

Original Article

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Association between vitamin D levels and urinary tract infections

Abstract

Background: Urinary tract infections (UTIs) are among the most prevalent infectious conditions, particularly in children. Vitamin D deficiency has been implicated in various infections, including UTIs. This study aimed to evaluate the association between serum vitamin D levels and UTIs in children at Amir Kola Children's Hospital.

Methods: This case-control study was conducted on 120 children, aged 2–18 years, diagnosed with UTIs and referred to Amir Kola Children's Hospital, Babol, Iran. Participants were divided into two groups: 60 UTI cases and 60 healthy controls. Peripheral blood samples were collected for vitamin D analysis, measured via ELISA assay. Statistical analysis was performed using SPSS Version 26.

Results: The mean serum vitamin D level was 17.70 ± 8.35 ng/mL in the case group and 37.91 ± 12.18 ng/mL in the control group, revealing a significant reduction in vitamin D levels among UTI patients ($P < 0.001$). Additionally, pyelonephritis was associated with severe vitamin D deficiency ($P = 0.02$). Female children aged 3–5 years exhibited a higher risk of vitamin D deficiency, although age and sex did not significantly influence vitamin D levels overall. Vitamin D status was not correlated with hospitalization duration.

Conclusion: Given its immunoprotective role, vitamin D screening and supplementation may serve as a preventive strategy against UTIs and contribute to improved clinical outcomes in affected children.

Keywords: Vitamin D, UTI, Urinary tract infections.

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Bowel Syndrome Vitamin D, specifically its active form 1,25-dihydroxyvitamin D ($1,25(\text{OH})_2\text{D}_3$), is a fat-soluble vitamin essential for various metabolic pathways (1). It can be obtained through dietary intake, supplementation, or exposure to sunlight, where ultraviolet (UV) radiation catalyzes the conversion of 7-dehydrocholesterol to pre-vitamin D₃ via photochemical and thermal reactions (2). The primary role of vitamin D is well-established in bone health and the regulation of calcium and phosphorus homeostasis. However, its significance extends beyond skeletal functions, influencing the overall health of multiple organs that express vitamin D receptors (VDRs). Research has linked vitamin D deficiency in preterm infants to respiratory infections, hypocalcemic seizures, and growth disorders such as rickets (3). In addition to its skeletal benefits, vitamin D serves as a critical modulator of immune responses, contributing to both the prevention and progression of various acute and chronic diseases. Recent evidence indicates that vitamin D has systemic effects on pathogens, influencing both innate and adaptive immunity. A deficiency in vitamin D is associated with lymphocyte and neutrophil dysfunction, primarily due to hypocalcemia, highlighting its integral role in immune regulation (4). Vitamin D exerts its biological effects by binding to VDRs, which are expressed on diverse immune cells.



Additionally, immune cells possess vitamin D-activating enzymes, enabling the local conversion of inactive vitamin D to its active form. The active form subsequently binds to VDRs and regulates DNA transcription, stimulating the expression of antimicrobial peptides (AMPs) such as cathelicidin and defensin (5). By binding to the vitamin D-responsive element (VDRE) within the human cathelicidin antimicrobial peptide (CAMP) promoter, vitamin D enhances CAMP expression, thereby strengthening innate immune defenses (4). Studies have also demonstrated that vitamin D suppresses pro-inflammatory cytokine production, including interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α), while simultaneously promoting anti-inflammatory cytokines such as interleukin-10 (IL-10). These regulatory actions suggest that vitamin D plays a pivotal role in modulating inflammatory responses, particularly during infections such as urinary tract infections (UTIs) (6).

UTIs are among the most common infectious diseases, particularly in infants during the first year of life. *Escherichia coli* (*E. coli*) is the predominant pathogen, responsible for approximately 90% of UTIs in girls and 80% in boys. Other common uropathogens include *Klebsiella*, *Proteus*, and *Enterobacter* species (7). Several host defense mechanisms, such as Tamm–Horsfall protein, lactoferrin, lipocalin, white blood cells, and the innate immune system, contribute to combating these infections. During UTIs, epithelial cells in the urinary tract are stimulated to produce and secrete cathelicidin, which may play a role in preventing bacterial colonization and invasion (6). This study aimed to investigate the association between serum vitamin D levels and UTIs in children referred to Amir Kola Children's Hospital in 2024.

Methods

Study design and population: This case-control study was conducted at Amir Kola Children's Hospital in Babol, Iran, between March and May 2024. A total of 120 children aged 2 to 18 years were enrolled and equally divided into two groups: 60 cases and 60 controls. The case group comprised children with a first-time UTI, including both cystitis and pyelonephritis, confirmed by clinical symptoms and a positive urine culture ($\geq 10^5$ CFU/mL). Cases were recruited consecutively from eligible patients referred to the hospital. The control group consisted of healthy children of similar age and sex, presenting for routine check-ups or minor non-infectious complaints, with no history of UTI or recent infections. Controls were frequency-matched to cases based on age (± 1 year) and sex and were enrolled immediately

after each case to ensure a 1:1 case-control ratio within each stratum.

Inclusion/exclusion criteria: The inclusion criteria were defined as follows:

- *Control group:* Children without infections, presenting no apparent illness.
 - *Case group:* Children presenting with a first-time UTI, including cystitis and pyelonephritis, as confirmed by clinical symptoms and a positive urine culture demonstrating colony counts exceeding 10^5 CFU/mL (3) no underlying chronic illness.
- Exclusion criteria (for both groups) included:
- Children with other febrile illnesses.
 - Children on medication use (particularly those affecting vitamin D metabolism or immune function) or vitamin D supplement use, to prevent exogenous influence on vitamin D status.
 - Children with malabsorption syndrome (e.g., celiac disease, inflammatory bowel disease, cystic fibrosis), or overweight status.
 - Patients with a history of UTI risk factors, such as urinary reflux or congenital urinary system disorders.

Data/sample collection and laboratory analysis: Demographic data (age, sex), clinical findings, and laboratory results were recorded. For children under 3 years of age, urine samples were obtained using the urine bag method, while midstream clean-catch collection was employed for older children. Laboratory assessments included: urinalysis (U/A), urine culture (U/C), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP).

Vitamin D measurement: After obtaining 5 mL of venous blood via standard pediatric antecubital venipuncture into BD Vacutainer serum-separating tubes (SST), samples were stored upright at room temperature and processed within 30 minutes. Tubes were centrifuged at $2,000 \times g$ for 10 minutes at 4 °C. Serum was aliquoted into 0.5 mL polypropylene cryovials (Eppendorf) under aseptic conditions, with no more than three freeze–thaw cycles permitted; aliquots were stored at – 80 °C in a monitored ultra-low freezer. Serum 25(OH)D levels were assessed using the ELISA method (25-OH Vitamin D ELISA Kit, Ideal Tashkhis Atieh, Iran) following the manufacturer's protocol. Results were expressed in ng/mL. Serum 25(OH)D levels were categorized as deficient (<20 ng/mL), insufficient (20–30 ng/mL), or sufficient (>30 ng/mL) based on Endocrine Society guidelines (5). This threshold accounts for the widely accepted cutoff for deficiency. All assays were done at the same laboratory under controlled conditions.

Statistical analysis: Collected data were analyzed using SPSS Version 26. Descriptive statistics, including

means±standard deviations for quantitative variables and frequencies and percentages for qualitative variables, were presented. To evaluate relationships between variables, t-tests and chi-square tests were used for statistical comparisons. Multivariate logistic regression analysis was employed to assess influencing factors. A $p < 0.05$ (two-sided) was considered statistically significant.

Results

A total of 120 children meeting the inclusion criteria were enrolled in this study, with 60 participants assigned to the case group (UTI) and 60 to the control group. The overall mean age of the study population was 7.76 ± 3.37 years. The control group exhibited a mean age of 8.73 ± 3.54 years, while the case group showed a slightly younger mean age of 6.62 ± 2.84 years ($p > 0.05$). The mean value of serum vitamin D in the case group was 17.70 ± 8.35 ng/mL, which was significantly lower than in the control group, where the mean was 37.91 ± 12.18 ng/mL. The results of statistical analysis confirmed a significant reduction in the mean serum vitamin D level in the case group relative to the control group ($P < 0.001$) (figure 1). Based on the established vitamin D levels, the study population was categorized into three groups: 40.8% of participants had serum levels above 30 ng/mL (sufficient group), 21.7% had levels between 21 and 29 ng/mL (insufficient group), and 37.5% had levels below 20 ng/mL (deficient group).

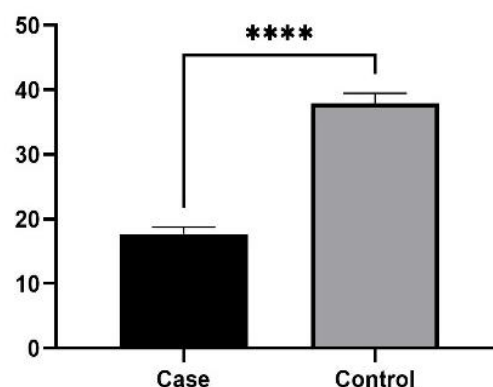


Figure 1. The serum vitamin D levels in cases and controls

Further analysis grouped participants into two broader categories based on their vitamin D status: Sufficient/normal (≥ 30 ng/mL) and insufficient/deficient (< 30 ng/mL). A statistically significant difference was observed between these two groups across the case and control populations ($p < 0.001$). Table 1 presents the assessment of vitamin D levels in control and patient groups, stratified by age and sex. As shown in table 2, no significant correlation was found between the number of days hospitalized and vitamin D levels ($P = 0.31$). Furthermore, a significant association was identified between the type of infection (cystitis or pyelonephritis) and vitamin D status ($P = 0.02$).

Table 1. Assessment of vitamin D levels in control and patient groups, stratified by age and sex

Table 1. Assessment of Vitamin D levels in control and patient groups, stratified by age and sex						
Variable	Total		Vit D level			P-value
			Deficient	Insufficient	Sufficient	
Age						
3-5 years	42 (35%)	Control	0 (0%)	3 (17.6%)	14 (82.4%)	<0.001
		Case	18 (72%)	6 (24%)	1 (4%)	
5-10 years	51 (42.5%)	Control	1 (4.3%)	5 (27.7%)	17 (73.9%)	<0.001
		Case	21 (75%)	4 (14.3%)	3 (10.7%)	
>10 years	27 (22.5%)	Control	2 (10%)	4 (20%)	14 (70%)	0.006
		Case	0 (0%)	4 (57.1%)	3 (42.9%)	
Sex						
Boy	26 (21.7%)	Control	1 (5.3%)	2 (10.5%)	16 (84.2%)	<0.001
		Case	5 (71.4%)	2 (28.6%)	0 (0%)	
Girl	94 (78.3%)	Control	2 (4.9%)	10 (24.4%)	29 (70.7%)	<0.001
		Case	37 (67.9%)	12 (22.6%)	4 (7.5%)	

Vit D: Vitamin D

Table 2. The relationship between clinical parameters and vitamin D levels

Variable	Vit D level			P-value
	Deficient	Insufficient	Sufficient	
Hospitalization Duration				
1-7 days	26 (66.7%)	9 (23.1%)	4 (10.3%)	0.31
>7 days	16 (76.2%)	5 (23.8%)	0 (0%)	
Infection Type				
Pyelonephritis	25 (86.2%)	4 (13.8%)	0 (0%)	0.02
Cystitis	17 (54.8%)	10 (32.3%)	4 (12.9%)	

Vit D: Vitamin D

The findings, summarized in table 3, revealed that in the multivariate logistic regression analysis, neither age nor gender significantly influenced vitamin D levels as independent predictors of UTI risk. Additionally, figure 2 illustrates the Receiver Operating Characteristic (ROC) curve of vitamin D levels in cases.

The optimal cut-off point for predicting UTI was determined at 20.15 ng/mL, demonstrating a sensitivity of

70% and a specificity of 98.33%. The Youden index was 0.68, and the likelihood ratio was 42. The area under the curve (AUC) was 0.98. These findings consistently demonstrated that vitamin D levels in children with UTIs were markedly lower than in their healthy counterparts. This trend was observed across all age groups and genders. Both cystitis and pyelonephritis were associated with diminished vitamin D levels.

Table 3. Multivariate analysis of variables predicting vitamin D levels in children.

Variable	P-value	Odds Ratio	Confidence interval 95%	
			Upper bound	Lower bound
Age				
3-5 years	0.96	1.028	3.554	0.298
5-10 years	0.40	1.818	7.123	0.464
>10 years	0.62	1	-	-
Sex				
Boy/Girl	0.37	1.740	5.899	0.513

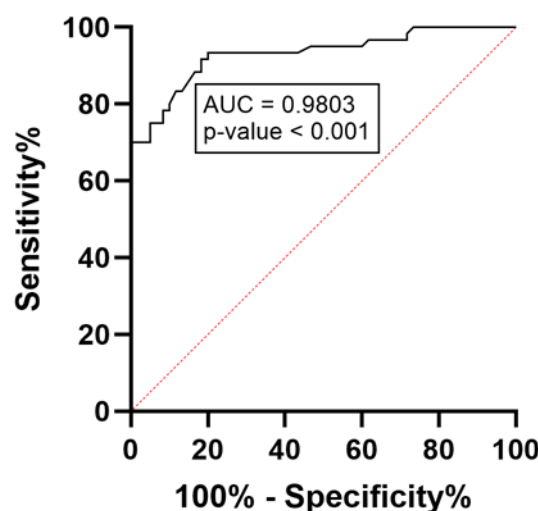


Figure 2. ROC Curve of Vitamin D

Discussion

This study investigated the association between serum vitamin D levels and UTIs in children, a topic of considerable importance given the high prevalence of UTIs in the pediatric population and the potential for serious sequelae such as renal scarring (8, 9). The novelty of this research lies in its specific focus on a pediatric cohort within our regional context, providing a detailed vitamin D categorization, and employing ROC curve analysis to identify a clinically relevant cut-off, while also attempting to understand its implications in the broader landscape of existing literature.

Our primary finding revealed a highly significant reduction in mean serum vitamin D levels in children with UTIs (17.70 ± 8.35 ng/mL) compared to healthy controls (37.91 ± 12.18 ng/mL; $p < 0.001$). This robust association is a cornerstone of our results and underscores the potential interplay between vitamin D status and UTI susceptibility. While this case-control design demonstrates a strong statistical link, it is crucial to acknowledge that it does not definitively establish causality. The observed lower vitamin D levels in the UTI group could imply that deficiency predisposes children to infection. Conversely, it is also plausible that an acute infectious and inflammatory process like a UTI might lead to a transient decrease in circulating vitamin D levels, potentially due to increased utilization by the immune system or altered metabolism during illness, as vitamin D has been suggested to act as a negative acute phase reactant in some contexts (10). Further longitudinal studies are essential to delineate this temporal relationship.

The categorization of vitamin D levels in our study (deficient <20 ng/mL, insufficient 20–30 ng/mL, sufficient >30 ng/mL) aligns with widely accepted Endocrine Society guidelines (11). The clinical significance of these cutoffs is substantial; levels below 20 ng/mL, and even below 30 ng/mL, are broadly associated with suboptimal immune function and increased risk for various infectious and inflammatory conditions. Our ROC curve analysis further refined this by identifying an optimal cut-off point of 20.15 ng/mL for predicting UTI with high specificity (98.33%) and good sensitivity (70%). This specific threshold suggests that maintaining serum vitamin D levels above this point might be particularly crucial for minimizing UTI risk in children. Clinically, this cut-off could guide screening practices or inform decisions regarding supplementation in at-risk pediatric populations, pending validation from interventional trials. Our findings are largely consistent with a substantial body of previous research. Numerous studies, including those by Shalaby et al. (4), Yang et al. (7), Tekin et al. (12), Sadeghzadeh et al. (13), Muntean and Sășăran

(14), and Qadir et al. (15), all reported a significant association between lower vitamin D levels and UTIs in children. The comprehensive meta-analyses by Deng et al. (6) and Gan et al. (5) further consolidate this evidence, indicating a 2.8 to 3-fold increased risk of UTI with vitamin D insufficiency/deficiency. Our results, therefore, add to this consistent pattern observed across diverse pediatric populations. However, some inconsistencies in the literature warrant discussion. While most studies, including ours, find lower vitamin D in UTI cases, Mahyar et al. (16) reported higher mean serum 25(OH)D in their UTI group. They hypothesized this could be due to infection-induced alterations in vitamin D metabolism or that, paradoxically, vitamin D supplementation might sometimes increase UTI risk, a notion also raised by Katikaneni et al. (17) concerning formula-fed infants. This highlights the complexity and suggests that the vitamin D-UTI relationship might be modulated by other factors like baseline vitamin D status, genetic predispositions (e.g., VDR polymorphisms), or the nature of vitamin D intervention if any (16, 18). Studies by Sherkatolabbasieh et al. (19), Noorbakhsh et al. (20) and the initially reported findings of Babar et al. (later withdrawn) (21) found no significant correlation, further emphasizing the need to consider methodological differences, population characteristics, and sample sizes when comparing studies.

The lack of a significant correlation between hospitalization duration and vitamin D levels in our study ($P=0.311$) is an interesting null finding. This might suggest that while vitamin D status is associated with susceptibility to UTI and perhaps the initial severity (as seen with pyelonephritis), once a child is hospitalized and receives standard medical care (e.g., antibiotics, hydration), the duration of stay may be more heavily influenced by other factors such as pathogen virulence, antibiotic efficacy, underlying (undiagnosed) comorbidities, or healthcare system variables, rather than the baseline vitamin D level alone. The significant association between the type of infection (cystitis vs. pyelonephritis) and vitamin D status ($P=0.018$), with pyelonephritis cases exhibiting more pronounced deficiency, is a key finding. Pyelonephritis, involving upper urinary tract and renal parenchyma, is a more severe and invasive infection (22). This could imply that a more profound vitamin D deficiency creates a greater immunological vulnerability, allowing pathogens to ascend and establish a more serious infection. Alternatively, the more intense systemic inflammatory response associated with pyelonephritis might lead to greater consumption or altered metabolism of vitamin D (13, 23-25). In addition, vitamin D-deficient mice exhibited more invasive urinary

tract infections, with increased bacterial spread to the kidneys, indicating a higher risk of pyelonephritis rather than localized cystitis. The deficiency led to greater bacterial dissemination, more intracellular bacterial communities, and a dysregulated immune response, highlighting vitamin D's role in urothelial defense (26). This finding warrants further exploration into whether vitamin D status could serve as a biomarker for predicting UTI severity or risk of upper tract involvement.

Our multivariate logistic regression analysis indicated that age and gender did not significantly influence vitamin D levels as independent predictors of UTI risk in the context of vitamin D status within our cohort. Chidambaram et al. (3) also reported that the mean serum vitamin D levels in UTI patients were significantly lower than in controls. However, their study also identified female sex and preterm birth as potential risk factors for UTI, whereas our findings did not support a significant relationship between age or sex as independent risk factors. These discrepancies may arise from differences in age categorization scales and variations in the age ranges examined. This is noteworthy. While UTIs are generally more common in girls after infancy (27), and vitamin D levels can vary with age due to diet, growth, and sun exposure (28), our model suggests that after accounting for vitamin D levels, these demographic factors did not add independent predictive power for UTI in this particular dataset. This could be because the impact of low vitamin D on immune susceptibility is a more dominant factor than subtle age/sex variations in this context, or perhaps our sample size lacked the power to detect smaller independent effects of age and gender once vitamin D was in the model. Other studies, such as Sadeghzadeh et al. (13) have emphasized a higher UTI risk in females related to vitamin D deficiency, suggesting population-specific interactions may exist. The biological mechanisms linking vitamin D deficiency to increased UTI susceptibility are becoming clearer and are critical to understanding the clinical implications of our findings. Vitamin D's role extends far beyond calcium homeostasis:

Modulation of innate immunity: Vitamin D is essential for the optimal functioning of the innate immune system. It upregulates the expression of AMPs like cathelicidin (LL-37) and β -defensins in urothelial cells and immune cells. These AMPs have direct bactericidal activity against uropathogens (29-32). Hacıhamdioğlu et al. (33) found higher urine cathelicidin in UTI children with sufficient vitamin D, implying impaired local defense in deficient states.

Enhancement of epithelial barrier function: Vitamin D contributes to maintaining the integrity of epithelial

barriers, including the urothelium (30). Low vitamin D levels can compromise urothelial barrier integrity by reducing the expression of tight junction proteins, such as occludin and claudin-14, which are essential for maintaining epithelial cohesion (32).

Regulation of immune cell activity: VDRs are present on macrophages, dendritic cells, and T-lymphocytes. Vitamin D can enhance macrophage phagocytosis and bactericidal capacity. It also modulates adaptive immunity, often promoting a shift from pro-inflammatory Th1 responses towards anti-inflammatory or regulatory T-cell (Treg) responses, which can be crucial in controlling infection-induced damage (29).

Control of inflammation: Vitamin D can suppress the production of pro-inflammatory cytokines like IL-6 and TNF- α (34), potentially limiting excessive inflammation and tissue damage during a UTI (6). A deficiency in vitamin D could, therefore, lead to reduced AMP production, compromised urothelial barrier integrity, dysregulated macrophage and T-cell function, and an imbalanced inflammatory response, all of which could heighten susceptibility to UTI development and progression. The clinical implications of our findings are noteworthy. The observed association and the identified ROC cut-off point suggest that assessing vitamin D status could be a valuable component in evaluating children at risk for UTIs or those with established infections. If low vitamin D levels are found, particularly below 20 ng/mL, it raises the question of whether supplementation could serve as a preventive or adjunctive therapeutic strategy. However, it is crucial to underscore that our observational study cannot establish this causality. While compelling, the leap to recommending widespread supplementation for UTI prevention based solely on these findings is premature without robust evidence from randomized controlled trials (RCTs). The study by Merrikhi et al. (35), for instance, found that 1000 IU/day of vitamin D did not significantly prevent recurrent UTIs, suggesting dose or duration might be critical, or that other factors play a more dominant role in recurrence.

This study has several limitations. First, its case-control design precludes definitive causal inference. Second, being a single-center study, its findings may not be generalizable to other populations with different genetic backgrounds, dietary habits, sun exposure patterns, or socioeconomic status, factors which were not exhaustively detailed in our data collection. While we excluded children on supplements, pre-existing subclinical differences in these unmeasured variables could exist. We also did not assess VDR polymorphisms which can influence UTI susceptibility. Measurement of AMPs or specific immune

cell functions in relation to vitamin D status would have provided more direct mechanistic insights. Future research should prioritize well-designed, prospective longitudinal studies to establish the temporal relationship between vitamin D status and UTI onset. Crucially, large-scale, multi-center RCTs are needed to definitively evaluate the efficacy of vitamin D supplementation (testing various doses and durations) in both the primary prevention of UTIs and as an adjunctive therapy to improve outcomes and reduce recurrence rates in children. Such trials should also investigate different pediatric age groups, stratify by baseline vitamin D status, and ideally, incorporate assessment of genetic factors like VDR polymorphisms and mechanistic markers such as AMP levels. In conclusion, this study provides strong observational evidence that lower serum vitamin D levels are significantly associated with an increased likelihood of UTIs in children, with a level below 20.15 ng/mL appearing particularly indicative of risk. Pyelonephritis was linked to more severe deficiency. While this association does not prove causality, the known immunomodulatory roles of vitamin D offer plausible biological mechanisms for this link. These findings underscore the potential importance of maintaining vitamin D sufficiency for pediatric urinary tract health. However, further rigorous research, especially RCTs, is imperative to confirm these observations, elucidate the precise mechanisms, and establish whether vitamin D supplementation can be a safe and effective strategy for the prevention or treatment of UTIs in children.

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Conflict of interests: The authors declare that there is no conflict of interests. All authors mentioned have approved the manuscript. Moreover, the authors have no relevant financial or non-financial interests to disclose.

Authors' contribution: Study concept and design were performed, Sahar Sadr Moharerpour, Masoumeh Piyadah Kouhsar, Morteza Alijanpour. Analysis and interpretation of data were performed by, Mohammad Pournasrullah, Hemat Gholinia. Drafting of the manuscript was performed by Masoumeh Piyadah Kouhsar and, Sahar Sadr Moharerpour.

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