D levels were measured by the ELISA method in the hospital laboratory. The definition of vitamin D deficiency is controversial. We defined vitamin D levels according to the endocrine society definition. The level of 25 OHD below 20 ng/ml was considered as vitamin D deficiency and vitamin D insufficiency defined as the level of 25OHD in the range of 20–30 ng/ml and levels more than 30 ng/ml was considered normal [10]. All patients with vitD deficiency in the case and control groups were treated with vitD supplements.

Demographic data were recorded in a pre-designed questionnaire. The height, weight and Body Mass Index (BMI) were determined and recorded. Statistical analysis was performed by SPSS V22 software.

Quantitative data were expressed by mean and standard deviation. T-test was used for independent groups to compare quantitative variables. Simple and multiple logistic regression analyses were conducted in which UTI (yes, no) was considered as a dependent variable and vitamin D level (classified into <30 ng/l and≥30 ng/l) as an independent variable. In multiple logistic regression analysis, age (categorised as 1–6 years, 7–12 years) and weight (normal weight and underweight) were taken into account as the confounding variables. $P < 0.05$ was considered statistically significant. Moreover, in multiple logistic (binary) analysis, we checked the multicollinearity that there was no problem.

This project was approved by the Ethics Committee of Zanjan University of medical sciences (IR.ZUMS.-REC.1398.446), and an informed written consent was obtained from the parents or patients' legal guardians before enrolling in the study.

Results

Forty children aged 1–12 years in each case and control groups were evaluated in this study. The case group consisted of 8 boys (20%) and 32 girls (80%), and the control group consisted of 13 boys (32.5%) and 27 girls (67.5%). The difference between the groups in terms of gender was not significant ($P = 0.204$).

In the case group, 26 children (65%) were between 1–6 years old and 14 children (35%) were 7–12 years old, while the control group consisted of 27 (67.5 %) children aged 1–6 years and 13children (32.5%) aged 7–12 years. The difference between groups in terms of age was not significant ($P = 0.813$).

Thirty seven children (92.5%) in the case group had normal weight, and 3 (7.5%) children had low weight. In the control group 35 children (87.5%) had normal weight, and 5 (12.5%) children were underweight. There was no significant difference in terms of weight between the two groups ($P = 0.456$).

In the case group, 75% of patients had serum vitamin D levels <30 ng/l compared to 47.5% of the control group. The Chi-square test showed that the serum level of vitamin D in the group with urinary tract infection was significantly lower than the control group ($p = 0.013$).

Table 1 shows the serum vitamin D levels of both groups according to sex, age and weight. In the case group, 81.3% of girls had a serum vitamin D levels <30 ng/l in contrast to 44.4% of control group ($p = 0.005$). Fifty percent of boys in the case group, had serum vitamin D levels <30 ng/l compared to 53.8% of the control group; this difference was not statistically significant ($p = 0.846$).

In the case group, 76.9% of children aged 1–6 years had serum vitamin D levels <30 ng/l compared to 51.9% of the control group. There was no significant difference between serum vitamin D levels in the case and control group in this age range ($p = 0.057$). In children 7–12 years old, 71.4% of the case

TABLE 1. The serum vitamin D levels based on sex, age and weight in case and control group

	Case group [n (%)]		Control group [n (%)]			
variable	Vit D level <30 ng/l	Vit D level ≥30 ng/l	Vit D level <30 ng/l	Vit D level ≥30 ng/l	OR (95%CI)	P value
Total population	30 (75%)	10 (25%)	19 (47.5%)	21 (52.5)	3.316 (1.286–8.550)	0.013
Sex						
Boys	4 (50%)	4 (50.0%)	7 (53.8%)	6 (46.2%)	0.857 (0.147–4.999)	0.864
Girls	26 (81.3%)	6 (18.8%)	12 (44.4%)	15 (55.6%)	5.417 (1.685–17.417)	0.005
Age						
1–6 years	20 (76.9%)	6 (23.1%)	14 (51.9%)	13 (48.1%)	3.095 (0.947–10.115)	0.061
7–12 years	10 (71.4%)	4 (28.6%)	5 (38.5%)	8 (61.5%)	4.000 (0.799–20.017)	0.082
Weight						
Normal Weight	28 (75.7%)	9 (24.3%)	17 (48.6%)	18 (51.4%)	3.294 (1.210–8.970)	0.020
under Weight	2 (66.7%)	1 (33.3%)	2 (40%)	3 (60%)	3.000 (0.150–59.890)	0.472

group and 38.5% of control group had serum vitamin D level <30 ng/l, and there was no significant difference between serum levels of vitamin D in the cases and controls (p = 0.085).

In the case group, 66.7% of underweight children (below the third percentile) had serum vitamin D level <30 ng/l compared to 40% of the control group; however, this difference was not statistically significant (p = 0.465). In 75.7% of normal-weight children in the case group, the serum vitamin D level was <30 ng/l in contrast to 48.6% of the control group. This difference was statistically significant (p < 0.018).

Table 2 shows the results of multiple logistic regression analysis on UTI as an outcome and the vitamin D status as an independent variable. Age, sex and weight were considered the confounding variables. Our results showed a significant association between vitamin D status and UTI, removing the confounding effects of the related confounders (OR = 2.884, 95% CI (1.075–7.738), P-value = 0.035). Based on our findings, the individuals with vitamin D deficiency were 2.884 times more likely to be infected than individuals without it.

Discussion

In our study, 75% of patients with urinary tract infection had serum vitamin D levels <30 ng/l that were significantly lower than the control group. This finding is similar to most other studies. A study by Tekin et al., in 2015, on 82 children with first-time UTI and 64 healthy children showed that mean vitamin D levels were lower in cases compared to the control group. The results of this study also showed that vitamin D levels in patients with lower UTI were significantly lower than patients with upper UTI, and vitamin D less than 15 ng/l was mentioned as a risk factor for developing UTI in children [10]. In the study of Yang et al. In China in 2016, the effect of vitamin D on the risk of urinary tract infections in infants was studied. A total of 238 infants 1–12 months old were enrolled in this study, 132 of whom experienced their first urinary tract infection, and 106 children were assigned to the control group. The study showed that vitamin D levels in infants with urinary tract infections were significantly lower than in the control group [11]. In a study by Shalaby et al., In 2018 in Egypt, the effect of vitamin D deficiency on the prevalence of UTI in children was investigated. This study was performed on 50 patients with first-time UTI and 50 matched control children. Vitamin D levels in children with urinary tract infections were significantly lower than the control group and were an independent risk factor for UTI [2]. In another study in the United States in 2012, Katikaneni and colleagues examined the effect of vitamin D supplementation in 315 infants and toddlers. The study showed that the prevalence of vitamin D deficiency was higher in the group with UTI than in the control group [12]. However, the study of Mahyar et al., in 2018 in Qazvin is in contrast to most studies. In the study of Mahyar et al. seventy patients aged 1 month to 12 years with first-time UTI and 70 matched control children were evaluated. The results of this study showed that vitamin D levels in children with urinary tract infections were significantly higher than in the control group (20.4 in the case group and 16.9 ng in the control group, P = 0.01) [13]. Moreover, in the study of Noorbaksh et al., in Tehran, on 25 patients below 5 years old with UTI and 40 children without UTI, there were no significant differences in vitamin D level between the two groups [14].

As mentioned, in most studies, vitamin D deficiency in patients with urinary tract infections was higher than in the control group. The antimicrobial role of vitamin D has been

TABLE 2. The results of multiple logistic regression analysis on UTI (as outcome)

Variable	OR (95%CI)	P-value
Age	1.723 (0.904–3.208)	0.098
Sex	0.575 (0.196–1.685)	0.313
Weight	0.789 (0.605–1.029)	0.080
Vit D	2.884 (1.075–7.738)	0.035

attributed to the production of antibacterial peptides such as cathelicidin and the regulation of beta-defensin in the cytokine system [6]. The effect of vitamin D on the regulation of inflammation and the production of cytokines, along with its antimicrobial effects, are well known. The immunomodulatory effect of vitamin D is applied by the expression of its receptors on immune cells. Vitamin D increases the oxidative ability of macrophages and influences the cytokine, phosphatase and hydrogen peroxide production. The motility of macrophages and their activity are increased by vitamin D. Vitamin D is converted to the active form by macrophages, and the active vitamin D3 regulates the gene expression of antimicrobial peptides that are important for the defense mechanism [9]. Besides the influence on the immune system, vitamin D can affect bacterial clearance [3]. Epithelial cell-derived mediators, including antimicrobial peptides, such as α- and β-defensins and cathelicidin, have a profound effect on urinary tract defense. Vitamin D stimulates cathelicidin expression in epithelial and immune cells, which increases chemokines and cytokines production and is important in maintaining the integrity of the urinary tract [6].

The results of our study showed that there is no significant relationship between serum levels of vitamin D and the incidence of UTI in both age groups. This finding is similar to some studies [10,11,13,15]. However, the study of Georgieva et al. showed that serum vitamin D level is inversely related to age [16]. This study that was performed in Sweden enrolled 120 children under 3 years, and vitamin D levels were measured by electrochemiluminescence [16]. Most studies suggest that serum levels of vitamin D in patients with urinary tract infections are not related to age. The difference in the results of Georgieva et al., may be due to the different sizes and ages of the study population.

Our results showed that in females, the serum level of vitamin D in the group with urinary tract infection was significantly lower than the control group ($p < 0.003$), but in males, there was no significant difference between serum levels of vitamin D in the case and control groups ($p = 0.846$). In the study of Shalaby et al., the serum vitamin D levels were significantly lower in females than males [2]. The study of Georgieva et al., showed lower levels of vitamin D among girls and concluded that vitamin D deficiency in girls significantly increased their susceptibility to UTI [16]. These results are consistent with our study. In a clinical trial study in 2016 conducted by Jorde et al. on 511 pre-diabetic patients matched with the control group, the effect of vitamin D supplementation on the prevention of UTI was evaluated. It was shown that vitamin D supplementation for UTI prevention was more effective in males compared to females [15]. However, the study of Mahyar et al. and Tekin et al., showed no significant differences between vitamin D levels of the case and control groups according to gender [10,13]. Vitamin D levels appear to be generally lower in females. As a result, vitamin D deficiency and the prevalence of UTI are more common in girls.

In our study, a total of 3 cases in the UTI group and 5 cases in the control group were underweight. In underweight children, there was no significant difference between serum levels of vitamin D in case and control group. However, at a normal weight, serum vitamin D levels were significantly lower in the group with UTI compared to the control group. Similar to our study, the study of Mahyar et al. showed that according to weight, height, head circumference and BMI, there were no significant differences between the two groups [13]. Also, this finding is similar to the study of Jorde et al. [15]. In general, BMI does not seem to affect the relationship between vitamin D levels and the prevalence of UTI.

Our study had some limitations. The low sample size in our study will reduce the study power. Although even with low power, our study was able to show a significant association between vitamin D levels and urinary tract infections in the general and female population, but, in other subgroup analyzes, especially by age, the study power was not sufficient. Conducting studies with higher sample sizes can help in this regard. Socioeconomic status, etiology and site of urinary tract infection can be considered as potential confounders that were not included in our study. Although this study can help the clinicians in clinical decision-making, an exact cause-and-effect relationship was not found in our study.

Due to the fact that serum vitamin D levels change over time, long-term control of these patients for UTI recurrence and its relationship with serum vitamin D levels is recommended. In addition, clinical trials with vitamin D supplementation in patients with recurrent infections are suggested.

Conclusion

Our study showed that vitamin D deficiency has a direct and significant relationship with the prevalence of UTI in children. UTI is more frequent in vitamin D deficiency and female gender. Meanwhile, male gender, age, and weight in children with urinary tract infections were not associated with vitamin D levels.

Transparency declaration

There is no conflict of interests.

Credit author statement

Concepts, Design, Definition of intellectual content, Literature search, Clinical studies, Manuscript preparation, Manuscript editing and review have been made by Mansour Sadeghzadeh, Parisa Khoshnevisasl. Data analysis and Statistical analysis have been done by Nima Motamed. Clinical studies, data acquisition and Manuscript draft writing, have been made by Ladan Faghfouri.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nmni.2021.100911.

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