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25-Hydroxy Vitamin D Level and Urinary Tract Infection in Children: A Case-Control Study

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Abstract

Background: Urinary tract infection (UTI) is a common bacterial infection in childhood, and vitamin D deficiency is considered a potential risk factor. This study compared serum 25-hydroxyvitamin D levels in children with uncomplicated UTI and healthy children.

Methods: This case-control study of 96 children was conducted in Birjand during 2024–2025. Serum 25-hydroxyvitamin D levels were measured using a blood sample from the arm vein. To diagnose UTI, patients underwent urine analysis (U/A) and urine culture (U/C). Data were collected through a checklist and analyzed using SPSS version 23 with the Mann-Whitney U test, Kruskal-Wallis H test, and Chi-square test at a significance level of <0.05.

Results: Most participants were girls (91.7%) and older than 5 years (62.5%). There was no significant difference between the two groups in age, sex, height, weight, place of residence, or breastfeeding history (p>0.05). The median (Q1–Q3) serum 25-hydroxyvitamin D level was 18.30 (12.90–28.15) ng/ml in the case group and 20.1 (14.925–28.525) ng/ml in the control group; this difference was not significant (p=0.47), and the effect size was very small (r=0.07). There was also no significant difference in the prevalence of vitamin D deficiency between the groups (60.4% vs. 50.0%, p=0.24).

Conclusion: This study found no significant association between serum vitamin D levels and first-episode uncomplicated UTI. The high background prevalence of vitamin D deficiency, restriction to first-episode uncomplicated infections, limited sample size, and very small effect size (r=0.07) may have contributed to the lack of a detectable association. These findings do not support a specific role for vitamin D in first-episode UTI risk in this population; however, the high prevalence of deficiency remains clinically important for general pediatric health monitoring.

Key Words: Children, Deficiency, Urinary tract infection, Vitamin D.

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1- INTRODUCTION

Urinary tract infection (UTI) is one of the most common bacterial infections in childhood and is the second most common bacterial infection in children (1). The risk of UTI before the age of 14 is approximately 1–3% in boys and 3–10% in girls (2). UTI may present as cystitis (lower urinary tract infection) or acute pyelonephritis (upper urinary tract infection). Acute pyelonephritis can lead to serious long-term complications, including renal scarring, reduced kidney function, secondary hypertension, and chronic kidney disease (3, 4). Classic risk factors for UTI in children include vesicoureteral reflux (VUR), anatomical abnormalities of the urinary tract, functional constipation, female sex (due to a shorter urethra), poor personal hygiene, and improper diaper use. In recent years, immunological, nutritional, and environmental factors have also been recognized as contributors to the pathogenesis of UTI (5, 6).

Vitamin D, a steroid hormone, is well known for its role in calcium and phosphorus homeostasis and bone health. In addition, it exerts broad immunomodulatory effects (7, 8). Vitamin D acts through the vitamin D receptor (VDR), which is expressed on most immune cells, including monocytes, macrophages, dendritic cells, and lymphocytes, and thereby regulates both innate and adaptive immunity (9, 10). Activation of the VDR induces the production of antimicrobial peptides such as cathelicidin. These peptides exert direct bactericidal effects by forming pores in bacterial membranes, particularly against Gram-negative bacteria such as Escherichia coli, the most common cause of UTI (11). The epithelium of the bladder and urinary tract also expresses VDR; upon pathogen exposure, vitamin D signaling increases local production of cathelicidin (12, 13). Consequently, vitamin D deficiency may impair local defense mechanisms and increase susceptibility to urinary tract infections.

Several epidemiological studies have reported an inverse association between serum vitamin D levels and the risk of UTI. A systematic review and meta-analysis published in 2023 concluded that serum vitamin D levels were significantly lower in children with UTI than in healthy children and that vitamin D deficiency was associated with an increased risk of UTI. The risk appeared to rise significantly when vitamin D levels fell below 20 ng/ml (14). Proposed mechanisms include reduced cathelicidin production, impaired macrophage function and phagocytosis, and a diminished appropriate inflammatory response against urinary pathogens (15).

Despite growing evidence, some studies have reported conflicting results, which may be attributable to geographical, seasonal, methodological, or population differences. In Iran, the prevalence of vitamin D deficiency among children is very high (up to 70–90% in some regions). This has been attributed to factors such as extensive body covering, limited consumption of vitamin D-rich foods, air pollution, and reduced sun exposure (16, 17). Investigating this relationship in Iranian children can therefore provide valuable information for risk screening and preventive interventions. Correction of vitamin D deficiency is a safe, inexpensive, and accessible approach that may help reduce the risk of UTI (18). Therefore, this study compared serum 25-hydroxyvitamin D levels in children with urinary tract infection (first episode or recurrent) with those of healthy children. The findings may inform public health policies aimed at reducing UTI risk through optimization of vitamin D status.

2- MATERIALS AND METHODS

2-1. Study Type and Statistical Population

This case-control study included all children with UTIs who were hospitalized in the pediatric ward of Vali-e-Asr Hospital (case group) and children referred to the pediatric nephrology clinic of Birjand University of Medical Sciences or other eligible healthy children (control group) from December 21, 2025, to March 15, 2025.

2-2. Inclusion and Exclusion Criteria:

Inclusion criteria for the case group were age 2–14 years and a diagnosis of first-episode UTI based on a positive urine culture (colony count >50 CFU/ml from catheterized specimens or >100,000 CFU/ml from midstream clean-catch specimens). The control group consisted of children referred for elective surgery (e.g., adenotonsillectomy), children attending health centers, or school students whose parents provided informed consent. Controls had no fever or infectious disease in the preceding week and had not used medications known to affect vitamin D metabolism.

Children were excluded if they had primary or secondary immunodeficiency, chronic systemic disease (such as diabetes or autoimmune disease), recurrent UTI, anatomical abnormalities of the urinary tract or kidneys, a history of kidney stones, vesicoureteral reflux or other nephrological disorders, bone metabolic disease or rickets, neural tube defects (neurogenic bladder, cerebral palsy, or spina bifida) based on parental report, malnutrition or severe obesity (growth parameters outside the normal range), or cognitive impairment that would impede participation.

2-3. Sample Size and Sampling Method

The minimum sample size was calculated for comparison of means between two independent groups using the following formula:

$$n = \frac{(z_{1-\alpha/2} + z_{1-\beta})^2 * (\sigma_1^2 + \sigma_2^2)}{(\bar{x}_1 - \bar{x}_2)^2}$$

Assuming $\alpha = 0.05$, $\beta = 0.20$ (power = 80%), and using mean ± SD values of 29.2 ± 12.27 ng/ml (case) and 32.04 ± 15.04 ng/ml (control) from the study by Sherkatolabbasieh et al. (19), the estimated effect size was Cohen's d = 0.21. Based on this calculation, a minimum of 47 children per group was required. This number was increased to 50 participants per group to account for a 5% anticipated dropout rate.

Sampling was performed by convenience sampling until the target sample size was reached. A total of 154 children were initially assessed for eligibility. 58 children were excluded based on the predefined exclusion criteria (previous UTI, urinary tract anomalies, recent antibiotic use, chronic disease, or incomplete data). Finally, 96 children (48 cases and 48 controls) were included in the analysis.

2-4. Data Collection

Data were collected using a checklist such as demographic information, including age, sex, height, weight, and residence (city or village), as well as UTI and vitamin D levels.

2-5. Study Implementation

All procedures were conducted in accordance with the ethical standards of the institutional and national research committees and with the Declaration of Helsinki (1964) and its later amendments. After explanation of the study objectives, written informed consent was obtained from parents or legal guardians. Participants in the case and control groups were matched for age and sex. Urinalysis and urine culture were used to diagnose UTI. All urine tests were performed in the laboratories of Vali-e-Asr Hospital or Imam Reza Hospital. Vitamin D levels

were measured from venous blood samples. Samples from both groups were sent to the same reference laboratory (Imam Reza Hospital). Analyses were performed by a laboratory scientist who was blinded to group allocation.

2-6. Sampling

Urine samples were collected by midstream clean-catch technique using a sterile container after appropriate instruction (for toilet-trained children) or by sterile catheterization (for children younger than 3 years). If analysis could not be performed within 10 minutes of collection, samples were refrigerated. Specimens were cultured on blood agar and EMB media. After 24 hours, microbial growth was evaluated by a laboratory scientist under the supervision of a pathologist. Laboratory results and clinical signs were assessed by pediatricians. For midstream samples, cultures yielding >100,000 CFU/ml in the presence of clinical signs were considered diagnostic of UTI.

Serum 25-hydroxyvitamin D was measured after plasma separation using the LIAISON® 25 OH Vitamin D assay (chemiluminescent immunoassay) in the laboratory of Imam Reza Hospital, Birjand. Vitamin D levels <20 ng/ml were classified as deficiency, 20–30 ng/ml as insufficiency, and ≥30 ng/ml as normal.

2-7. Statistical Analysis

Data were analyzed using SPSS version 23. Normality of continuous variables was assessed with the Kolmogorov–Smirnov test (Table 1). Since some variables showed a non-normal distribution, the Mann-Whitney U test and Kruskal-Wallis H test were used to compare quantitative variables between groups, and the Chi-square test was used for qualitative variables. A p-value <0.05 was considered statistically significant.

Table-1. Results of Kolmogorov-Smirnov test for normality of quantitative variables.

Variable	Statistic	df	p-value
Age (years)	0.113	96	0.004
Height (cm)	0.058	96	0.200
Weight (kg)	0.155	96	0.000
Vitamin D level (ng/ml)	0.140	96	0.000

2-8. Ethical considerations

This study was approved by the ethics committee of Birjand University of Medical Sciences, IR.BUMS.REC.1403.336. Before children's participation, their parents completed the informed consent form. In addition, they were assured that individual information would not be disseminated..

3- RESULTS

Data from 96 participants (48 with UTI and 48 healthy controls) out of the initial 50 in each group were included in the final analysis. The mean age of participants was 6.90 ± 3.08 years (range 2–14 years). The majority of participants (91.7%) were girls, and 62.5% were older than 5 years. There was no significant difference between the groups in age group, sex, or place of residence (p > 0.05). Most children (79.2%) had been exclusively or predominantly breastfed, and the distribution of feeding type did not differ significantly between groups (p = 0.16) (Table 2).

There were no significant differences in demographic and anthropometric characteristics, including age, height, weight, and vitamin D levels, between the case and control groups (p > 0.05). Specifically, the median vitamin D level was slightly lower in the case group [18.30

ng/ml; Interquartile Range (IQR): 12.90–28.15] compared to the control group [20.10 ng/ml; IQR: 14.93–28.53], but this difference was not statistically significant (p = 0.47, r = -0.07). Similarly, no significant differences were observed for age (p = 0.99, r = -0.001), height (p = 0.90, 95% CI of difference: -7.27 to 8.26), and weight (p = 0.94, r = -0.01) (Table 3).

Table-2. Demographic characteristics of participants based on study groups.

Characteristics		Case group (n (%))	Control group (n (%))	Total (n (%))	* p-value
Gender	**Boy**	4 (8.3)	4 (8.3)	8 (8.3)	1.00
	Girl	44 (91.7)	44 (91.7)	88 (91.7)	
Age group	**<5 years**	18 (37.5)	18 (37.5)	36 (37.5)	1.00
	≥5 years	30 (62.5)	30 (62.5)	60 (62.5)	
Resident area	**Rural**	14 (29.2)	10 (20.8)	24 (25.0)	0.24
	Urban	34 (70.8)	38 (79.2)	72 (75.0)	
Nutrition in the neonatal and childhood ages	**Breast feeding**	40 (83.3)	36 (75.0)	76 (79.2)	0.16
	Milk powder	2 (4.2)	1 (2.1)	3 (3.1)	
	Mainly breast feeding	5 (10.4)	4 (8.3)	9 (9.4)	
	Mainly milk powder	1 (2.1)	7 (14.6)	8 (8.3)	

* Chi-square test

Table-3. Comparison of mean age, height, and vitamin D level in study groups.

Variable	Case group	Control group	p-value	Effect size (r)
Age (years) median (Q1-Q3)	6.50 (4.25-9.00)	7.00 (4.00-9.00)	0.99*	-0.001
Height (cm) (mean± SD)	121.58 ± 19.80	121.08 ± 18.50	0.90**	95% CI: -7.27 to 8.26
Weight (kg) median (Q1-Q3)	21.00 (16.00-32.875)	23.00 (15.70-31.50)	0.94*	0.01
Vitamin D level (ng/ml) median (Q1-Q3))	18.30 (12.90-28.15)	20.1 (14.925-28.525)	0.47*	0.07

* Mann-Whitney U test; ** Independent samples T-test

In the case group, the most common clinical symptoms were fever (43.8%), dysuria (41.7%), and urinary frequency (39.6%). Other symptoms included abdominal pain (31.2%), nocturnal enuresis (16.7%), nausea (14.6%), hematuria and urinary incontinence (each 10.4%), vomiting (8.3%), and cloudy urine (6.2%) (Table 4).

Table-4. Frequency of clinical symptoms in the case group.

Symptom	No (n (%))	Yes (n (%))
Fever	27 (56.2)	21 (43.8)
Dysuria	28 (58.3)	20 (41.7)
Urinary frequency	29 (60.4)	19 (39.6)
Abdominal pain	33 (68.8)	15 (31.2)
Hematuria	43 (89.6)	5 (10.4)
Urinary incontinence	43 (89.6)	5 (10.4)
Nausea	41 (85.4)	7 (14.6)
Vomiting	44 (91.7)	4 (8.3)
Cloudy urine	45 (93.8)	3 (6.2)
Enuresis	40 (83.3)	8 (16.7)

Vitamin D deficiency was present in 60.4% of children in the case group and 50.0% of children in the control group. The distribution of vitamin D status (deficiency, insufficiency, normal) did not differ significantly between the two groups (p = 0.24) (Table 5).

Table-5. Distribution of vitamin D levels between study groups.

Vitamin D level	Case group (n (%))	Control group (n (%))	Total (n (%))	*p-value	Effect Size (Cramer's V)
Deficiency (<20 ng/ml)	29 (60.4)	24 (50.0)	53 (55.2)	0.25	0.17
Insufficient (20-30 ng/ml)	8 (16.7)	15 (31.2)	23 (24.0)		
Normal (>30 ng/mL)	11 (22.9)	9 (18.8)	20 (20.8)		

* Chi-square

Subgroup analysis showed that mean vitamin D levels were higher in boys than in girls, in children younger than 5 years than in those aged ≥5 years, and in rural residents than in urban residents. None of these differences reached statistical significance. Mean vitamin D levels also did not differ significantly according to feeding type (p = 0.61) (Tables 6 and 7).

Table-6. Comparison of vitamin D levels based on demographic level in case group.

Variable	Subgroup	Case group			
		No	median (Q1-Q3)	p-value	Effect Size (r)
Gender	Boy	4	22.50 (17.77-36.75)	0.279*	−7916
	Girl	44	17.60 (12.62-28.15)		
Age group	<5	18	18.80 (14.00-26.85)	0.551*	−5100
	≥5	30	16.90 (11.67-32.62)		
Resident area	Rural	14	19.00 (12.67-40)	0.461*	−6190
	Urban	34	16.95 (13.10-26.85)		
Nutrition type in neonatal and childhood ages	Breast feeding	40	15.50 (12.90-32.32)	0.904**	0.00
	Infant formula	2	15.25[a]		
	Mainly breast feeding	5	19.00 (12.445-28.00)		
	Mainly infant formula	1	17.20[a]		

* Mann-Whitney U test, ** Kruskal-Wallis H test, [a] For subgroups with very small sample sizes (n<3), only the median is reported as IQR cannot be reliably calculated.

Note: These subgroup comparisons are exploratory. No correction for multiple testing was performed. Results should be interpreted with caution.

Table-7. Comparison of vitamin D levels based on demographic level in control group.

Variable	Subgroup	Control group			
		No	median (Q1-Q3)	p-value	Effect Size (r)
Gender	Boy	4	28.50 (20.85-31.50)	0.117*	−1795
	Girl	44	19.45 (14.82-27.72)		
Age group	<5	18	25.50 (17.25-30.95)	0.157*	−5738
	≥5	30	18.25 (14.22-27.35)		
Resident area	Rural	10	24.35 (13.75-32.97)	0.509*	−0927
	Urban	38	18.85 (14.97-28.17)		
Nutrition type in neonatal and childhood ages	Breast feeding	36	20.10 (14.85-28.52)	0.338**	0.01
	Infant formula	1	10.10[a]		
	Mainly breast feeding	4	20.70 (12.15-30.45)		
	Mainly infant formula	7	25.80 (18.00-30.00)		

* Mann-Whitney U test, ** Kruskal-Wallis H test, [a] For subgroups with very small sample sizes (n<3), only the median is reported as IQR cannot be reliably calculated.

Note: These subgroup comparisons are exploratory. No correction for multiple testing was performed. Results should be interpreted with caution.

4- DISCUSSION

Although no significant association was found between serum vitamin D levels and first-episode UTI in this case-control study of children aged 2–14 years, these results must be interpreted with caution. Vitamin D deficiency was not identified as an independent significant risk factor for UTI, and mean serum 25-hydroxyvitamin D levels, as well as the frequency distribution of vitamin D status (deficiency, insufficiency, and normal) did not differ significantly between the case and control groups. The very high prevalence of deficiency (>55%) in both groups likely limited the statistical variation needed to detect an association, thereby contextualizing this null finding.

Previous studies have yielded conflicting results regarding the relationship between vitamin D status and urinary tract infection in children. These findings can be broadly categorized into three groups. First, several investigations have reported that vitamin D deficiency is associated with an increased risk of UTI, suggesting a protective effect of higher vitamin D levels. Studies by Piyadah Kouhsar et al. (20), Chidambaram et al. (21), Sadeghzadeh et al. (22), Gan et al. (14), and Yang et al. (23) found that vitamin D deficiency in infants and children was linked to higher odds of UTI, while adequate or high levels appeared to confer protection against infection. Second, some studies have found no significant association. Sherkatolabbasieh et al. (19) reported no meaningful relationship between higher vitamin D levels and the incidence of UTI. Third, a paradoxical finding has also been described. Mahyar et al. (24) observed that serum 25-hydroxyvitamin D levels were significantly higher in children with UTI than in controls. They concluded that 25(OH) D may play a role in the pathogenesis of UTI and suggested that this elevation might represent a physiological response to inflammation or a compensatory mechanism to enhance the immune response (24). Meta-analyses have similarly noted these inconsistencies, particularly in populations with a high background prevalence of vitamin D deficiency (14, 15). Such discrepancies are often attributed to geographical factors, small sample sizes, or socioeconomic differences (14, 15).

Several factors may explain the lack of association observed in the present study. First, Birjand is located at a relatively high latitude, and factors such as limited sun exposure, clothing practices, and air pollution contribute to persistently low vitamin D levels in the population. The high prevalence of vitamin D deficiency (55.2%) and insufficiency (24%) in the overall sample indicates that deficiency is widespread, making it difficult to isolate vitamin D status as a specific risk factor for UTI when both groups are similarly affected. Second, the exclusion of children with recurrent UTI, congenital anomalies of the genitourinary tract, chronic diseases, or immunodeficiency restricted the study to first-episode uncomplicated UTI. Stronger associations have often been reported in recurrent or complicated cases (25). Third, although the sample size met the calculated minimum (48 per group), the large standard deviation in the case group (13.55 ng/ml) reduced statistical power to detect small differences. Methodological differences, including the choice of the 20 ng/ml cut-off, may also contribute to discordance across studies. Some recent guidelines emphasize the avoidance of rigid serum targets and focus instead on adequate supplementation (26).

The proposed biological mechanism centers on the role of vitamin D in innate immunity. Vitamin D receptors are expressed on immune cells and urinary tract epithelial cells; their activation induces the production of antimicrobial peptides such as cathelicidin (LL-37). Cathelicidin is active against E. coli, the

predominant UTI pathogen, and constitutes an important local defense. Vitamin D deficiency may impair this mechanism and thereby increase susceptibility to infection. Muntean et al. reported even lower vitamin D levels in children with recurrent UTI, suggesting a possible role in disease recurrence (25). However, the expected association between vitamin D status and UTI risk may not appear in populations where vitamin D deficiency is extremely common, such as the present study sample (more than 55% deficient). One plausible explanation is a threshold effect. The relationship between serum 25-hydroxyvitamin D levels and immune function is probably not linear across the full range of values. Once vitamin D concentrations drop below a certain critical level, the production of cathelicidin and other key components of innate immunity may already be maximally impaired. At this point, further differences within the deficient range have little biological or statistical meaning. As a result, both children with UTI and healthy controls experience similarly weakened local antimicrobial defenses, and vitamin D status can no longer distinguish between the two groups. This threshold concept helps explain why studies conducted in regions with widespread severe vitamin D deficiency are more likely to report null findings.

In subgroup analyses, vitamin D levels showed no significant association with sex, age, place of residence, or type of infant feeding. This contrasts with the findings of Sadeghzadeh et al. (22) who reported a stronger association in girls, and is likely explained by the uniformly high prevalence of deficiency across all demographic subgroups in the present population.

Socioeconomic status (SES) is another important consideration. In larger families with higher household density and poorer hygiene, the risk of UTI is elevated. Low SES may increase UTI risk through multiple pathways, including inadequate nutrition, limited health knowledge, poor adherence to preventive practices, and reduced access to healthcare. Both vitamin D deficiency and UTI risk are linked to SES; therefore, part of any apparent association (or lack thereof) may be confounded by SES rather than reflecting a direct effect of vitamin D. Multivariate adjustment for SES is necessary to clarify the independent role of vitamin D.

Overall, the present study did not demonstrate a significant association between serum vitamin D levels and UTI. This negative finding is most likely the result of the high background prevalence of vitamin D deficiency, restriction of the study to first-episode uncomplicated UTI, limited sample size, and the influence of unmeasured socioeconomic factors. The conflicting literature suggests that the role of vitamin D may vary according to geographical context, the severity of underlying deficiency, and the type of UTI (first episode versus recurrent). In communities with a very high prevalence of deficiency, vitamin D status may not emerge as a distinguishable risk factor.

Given the well-established biological role of vitamin D in innate immunity and the positive findings from other studies, the possible contribution of vitamin D cannot be entirely dismissed. Future research should include larger sample sizes to increase statistical power, enrollment of children with recurrent and complicated UTI, rigorous control of SES and seasonal factors in multivariate analyses, standardized measurement methods, and interventional trials of vitamin D supplementation to assess causality. Multicenter studies conducted in regions with differing prevalence of vitamin D

deficiency would also help clarify the true role of vitamin D in UTI pathogenesis.

Until a clearer relationship is established, routine recommendation of vitamin D supplementation solely for the prevention of UTI is not fully justified by the present data. Nevertheless, correction of vitamin D deficiency remains important for overall child health.

Strengths of this study include the case-control design with age- and sex-matched controls, which controlled for major confounding factors; precise inclusion and exclusion criteria that increased group homogeneity; use of urine culture as the diagnostic gold standard; and reliable measurement of serum vitamin D in a single reference laboratory with blinded analysis.

Limitations include the lack of control for seasonal variation, current diet, sun exposure, and maternal vitamin D status; the failure to measure or adjust for socioeconomic status, which is a major potential confounder that may have masked a true association or contributed to the observed null findings, thereby precluding firm conclusions; the marked predominance of girls (91.7%); restriction to uncomplicated first-episode UTI; and reliance on parental report for some variables, which may introduce recall bias. Furthermore, seasonal subgroup analysis was not feasible due to the study period covering only part of winter and spring; thus, we acknowledge the potential impact of uncontrolled seasonal variation. Additionally, the convenience sampling method may have introduced selection bias, the direction and magnitude of which could affect the generalizability of the results. Another limitation concerns statistical power: the a priori sample size calculation was based on parametric data from a previous study, whereas serum 25-hydroxyvitamin D levels in our sample were non-normally distributed. The observed difference between groups was very small (effect size r = 0.07) and not statistically significant. Although this suggests that any true difference is clinically negligible, the possibility that the study was underpowered to detect very small effects cannot be excluded. These factors limit the generalizability of the findings.

5- CONCLUSION

Serum 25-hydroxyvitamin D levels did not differ significantly between children with uncomplicated UTI and healthy controls in this study. The high prevalence of vitamin D deficiency in both groups (>50%) highlights the importance of routine screening and maintaining adequate vitamin D status for general child health. The limited sample size and restriction to first-episode uncomplicated infections may have contributed to the lack of a detectable association. While these findings do not support routine vitamin D supplementation solely for UTI prevention, the high prevalence of deficiency underscores the importance of maintaining adequate vitamin D status for general health. Future larger multicenter studies that include more diverse populations—particularly children with recurrent or complicated UTI—are needed to better clarify the potential role of vitamin D in UTI prevention.

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