Association between vitamin D and urinary tract infection in children

Abolfazl Mahyar, MD1, Parviz Ayazi, MD1, Sara Safari, MD1, Reza Dalirani, MD2, Amir Javadi, MSc3, Shiva Esmaeily, MSc3
1Qazvin Children Hospital, Qazvin University of Medical Sciences, Qazvin, 2Mofid Children Hospital, Pediatric Nephrology Department, Shahid Beheshti University of Medical Sciences, Tehran, 3Statistic Department, Qazvin University of Medical Sciences, Qazvin, Iran

Purpose: The present study aimed to determine the relationship between serum 25-hydroxyvitamin D (25(OH)D) level and Urinary tract infections (UTIs) in children.
Methods: In this case-control study, 70 children with UTI (case group) were compared with 70 healthy children (control group) in terms of serum 25(OH)D levels. The children were between 1 month and 12 years of age. Serum 25(OH)D levels were measured using enzyme-linked immunosorbent assay (ELISA). The results were analyzed and compared between both groups.
Results: Among 70 children with UTI (case group), 5 children (7.2%) were male and 65 (92.8%) were female. Among the healthy children (control group), 9 (12.8%) and 61 children (87.2%) were male and female, respectively ($P=0.39$). The mean±standard deviation of age in the case and control groups were 53.2±35.6 and 36.1±60.2 months, respectively ($P=0.24$). The mean level of serum 25(OH)D in the case group was significantly higher than that of the control group (20.4±8.6 ng/mL vs. 16.9±7.4 ng/mL, $P=0.01$)
Conclusion: This study showed that there was a relationship between serum 25(OH)D levels and UTI in children. It seems that 25(OH)D plays a role in the pathogenesis of UTI.

Key words: 25-Hydroxyvitamin D, Urinary tract infection, Child

Introduction

Urinary tract infection (UTI) is one of the most common infectious diseases in children. The prevalence of the disease in boys and girls is 1% and 5.3%, respectively. The disease appears in 3 forms of cystitis, acute pyelonephritis, and asymptomatic bacteriuria. The most severe form of disease is acute pyelonephritis that is caused by invasion of pathogenic microorganisms to renal parenchyma. Although various microorganisms can cause UTI, Escherichia coli is the most common cause of disease in 80%–90% of cases.1-3 Delayed diagnosis and treatment will lead to severe diseases such as renal scarring, hypertension and chronic renal failure.4-7 Several risk factors such as vesicoureteral reflux predispose the patients for UTI.8 The question has been raised whether vitamin D is a risk factor for UTI. There are some limited and contradictory studies in this field.9-11 Some believe that vitamin D deficiency predisposes the patients to have UTI and administration of vitamin D can prevent UTI.9,10 In contrast, Katikaneni et al.11 believes that administration of vitamin D supplements increases the risk of UTI.

Vitamin D is a secosteroid hormone which is mainly produced in the skin after exposure to ultraviolet radiation.12 Studies show that vitamin D, in addition to calcium–phosphate homeostasis and bone metabolism, has multiple extra skeletal proprieties.13 Immunomodulatory and antibacterial properties are 2 extra skeletal effects of vitamin D.14,15 Several studies have been conducted on the role of vitamin D in some infectious diseases including tuberculosis, lower respiratory tract infections (such as pneumonia), and upper respiratory
tract infections (such as tonsillitis and otitis). Considering the importance of recognizing the risk factors associated with UTI and preventing serious complications, the present study was performed to determine the relationship between serum 25-hydroxyvitamin D (25(OH)D) levels and UTI in children.

Materials and methods

1. Study participants

In this case-control study, 70 children with UTI (case group) were compared with 70 healthy children (control group) in terms of serum 25(OH)D levels. The study was conducted in Qazvin Children Hospital affiliated to Qazvin University of Medical Sciences. This hospital is the only pediatric referral hospital in Qazvin province.

2. Study design

The age of children was between 1 month and 12 years old. Inclusion criteria for case group included: The first UTI, existence of symptoms for UTI such as fever, poor feeding, poor appetite, vomiting, malaise, abdominal and flank pain, dysuria, frequency; abnormal urinalysis such as pyuria (more than 5 leukocytes per microscopic field) and positive nitrite test; positive urine culture (more than 10⁵ colony forming unit [CFU]/mL of a single pathogen in a midstream urine sample or clean catch method or 10⁴ CFU/mL of a single pathogen via urinary catheterization, or presence of any number of colonies of an organism in urine culture taken by suprapubic method) and absence of known risk factors (such as vesicoureteral reflux, abnormalities of the urinary system including hydronephrosis, urethral stricture into bladder, neurogenic bladder, posterior urethral valves and labial adhesion) and circumcision of boys. Children with more than once attack of UTI, received antibiotics before admission, underlying disease, and well-known risk factors for UTI were excluded. Group matching was applied to select 70 healthy children (control group) who presented to the hospital for vaccination or elective surgeries such as tonsillectomy. Consecutive sampling continued until the desired sample size was reached. The 2 groups were matched for age, sex, height, weight, head circumference (up to 3 years), adequate nutrition during breastfeeding (at least for 6 months), social and economic situation (the ratio of family members to bedrooms was used as a measure of socioeconomic situation), average income and family size. Both groups lived in Qazvin and all children were under control and care of health centers until 2 years and received vitamin D regularly. Ultrasonography and voiding cystourethrogram were performed to rule out abnormalities of the urinary system and vesicoureteral reflux. Labial adhesion was excluded by clinical examination. Dimercaptosuccinic acid (DMSA) renal scan (as the gold standard) was used to distinguish between acute lower UTI (cystitis) and acute pyelonephritis. Acute pyelonephritis was confirmed by observing focal or diffuse areas of diminished uptake associated with preservation of renal cortical outline in DMSA renal scan.

After approval of the plan by the Research Ethics Committee of the University the plan was first introduced to parents. After obtaining parental written consent form and verbal consent from older children, 3 mL of blood was taken from peripheral vein to measure serum 25(OH)D. After centrifugation, sera were isolated from samples and were kept at 20°C until performing the tests. Serum 25(OH)D test was performed based on the ELISA method using EUROIMMUN kit (No. EQ 6411-9601, Mediziische Labordiagnostika AG Company, Lübeck, Germany). Based on serum 25(OH)D levels, children were divided into 5 groups: less than 5 ng/mL (very severe vitamin D deficiency), 5–10 ng/mL (severe vitamin D deficiency), 10–20 ng/mL (vitamin D deficiency), 20–30 ng/mL (vitamin D level lower than the optimal level) and 30–50 ng/mL (optimal vitamin D level). The tests were performed in Pars laboratory in Qazvin.

3. Statistics

The results were presented in the form of statistical tables and numeric indicators. Chi-square test, t test and Mann-Whitney U test were applied to analyze the obtained data. All analyses were performed with SPSS ver. 16.0 (SPSS Inc., Chicago, IL, USA). P value of <0.05 was considered statistically significant.

4. Ethics statement

The ethics committee of the Research Department in the Qazvin University of Medical Sciences Qazvin, Iran approved the study (project number: 296). All parents were provided information regarding the research method in simple language. The children were included in the study after their parents agreed and signed the informed consent form.

Results

Among 70 children with UTI (case group), 5 children (7.2%) were male and 65 (92.8%) were female. In healthy children (control group), 9 (12.8%) and 61 children (87.2%) were male and female,

| Table 1. Comparison of variables between case and control groups |
|---------------------------------|----------------|---------------|------------|
| Variable                        | Case group     | Control group | P value    |
| Sex (male:female)               | 5:65           | 9:61          | 0.39*      |
| Age (mo)                        | 53.2±35.6      | 62.2±36.1     | 0.24†      |
| Weight (kg)                     | 13±8.6         | 15.2±9.2      | 0.07‡      |
| Height (cm)                     | 99.3±22.3      | 102.3±22.3    | 0.42†      |
| Head circumference (cm)         | 46±2.6         | 46±3          | 0.82†      |
| Breast feeding (mo)             | 18.5 (13)      | 22.5 (8)      | 0.09‡      |

Values are presented as number, mean±standard deviation, median (interquartile range).

*Chi-square test, †t test, ‡Mann-Whitney U test.
Mahyar A, et al. * Vitamin D and urinary tract infection

| Serum 25(OH)D (ng/mL) | Case group | Control group | P value |
|-----------------------|------------|---------------|---------|
| <5                    | 2 (2.9)    | 2 (2.9)       | 1.00    |
| 5–10                  | 6 (8.6)    | 14 (20)       | 0.07    |
| 10–20                 | 29 (41.4)  | 32 (45.8)     | 0.70    |
| 20–30                 | 20 (28.6)  | 19 (27.1)     | 0.87    |
| >30                   | 13 (18.5)  | 3 (4.2)       | 0.01    |
| Total                 | 70 (100)   | 70 (100)      |         |

Values are presented as number (%). Chi-square test.

Table 4. Comparison of serum 25-hydroxyvitamin D (25(OH)D) level in acute pyelonephritis and cystitis groups

| Group                  | Serum 25(OH)D level (ng/mL) | P value |
|------------------------|-----------------------------|---------|
| Acute pyelonephritis (n=9) | 23.9±10.6                    | 0.25    |
| Cystitis (n=61)         | 20±8.3                       |         |

Values are presented as mean±standard deviation. t-test.

Discussion

The present study revealed that there is a correlation between serum 25(OH)D levels and UTI in children. There are limited studies on the role of vitamin D in children with UTI. The study conducted by of Nseir et al.2,26 on 93 patients with a history of recurrent UTI has shown that serum 25(OH)D levels in patients with recurrent UTI are significantly lower than the control group. These authors indicated that vitamin D deficiency is a risk factor for recurrent UTI. Nielsen et al.21 study on 50 patients with UTI and 53 healthy people (control group) showed that there is a significant relationship between urine cathelicidin (LL-37) level and incidence of UTI. The authors concluded that the concentration of LL-37 in the urinary tract system and low susceptibility to LL-37 can raise the probability of UTI in a complex interaction between host and pathogen attributes. The study conducted by Kwon et al.46 on 410 patients showed that vitamin D deficiency is an independent risk factor for UTI after kidney transplantation. They concluded that, physician can predict the incidence of infectious complications after kidney transplantation by measuring serum 25(OH)D level. They suggested that the antibacterial role of vitamin D is associated with the production of antibacterial peptides such as cathelicidin and modulate, β-defensin production, and suppressing inflammation.46 Also, the study performed by Tekin et al.26 on 82 children with 2–18 years with first UTI showed that vitamin D deficiency is a risk factor for UTI. In addition, the Yang et al.23 study performed by Kwon et al.23 on 132 infants between 1 to 12 months with first UTI and 10 healthy infants (control group) showed that serum 25(OH)D levels in the case group were significantly lower than the control group. These authors indicated that the incidence of UTI in the group receiving vitamin D supplementation was less than the other group. They concluded that the risk of UTI is high in children with vitamin D deficiency. Another study conducted on 36 children with UTI and 38 healthy children indicated that children with vitamin D deficiency are not able to increase their urine cathelicidin level during UTI. They concluded that vitamin D can prevent the occurrence of UTI using increasing mechanism of urine cathelicidin level.24 It was reported that cathelicidin stimulated the production of chemokines and cytokines by different cells and provided the integrity of the urinary system.25–28 It is believed that when there is a vitamin D deficiency, macrophages infected with bacterial agents (such as gram-negative bacteria) are not able to produce adequate antibacterial peptides. Failure to produce these
peptides predisposes the human to UTI and also increases the severity of the disease.\textsuperscript{33,34}

Contrary to the mentioned studies, study of Katikaneni et al.\textsuperscript{11} has shown that vitamin D supplementation increases the risk of UTI in formula-fed infants up to 76\%. The study of Katikaneni et al.\textsuperscript{11} was conducted on 315 infants under 3 months old. These authors suggested that administration of vitamin D to 0–3 month old infants should be done with caution. They did not measure serum 25(OH)D level. In our study, the mean serum 25(OH)D level in children with UTI was significantly higher than healthy children. Based on the elimination of confounding variables in our study and the results obtained by Katikaneni et al.\textsuperscript{11}, this question is raised that: how vitamin D administration can lead to UTI? It is believed that supplementation vitamin D can increase the risk of UTI with several mechanisms. Creation of a slight nephrocalcinosis due to administration of vitamin D is one of these mechanisms. Nephrocalcinosis is an excellent context for bacterial growth. 25(OH)D is an immune modulator which has a tendency to decrease immune responses.\textsuperscript{31} Since the conversion of 25(OH)D to 1, 25-dihydroxy vitamin D is locally done over the infected area, vitamin D prescription results to high production of 25(OH)D. This phenomena results in greater inhibition of the immune system and also, increased risk and aggravation of UTI. As well, 25(OH)D is an antagonist to 1, 25-dihydroxy vitamin D at the vitamin D receptor, and overload of 25(OH)D level could therefore result in an unregulated hyperactive immune response to infection. Theses mechanisms could be answerable for the augmented UTI risk seen by vitamin D administration.\textsuperscript{11}

This study had some limitations. The sample size was small and this project was a cross-sectional study. Also, we could not measure the serum 25(OH)D levels after completion of treatment. Overall, our data indicate that high level of vitamin D may be a risk factor of UTI in children, thus we recommend further investigations in this regard.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

Our thanks and best regards go to Research Department of Qazvin University of Medical Sciences and parents of children for their corporations.

References

1. Elder JS. Urinary tract infections. In: Kliegman RM, Stanton BF, St.

2. Bensman A, Dunand O, Ulinska T. Urinary tract infection. In: Avner ED, Harman WE, Niakudz F, Yoshikawa N, editors. Pediatric nephrology. 6th ed. Berlin: Springer; 2009:1007–25.

3. Wald ER. Cystitis and pyelonephritis. In: Feigin RD, Cherry J, Demmler-Harrison GL, Kaplan SL, editors. Feigin and Cherry's text book of infectious diseases. 6th ed. Philadelphia (PA): Elsevier Sanders; 2009:554-69.

4. Ayazi P, Mahyar A, Daneshi MM, Jahani Hashemi H, Pirouzi M, Esmaillzadehbha N. Comparison of procalcitonin and C-reactive protein tests in children with urinary tract infection. Iran J Pediatr 2009;19:381-6.

5. Ayazi P, Moshiri SA, Mahyar A, Moradi M. The effect of vitamin A on renal damage following acute pyelonephritis in children. Eur J Pediatr 2011;170:347-50.

6. Stokland E, Hellström M, Jacobsson B, Jodal U, Sixt R. Renal damage one year after first urinary tract infection: role of dimercapto succinic acid scintigraphy. J Pediatr 1996;129:815–20.

7. Rushton HG. Urinary tract infections in children. Epidemiology, evaluation, and management. Pediatr Clin North Am 1997;44:1133-69.

8. Leonardo CR, Filgueiras MF, Vasconcelos MM, Vasconcelos R, Marino VP, Pires C, et al. Risk factors for renal scarring in children and adolescents with lower urinary tract dysfunction. Pediatr Nephrol 2007;22:1891-6.

9. Yang J, Chen G, Wang D, Chen M, Xing C, Wang B. Low serum 25-hydroxyvitamin D level and risk of urinary tract infection in infants. Medicine (Baltimore) 2016;95:e4137.

10. Jorde R, Sollid SL, Svartrberg J, Joakimsen RM, Grimnes G, Hutchison MY. Prevention of urinary tract infections with vitamin D supplementation 20,000IU per week for five years. Results from an RCT including 511 subjects. Infect Dis (Lond) 2016;48:823-8.

11. Katikaneni R, Ponnapakkam T, Ponnapakkam A, Gensure R. Breastfeeding does not protect against urinary tract infection in the first 3 months of life, but vitamin D supplementation increases the risk by 76\%. Clin Pediatr (Phila) 2009;48:750-5.

12. Guillot X, Semerano L, Saidenberg-Kermanach N, Falgarone G, Boissier MC, Vitamin D and inflammation. Joint Bone Spine 2010;77:552-7.

13. Holick MF. Vitamin D: extraskeletal health. Endocrinol Metab Clin North Am 2010;39:381-400.

14. Lagishtetty V, Liu NQ, Hewison M. Vitamin D metabolism and innate immunity. Mol Cell Endocrinol 2011;347:97-105.

15. Hewison M. Antibacterial effects of vitamin D. Nat Rev Endocrinol 2011;7:337-45.

16. Wilkinson RJ, Llewelyn M, Toossi Z, Patel P, Pasvol G, Dalvani A, et al. Influence of vitamin D deficiency and vitamin D receptor polymorphisms on tuberculosis among Gujarati Asians in west London: a case-control study. Lancet 2000;355:618-21.

17. Muhe L, Lubsegel S, Mason KE, Simoes EA. Case-control study of the role of nutritional rickets in the risk of developing pneumonia in Ethiopian children. Lancet 1997;349:1801-4.

18. Luksi I, Ruohola JP, Tuohimaa P, Auvinen A, Haataja R, Pihlajamäki H, et al. An association of serum vitamin D concentrations <40 nmol/l with acute respiratory tract infection in young Finnish men. Am J Clin Nutr 2007;86:714-7.

19. McNally JD, Leis K, Matheson LA, Karuananyake C, Sankaran K, Rosenberg AM. Vitamin D deficiency in young children with severe acute lower respiratory infection. Pediatr Pulmonol 2009;44:981-8.

20. Schuler P, Carter S, Kokaia J. Indices and perception of crowding in

https://doi.org/10.3345/kjp.2018.61.3.90
Pacific households domicile within Auckland, New Zealand: findings from the Pacific Islands Families Study. N Z Med J 2007;120:U2393.
21. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266-81.
22. Nseir W, Taha M, Nemary H, Mograbi J. The association between serum levels of vitamin D and recurrent urinary tract infections in premenopausal women. Int J Infect Dis 2013;17:e1121-4.
23. Nielsen KL, Dynesen P, Larsen P, Jakobsen L, Andersen PS, Frimodt-Møller N. Role of urinary cathelicidin LL-37 and human β-defensin 1 in uncomplicated Escherichia coli urinary tract infections. Infect Immun 2014;82:1572-8.
24. Kwon YE, Kim H, Oh HJ, Park JT, Han SH, Ryu DR, et al. Vitamin D deficiency is an independent risk factor for urinary tract infections after renal transplants. Medicine (Baltimore) 2015;94:e594.
25. Tekin M, Konca C, Celik V, Almis H, Kahramaner Z, Erdemir A, et al. The association between vitamin D levels and urinary tract infection in children. Horm Res Paediatr 2015;83:198-203.
26. Övünç Hacıhamdioğlu D, Altun D, Hacıhamdioğlu B, Çekmez F, Aydemir G, Kul M, et al. The association between serum 25-hydroxyvitamin D level and urine cathelicidin in children with a urinary tract infection. J Clin Res Pediatr Endocrinol 2016;8:325-9.
27. Liu PT, Stenger S, Li H, Wenzel I, Tan BH, Krutzik SR, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science 2006;311:1770-3.
28. Wang TT, Nestel FP, Bourdeau V, Nagai Y, Wang Q, Liao J, et al. Cutting edge: 1,25-dihydroxyvitamin D3 is a direct inducer of antimicrobial peptide gene expression. J Immunol 2004;173:2909-12.
29. Cantorna MT, Yu S, Bruce D. The paradoxical effects of vitamin D on type 1 mediated immunity. Mol Aspects Med 2008;29:369-75.
30. White JH. Vitamin D as an inducer of cathelicidin antimicrobial peptide expression: past, present and future. J Steroid Biochem Mol Biol 2010;121:234-8.
31. Chromek M, Slamová Z, Bergman P, Kovács L, Podraká L, Ehrén I, et al. The antimicrobial peptide cathelicidin protects the urinary tract against invasive bacterial infection. Nat Med 2006;12:636-41.
32. Lai Y, Gallo RL. AMPed up immunity: how antimicrobial peptides have multiple roles in immune defense. Trends Immunol 2009;30:131-41.
33. Zasloff M. Antimicrobial peptides, innate immunity, and the normally sterile urinary tract. J Am Soc Nephrol 2007;18:2810-6.
34. White JH. Vitamin D signaling, infectious diseases, and regulation of innate immunity. Infect Immun 2008;76:3837-43.
35. Deluca HF, Cantorna MT. Vitamin D: its role and uses in immunology. FASEB J 2001;15:2579-85.