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Do Vitamin D Levels Play a Role in Urinary Tract Infection in Children?

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Abstract

Previous studies have shown the protective effects of vitamin D supplementation against urinary tract infection (UTI). However, there are a few contradictory studies on the negative effect of vitamin D supplementation on UTI. Our objective was to establish whether there existed a relationship between serum vitamin D levels and UTIs in children. This study compared the serum 25-hydroxy vitamin D [25(OH)D] levels of children diagnosed with UTIs with those of healthy children (control group). We found a high rate of 25(OH)D deficiency in both the control and case groups (90% and 66.7%, respectively). Therefore, we added the laboratory parameters calcium, phosphate, and parathormone (PTH) to our analysis. We assessed the medical records of 60 patients diagnosed with UTIs and 20 healthy controls. The mean serum 25(OH)D level and PTH level were significantly higher in the patient group than in the control group. The PTH level was significantly lower in the acute pyelonephritis (APN) group than in the control group (p=0.016). Phosphate levels in the APN group were significantly lower than those in the control and cystitis groups (p=0.04, p=0.006 respectively). Because there was no correlation between 25(OH)D level and UTI, we concluded that 25(OH)D had no effect on UTI.

Keywords: Urinary tract infection, children, vitamin D, parathormone, fibroblast growth factor 23

Introduction

Urinary tract infection (UTI) is a common infection in the pediatric age group.[1] The lifetime incidence is approximately 8% in girls and 2% in boys, and it is 3-5 times higher in girls than boys.[2] Recurrent UTI and acute pyelonephritis (APN) may cause renal scarring, hypertension, and ultimately chronic kidney disease.[3] 25-hydroxy vitamin D [25(OH)D] has an immunomodulatory effect through the synthesis and production of cytokines.[4] Some studies have shown its positive role in respiratory tract infections.[5,6] Additionally, studies have shown the protective effect of 25(OH)D in UTI.[7,8] However, there are a few contradictory studies about the negative effect of 25(OH)D on UTI, which have shown that the administration of 25(OH)D supplements increases the risk of UTI.[9,10] In this study, we aimed to evaluate vitamin D levels in children with upper and lower UTIs and compare them with healthy individuals, thus investigating whether there is a relationship between UTI and vitamin D. As is well known, 25(OH)D has a stimulatory effect on

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calcium and phosphate homeostasis and a negative feedback effect on parathormone (PTH).[11] Therefore, we also examined the relationship of these parameters (calcium, phosphate, PTH) with UTI.

Material and Method

Children with UTI (case group) who presented to our pediatric nephrology clinic were compared with a randomly selected control group. A "true" UTI is defined as urinalysis positive for leukocytes ± nitrites, a urine culture consisting of >50,000 colony-forming units/milliliter (CFU/mL) from a urinary catheter, or >100,000 CFU/mL in a midstream urine sample.[12] We also compared the UTIs in 2 groups: APN and cystitis. Symptoms such as fever, chills, fatigue, flank pain, nausea/vomiting, and laboratory findings such as elevated white blood cell count, C-reactive protein, or erythrocyte sedimentation rate distinguish APN from cystitis.[2] As is well known, 25(OH)D has a stimulatory effect on calcium and phosphate homeostasis and a negative feedback effect on PTH.[11] Therefore, we added the laboratory parameters calcium, phosphate, and PTH to our analysis. We excluded patients younger than 2 years of age because most infants in our study population receive vitamin D supplementation until 1-2 years of age. Children with malnutrition, chronic diseases, or vitamin D supplementation were excluded. The inclusion criteria for the case group were patients diagnosed with UTI with pyuria and/or positive nitrite test and positive urine culture of a single pathogen.[11] The two groups were also compared in terms of age, gender, height, weight, and body mass index (BMI). After obtaining written consent from the parents, 3 mL of blood was collected from both the control and patient groups during outpatient clinic visits throughout the day to assess serum 25(OH)D levels. The blood samples were centrifuged to separate the serum, which was then stored at 20°C until the tests were conducted. Serum 25(OH)D levels were measured using the ELISA method.

Ultrasonography and voiding cystourethrogram were performed to rule out urinary system abnormalities and vesicoureteral reflux (VUR) in patients with atypical and recurrent UTIs. Labial adhesions and phimosis were excluded by clinical examination. Patients with 25(OH)D levels 20 ng/mL (<50nmol/L) were classified as having 25(OH)D deficiency.[9] Ethics committee approval of the study was obtained from the Kırıkkale University Non-Interventional Clinical Research Ethics Committee (decision no: 2022.04.25, date: 27.04.2022). The authors confirm that informed consent was obtained from the participants or their legal guardians, and all required ethical approvals were obtained for the study.

Highlights

- 25-hydroxy vitamin D [25(OH)D] exhibits immunomodulatory effects through the synthesis and generation of cytokines.
- Additionally, previous studies have demonstrated the protective impact of 25(OH)D against urinary tract infections (UTIs).
- Given the absence of a connection between 25(OH)D levels and UTI, we deduced that 25(OH)D does not influence UTI.
- Findings regarding parathormone (PTH), particularly in the acute pyelonephritis (APN) group, might be associated with fibroblast growth factor (FGF)-23; decreased PTH in the APN group could result from elevated FGF-23 levels in these individuals.

Statistical Analysis

The normality of data distribution was examined using the Kolmogorov-Smirnov test. All the parameters under investigation were normally distributed. Differences between the groups in terms of continuous variables in the two and three groups were evaluated using the Student's t-test, and when appropriate, ANOVA was employed. Differences in proportion were evaluated using the chi-square test. Correlations between parameters were assessed using Pearson's and Spearman's correlation tests. Regression analysis was used to assess the relationship of 25(OH)D, PTH, calcium, and phosphate with outcome parameters, including UTI and APN.

Results

We evaluated the medical records of 60 patients with UTI and 20 healthy controls. The mean age of the UTI patients was 87.7±43.1 months and 55 (91.7%) were women. The control group was composed of 10 (50%) women, and the mean age of 103.2±35.4 months. There was a significantly higher proportion of women in the UTI group than in the control group ($p<0.001$). No significant difference was found between the two groups in terms of age, height, weight, and BMI ($p>0.05$). We found a high rate of 25(OH)D deficiency in both the control and case groups (90% and 66.7%, respectively) (**Table 1**). The mean serum 25(OH)D level was significantly higher in the patient group than in the control group (18.1±8.1ng/mL vs. 12.7±5.6 ng/mL, $p=0.002$). Although there were no significant differences in serum calcium and phosphate levels ($p=0.055$, $p=0.386$, respectively), the PTH level was significantly lower in the patient group than in the control group (27.7±13.6 pg/mL, vs. 36.7±14.6 pg/mL, $p=0.044$). The proportion of individuals with 25(OH)D deficiency was significantly higher in the control group than in the UTI group ($p=0.043$) (**Table 1**).

In the UTI group, 41 (68.3%) patients were diagnosed with cystitis and 19 (31.7%) with APN. The most common causative agent was *E. coli* (81.67%), followed by *Klebsiella* spp. (6.67%), *Proteus* spp. (3.33%), *Pseudomonas* spp. (3.33%), *Citrobacter* spp. (3.33%) and *Enterobacter* (1.67%). Of the 49 patients with *E. coli* growth, 9 (18.4%) were extended-spectrum beta-lactamase (ESBL) positive. In addition, 27 (45%) patients were nitrite-positive. In terms of concomitant urinary disorders, VUR and nephrolithiasis were present in 3 (5%) patients. Eight patients experienced recurrent UTI.

There was no significant difference in mean age between the control, cystitis, and APN groups ($p=0.113$). Similarly, no significant difference was found between the groups in terms of BMI ($p=0.736$) (**Table 2**). The proportion of

girls in the APN and cystitis groups were significantly higher than that in the control group (p<0.001). However, there was no significant difference between the cystitis and APN groups in terms of gender (p=0.558). There were significant differences between the groups in terms of mean 25(OH)D, PTH, calcium, and phosphate levels (p=0.003, p=0.020, p=0.006, p=0.007 respectively). The 25(OH)D level was significantly higher in the cystitis group than in the control group (p=0.002); there was no significant difference between the APN and control groups (p=0.361). The proportion of individuals with 25(OH)D deficiency was significantly different between groups (p=0.045); the proportion was significantly higher in the control group than in the cystitis group (p=0.020). The PTH level was significantly lower in the APN group than in the control group; however, there was no significant difference between the cystitis and control groups or between the APN and cystitis groups (p=0.016, p=0.901, p=0.160, respectively). The calcium level in the APN group was significantly lower than that in the control and cystitis groups (p=0.011, p=0.016, respectively). There was no significant difference between the cystitis and control groups in terms of the mean calcium level (p=0.874). The phosphate level in the APN group was significantly lower than that in the control and cystitis groups (p=0.040, p=0.006, respectively). There was no significant difference between the cystitis and control groups in mean phosphate level (p=0.967).

25(OH)D levels were significantly lower in patients with positive urinary nitrite than in those with negative urinary nitrite (15.9±6.1 vs. 20.0±9.1; p=0.047). There was no significant difference in mean 25(OH)D levels between patients with *E. coli* growth and those without (17.6±7.9 vs. 19.5±8.9; p=0.464). In addition, there was no significant difference in the mean 25(OH)D level between patients with and without ESBL-positive urine culture versus those without (17.3±10.0 vs. 18.3±7.8; p=0.783, respectively).

Table 1.
Comparison of variables between case and control groups

Variable	Case group (n=60)	Control group (n=20)	P-value
Gender (female) n (%)	55 (91.7)	10 (50)	**<0.001***
Mean age (month)	87.7±43.1	103.2±35.4	0.118
Height (cm)	124±21	135±23	0.102
Weight (kg)	29.2±14.4	32.6±14.8	0.398
Body mass index	17.9±4.2	17.0±4.0	0.426
Serum 25(OH)D (ng/mL)	18.1±8.1	12.7±5.6	**0.002***
25(OH)D deficiency n (%)	40 (66.7)	18 (90)	**0.043***
Serum calcium (mg/dL)	9.8±0.5	10.1±0.3	0.055
Serum phosphate (mg/dL)	4.5±1.1	4.7±0.7	0.386
PTH (pg/mL)	27.7±13.6	36.7±14.6	**0.044***

*;p<0.05, 25(OH)D; 25-hydroxy vitamin D

Table 2.
Comparison of demographic and laboratory data between control, cystitis and acute pylenephritis groups (ANOVA test)

Variable	Control (n=20)	Cytitis (n=41)	APN (n=19)	P-value	Post-hoc analysis A=between control and cystitis B=between control and APN C=between APN and cystitis
Gender (female) n (%)	10 (50)	37 (90.2)	18 (94.7)	**<0.001***	**A=<0.001*** **B=<0.001*** C=0.558
Mean age (month)	103.2±35.4	83.7±43.2	96.3±42.7	0.113	
Body mass index	17.0±4.0	17.9±4.2	17.9±4.1	0.736	
Serum 25(OH) D (ng/mL)[1]	12.7±5.6	19.4±8.8	15.4±5.6	**0.003***	**A=0.002*** B=0.361 C=0.107
25(OH)D deficiency n (%)	18 (90)	25 (61)	15 (78.9)	**0.045***	**A=0.020*** B=0.339 C=0.170
Serum PTH (pg/mL)	36.7±14.6	31.8±14.4	20.0±7.7	**0.020***	A=0.901 **B=0.016*** C=0.160
Serum calcium (mg/dL)	10.1±0.3	10.0±0.5	9.6±0.5	**0.006***	A=0.874 **B=0.011*** **C=0.016***
Serum phosphate (mg/dL)	4.7±0.7	4.8±1.0	3.9±1.2	**0.007***	A=0.967 **B=0.040*** **C=0.006***

*;p<0.05, 25(OH)D; 25-hydroxy vitamin D, PHT; Parathormone, ANOVA; One-way analysis of variance

There was a negative correlation between age and 25(OH)D level (r=-0.267, p=0.039) in the patient group. In contrast, there was a positive correlation between age and PTH level (r=0.421, p=0.045). There was no correlation between 25(OH)D level and PTH level (r=-0.274, p=0.206).

Female gender and a high 25(OH)D level were found to be risk factors for UTI, although only female gender was found to be an independent risk factor in multiple regression analysis [odds ratio (OR)=0.058, 95% confidence interval (CI) 0.006-0.549; p=0.013*] (**Tables 3 and 4**).

Low calcium and phosphate levels were identified as risk factors for APN. However, multiple regression analysis showed that these variables were not independent risk factors (for calcium: OR=0.308, 95% CI 0.029-3.287; p=0.329; for phosphate: OR=0.547, 95% CI 0.161-1.862; p=0.334) (**Tables 5 and 6**).

Discussion

In the present study, we found a significantly higher 25(OH)D level and lower PTH level in patients with UTI. In addition, although there was no significant difference with respect to mean 25(OH)D and PTH levels, we found lower calcium and phosphate levels in APN than in cystitis.

In our study, we found a female sex preponderance in UTI, consistent with previous studies.[1] UTIs are more common in females than in males because of anatomic and physiologic factors.[1] In recent years, UTI caused by ESBL-positive microorganisms has not only been encountered in hospitals but also spread widely in the community.[13] Two studies from Thailand and Korea reported ESBL UTI rates of approximately 20%, which are comparable to the rate reported in our study.[14,15] VUR is found in 1-3% of the general population, whereas its prevalence is 30-45% in children with UTI.[16] Our patients had a relatively low VUR prevalence (5%) because our

Table 3.
Univariate regression analysis of variables in terms of risk for urinary tract infection

Variables	Univariate regression analysis
Gender (female)	OR=11.0, 95% CI=3.097-39.070; **p=<0.001***
Serum 25(OH)D (ng/mL)[1]	OR=1.135, 95% CI=1.029-1.252; **p=0.011***
Serum calcium (mg/dL)	OR=0.422, 95% CI=0.138-1.289; **p=0.130****
Serum phosphate (mg/dL)	OR=0.842, 95% CI=0.519-1.364; **p=0.484**
PTH (pg/mL)	OR=0.951, 95% CI=0.904-1.001; **p=0.057****

*; p<0.05, **; p<0.200, 25(OH)D; 25-hydroxy vitamin D, OR; Odds ratio, CI; Confidence interval, PTH; Parathormone

Table 4.
Multivariate regression analysis of variables in terms of risk for urinary tract infection

Variables	Multivariate regression analysis
Gender (female)	OR=0.058, 95% CI=0.006-0.549; **p=0.013***
Serum 25(OH)D (ng/mL)[1]	OR=1.097, 95% CI= 0.946-1.271; p=0.220
Serum calcium (mg/dL)	OR=0.373, 95% CI=0.063-0.549; p=0.278
PTH (pg/mL)	OR=0.940, 95% CI=0.0877-1.008; p=0.084

*; p<0.05, 25(OH)D; 25-hydroxy vitamin D, OR; Odds ratio, CI; Confidence interval, PTH; Parathormone

Table 5.
Univariate regression analysis of variables in terms of risk for pyelonephritis

Variables	Univariate regression analysis
Gender	OR=0.514, 95% CI=0.053-4.937; p=0.564
Serum 25(OH)D (ng/mL)[1]	OR=0.930, 95% CI=0.857-1.009; **p=0.082***
Serum calcium (mg/dL)	OR=0.220, 95% CI=0.062-0.778; **p=0.019***
Serum phosphate (mg/dL)	OR=0.432, 95% CI=0.229-0.814; **p=0.009****
PTH (pg/mL)	OR=0.915, 95% CI=0.833-1.006; **p=0.066***

*; p<0.05, **; p<0.200, 25(OH)D; 25-hydroxy vitamin D, OR; Odds ratio, CI; Confidence interval, PTH; Parathormone

Table 6.
Multivariate regression analysis of variables in terms of risk for pyelonephritis

Variables	Multivariate regression analysis
Serum 25(OH)D (ng/mL)[1]	OR=0.805, 95% CI=0.600-1.081; p=0.150
Serum calcium (mg/dL)	OR=0.308, 95% CI=0.029-3.287; p=0.329
Serum phosphate (mg/dL)	OR=0.547, 95% CI=0.161-1.862; p=0.334
PTH (pg/mL)	OR=0.884, 95% CI=0.766-1.020; p=0.091

25(OH)D; 25-hydroxy vitamin D, OR; Odds ratio, CI; Confidence interval, PTH; Parathormone

study population was mostly composed of patients with first-time UTI; thus, the indication for voiding cystography had not yet been established, potentially missing some VUR cases.

Previous studies have indicated that 25(OH)D deficiency is a risk factor for recurrent UTI.[17,18] Tekin et al.[8] showed that the serum 25(OH)D levels of 82 pediatric patients with UTI were lower than those of healthy children. It has been shown that 25(OH)D increases the secretion of the antimicrobial peptide cathelicidin by bladder epithelial cells, which protect against bacterial infections.[19-21] However, our results were contradictory, as 25(OH)D levels were higher in the UTI group than in the control group. Likewise, Katikaneni's study[9] with 315 infants aged 3 months demonstrated that 25(OH)D supplementation increases the risk of UTI in formula-fed infants by up to 76%. Mahyar et al.[10] from Qazvin, Iran enrolled children aged 1 month to 12 years who presented with UTI. Similar to our study, Mahyar et al.[10] found a significantly higher mean serum 25(OH)D level in children with UTI than in the control group.

Some hypotheses have been put forth in the literature in relation to this subject; Katikaneni et al.[9] proposed a slight nephrocalcinosis effect of 25(OH)D administration because nephrocalcinosis is an excellent context for bacterial growth. Second, the selective immunosuppressive role of 25(OH)D has been demonstrated in animal models of autoimmune disease; thus, it is known that 25(OH)D has immunosuppressive properties in autoimmune diseases.[22] 25(OH)D induces the production of transforming growth factor beta 1 and interleukin 4, potentially dampening inflammatory T-cell activity.[23] Another hypothesis suggests that 25(OH)D acts as an antagonist to 1,25-dihydroxy vitamin D3 [1,25(OH)2D3] at the vitamin D receptor (VDR) level, possibly leading to a dysregulated hyperactive immune response against infection in cases of elevated 25(OH)D levels.[9] We think that the answer to the contradictory effects of vitamin D, protective versus predisposing, against UTI may lie in the VDR. The direct effect of 1,25(OH)2D3 is variable, which may be due to the concentration of VDR associated with T lymphocyte activation.[24,25] Genetic and epigenetic factors are known to affect VDR concentration.[26] This may cause differences between populations. While studies focusing on the protective effects of vitamin D are abundant in the literature, research on its adverse effects is limited.

Interestingly, although serum 25(OH)D was significantly higher in the cystitis group than in the control group, there was no significant difference between the APN and control groups. Similar to our study, Yang et al.[7] concluded in their study that patients with lower UTI had higher vitamin D levels than those with APN. Most previous studies have focused on the protective effects of vitamin D, but there is very limited research on its negative effects. We believe that our study is important in this regard. Through our research, we can shed light on the fact that vitamin D is not as harmless as is often assumed to be.

We found lower PTH levels in the UTI and APN groups than in the control group; however, there was no significant difference between the cystitis and control groups in terms of mean PTH levels. This finding does not align with the previous study by Shalaby et al.[27] found higher PTH levels in UTIs in a relatively younger group of patients (0.98±1.15 year). They also found a significantly lower 25(OH)D level in the APN group ($p<0.001$) than in the cystitis group. The results related to PTH, especially in the APN group, may be related with fibroblast growth factor 23 (FGF-23): A lower PTH level in the APN group may have been caused by a high FGF-23 level in these patients. In our opinion, these findings point to a possible FGF-23 effect, which has not been demonstrated previously.

The relatively low levels of phosphate in our APN group support this hypothesis. FGF-23 decreases *PTH* gene expression and secretion from the parathyroid gland and acts directly on renal proximal tubules to induce phosphaturia.[28,29] We believe that infection of the renal parenchyma creates resistance to FGF-23. We speculate that this occurs through epithelial damage in the proximal tubule, followed by a decrease in FGF-23 activity. To our knowledge, no previous study has examined this relationship. When such a study is conducted, high levels of FGF-23 can serve as a marker for APN damage and scar formation.

A positive nitrite test result is specific for UTI, mainly due to urease-positive organisms.[30] Our results indicate a similar rate of nitrite positivity as that reported in previous studies (45% vs. 43.1%).[31] Herein, 25(OH)D levels of patients with positive urinary nitrite were significantly lower than those with negative urinary nitrite levels. We hypothesized that 25(OH)D deficiency could lead to the colonization of bacteria with the capability of producing urease. However, we recommend further investigations in this area to validate this hypothesis. We found a negative correlation between age and 25(OH)D levels, similar to previous studies.[32] Regression analysis showed that high 25(OH)D level is a risk factor for UTI, but not an independent risk factor. Female gender was a risk factor, as mentioned before.

Study Limitations

In terms of limitations, the sample size was relatively small, and this was a cross-sectional study. Second, the gender ratios were not equalized in both the control and study groups although vitamin D levels were not greatly affected by gender and age interval sex ratios. In contrast to many studies on the protective effects of vitamin D against infectious diseases, our findings provide a new perspective, which is a significant strength of our study.

Conclusion

Because there was no correlation between 25(OH)D level and UTI, we concluded that 25(OH)D had no effect on UTI. The results related to PTH, particularly in the APN group, may be related to FGF-23; lower PTH in the APN group may be due to the high FGF-23 levels in these patients. However, we believe that the effects of FGF-23 on APN should be thoroughly investigated. More studies are needed to validate these findings.

Ethics

Ethical Approval: Ethics committee approval of the study was obtained from the Kırıkkale University Non-Interventional Clinical Research Ethics Committee (decision no: 2022.04.25, date: 27.04.2022) the study was conducted according to the principles of the Declaration of Helsinki.

Informed Consent: The authors confirm that informed consent was obtained from the participants or their legal guardians, and all required ethical approvals were obtained for the study.

Footnotes

Author Contributions: Mergan Çetiner G: Surgical and Medical Practices, Concept, Design, Analysis or Interpretation, Literature Search.; Kandur Y: Surgical and Medical Practices, Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.

Conflict of Interest: The authors have no conflicts of interest to declare.

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