

Is Vitamin D Supplementation Effective in Prevention of Recurrent Urinary Tract Infections in the Pediatrics? A Randomized Triple-Masked Controlled Trial

Abstract

Background: This study aimed to evaluate the impact of Vitamin D supplementation on prevention of recurrent urinary tract infections (UTIs) in the peditrics. **Materials and Methods:** This randomized, triple-blind, placebo-controlled clinical trial was conducted in 2014 among 68 children and adolescents with recurrent UTI. They were randomly assigned to two groups, receiving either Vitamin D (1000 IU/daily) or placebo for 6 months. The serum concentration of Vitamin D before and after the study and the frequency of UTI during the study were recorded. **Results:** Overall 33 patients in the group of receiving Vitamin D and 32 in the placebo group completed the trial. The mean serum level of Vitamin D had a significant increase in the intervention group (15.80 ± 8.7 vs. 20.56 ± 8.30 ng/mL, $P < 0.001$) and significant decrease in the placebo group (20.43 ± 13.28 vs. 17.43 ± 9.99 ng/mL, $P = 0.041$). During the trial, the frequency of UTI was not significantly different between the two groups studied ($P = 0.72$). Both before and after the trial, the frequency of Vitamin D deficiency, insufficiency, and adequacy was not significantly different within and between groups ($P > 0.05$). **Conclusion:** The findings of this trial revealed that Vitamin D supplementation with the mentioned dose have not significant impact on preventing recurrent UTI. Future studies with higher doses of Vitamin D and longer follow-up are suggested.

Keywords: Children, prevention, urinary tract infection, Vitamin D

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Introduction

Urinary tract infections (UTIs) are considered as one of the most common bacterial infections in peditrics which is associated with morbidities such as hypertension, proteinuria, growth retardation, and renal function impairment.^[1,2]

Estimated prevalence rate of UTI has been reported to be 2%–5% among pediatric population.^[3] The rate of transient and permanent renal failure, as a consequence of UTI, have been estimated to be 40% and 5%, respectively.^[4]

Treatment of UTI is considered as a challenging issue for peditrics nephrologists because of the factors such as antibiotics resistance, side effects, and recurrence.^[5] Different treatment approaches have been introduced for both treatment and prevention of recurrent UTI. Recently, the protocols have been simplified.^[6] Considering the role of

vitamins and minerals on proper function of immune system, using of some supplements including cranberry, probiotics, and Vitamin A have also recommended, but still, there are controversies regarding the effectiveness of these supplements.^[7]

There is a growing body of evidence that beyond its main effect on bone and mineral homeostasis, Vitamin D could have an important immunoregulatory role to defend against bacterial and viral infections.^[8] Several epidemiological studies have supported the association between Vitamin D deficiency and immune system as well as increased occurrence of infectious diseases.^[9,10] Preliminary evidence suggest that Vitamin D supplement could improve the clinical responses to acute infection.^[11]

Recently, the association between Vitamin D receptor gene polymorphisms and UTI in children has been also reported.^[12] Thus, the link between Vitamin D, immune function, and infections among children

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demonstrates the possible role of Vitamin D supplement as a proper interventional or adjuvant therapeutic agent for the management of UTI.

Considering the high prevalence of Vitamin D deficiency and insufficiency among Iranian children,^[13] its possible association with recurrent UTI and recommendations for clarifying the association through interventional studies, and importance of proper management of UTI for preventing its related morbidities, we aimed to evaluate the impact of Vitamin D supplement in prevention of recurrent UTI among pediatrics population.

Materials and Methods

This randomized, triple-blind, placebo-controlled clinical trial was conducted in 2014 among children and adolescents with recurrent UTI, referred to nephrology clinics of Al Zahra and Imam Hossein Hospitals, affiliated to Isfahan University of Medical Sciences and the private clinics of pediatrics nephrologists in Isfahan city.

The sample size of 34 patients (children and adolescents) in each group to compare the proportions was estimated based on a confidence level of 95% and power of 80%, in the patients treated by Vitamin D and placebo a prevalence of UTI of 0.31 and 0.23 and error level of 0.3.

Children with documented recurrent UTIs^[14] who were not in the active phase of UTI, have not any anatomical defects, renal stone, neurogenic bladder, higher grade of reflex (\geq Grade II), obstructive uropathies, and congenital or acquired immune deficiency and circumcised boys were not included. Patients who have not appropriate cooperation and regular follow-up or treatment were excluded from the study.

After obtaining the ethical code (IR. MUI. REC.1393.734) from ethics committee of pediatrics review board and regional ethics committee of Isfahan University of Medical Science and obtaining written informed consent from patients or their parents, the children were assigned to two intervention (case group) and placebo (control group) groups consecutively based on simple randomization.

Patients in the intervention group received oral Vitamin D drop (Co. Amin; Under the British license, Iran), which was diluted with paraffin with a dose of 1000 IU/daily and control group received placebo for 6 months.

The patients follow-up monthly for recurrence of UTI and receiving the supplement and placebo. In addition to monthly follow-up, if patients presented with any sign and symptoms of UTI, urine analysis and culture were performed for mentioned cases.

Demographic characteristics of each patient were recorded before intervention. The level of serum Vitamin D before and after study and frequency of UTI during study

were recorded for each patient and compared between intervention and placebo groups.

Based on serum Vitamin D level, children were classified as having Vitamin D deficiency (\leq 19 ng/ml), insufficiency (20–30 ng/ml), and adequacy ($>$ 30 ng/ml). Patients in each group were compared according to this classification before and after intervention.

The trial also was registered in the Iranian Registering of Clinical Trials (IRCT) with the registration number IRCT2017052221968N2.

Laboratory measurements

Sterile urine samples were taken in each participant using midstream, catheter, or suprapubic methods according to the age of patients. Urine analysis was performed using a dip-stick in fresh uncentrifuged urine.

Diagnosis of UTI was defined as any colony-forming units/mL of a single organism on a suprapubic aspiration method or $\geq 10^5$ colony-forming units/mL on a clean-catch specimen of freshly voided urine using urine bag and midstream methods.^[14]

Serum concentration of 25-hydroxyvitamin D was measured using the chemiluminescent immunoassay method.

Statistical analysis

Statistical analysis was performed using SPSS version 20 (SPSS Inc., Chicago, IL, USA.) software and independent sample *t*-test, paired *t*-test, and Chi-square test. $P < 0.05$ was considered statistically significant.

Results

During this trial, from 68 children were selected (34 patients in each group) and 3 of them were excluded during follow-up (1 from case group and 2 from control groups) [Figure 1].

In the case group, there were 31 (93.9%) girls and 2 (6.1%) boys with a mean age of 5.97 ± 2.90 years, and in the control group, 31 (96.9%) girls and 1 boy (3.1%) with the mean age of 6.41 ± 3.43 years. There was no significant difference between the two groups in terms of age and sex ($P > 0.05$). In addition, Vitamin D was not significantly different in the three levels of deficiency, insufficiency, and adequacy ($P > 0.05$) [Table 1].

On the other hand, there was no significant difference in the level of Vitamin D between the two groups before the intervention ($P = 0.196$); but, after the intervention, the level of Vitamin D in the case group with a mean of 20.56 ± 8.30 ng/mL was significantly higher than the control group with the mean of 17.53 ± 9.84 ng/mL ($P = 0.041$), so that the mean of Vitamin D level significantly increased in case group and decreased in control group after study ($P < 0.01$). Frequency of UTI during the study in case and control groups was not different significantly ($P = 0.72$) [Table 2].

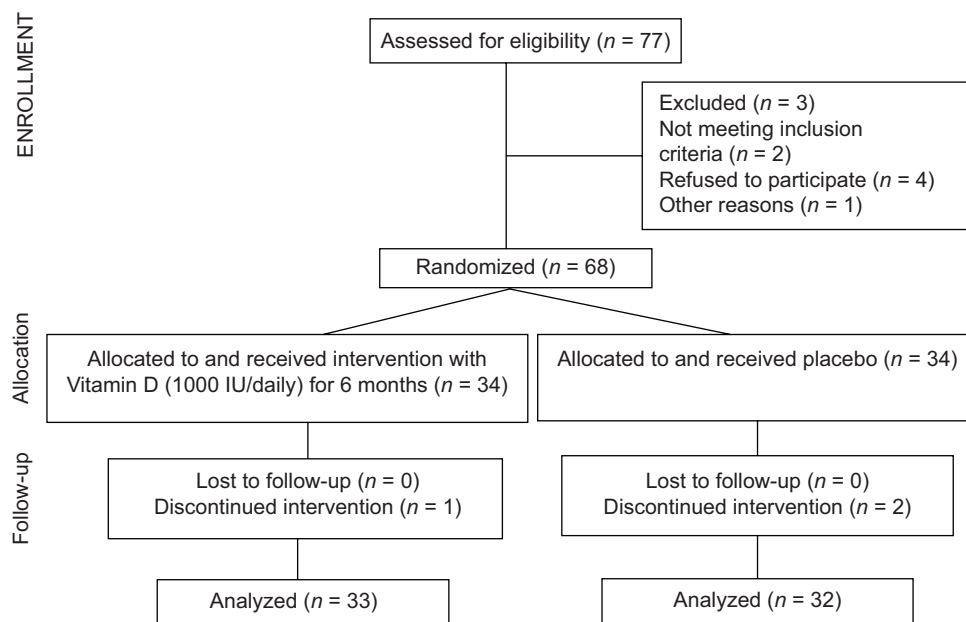


Figure 1: Consort diagram of the study

Characteristics	Case group (n=33), n (%)	Control group (n=32), n (%)	P
Sex			
Girl	31 (93.9)	31 (96.9)	0.573*
Boy	2 (6.1)	1 (3.1)	
Age (year)	5.97±2.90	6.41±3.43	0.581**
Vitamin D level			
Deficiency	25 (75.8)	20 (62.5)	0.182***
Insufficiency	6 (18.2)	5 (15.6)	
Adequacy	2 (6.1)	7 (21.9)	

*Significant level of the Fisher exact test for comparison between the two groups, **Significant level of the independent sample *t*-test for comparison between the two groups, ***Significant level of the Chi-square test for comparison between the two groups

In addition, the association of the UTI frequencies during the study with the increase or decrease of Vitamin D was 0.031 and -0.067 in the case and control groups, respectively, and there was an inverse and nonsignificant relation in the both groups ($P > 0.05$).

In other words, the higher the levels of Vitamin D, the lower the chance of a subsequent UTI in the patient, although this relationship has not been significant in the present study. In Figure 2, the mean of Vitamin D changes based on the UTI frequencies is well documented.

Discussion

In this interventional study, we have investigated the effect of Vitamin D supplement on prevention of recurrent UTI in children. Our results indicated that Vitamin D administration with a dose of 1000 IU/daily had not significant effect on recurrent UTI in children.

Although antibiotics could be used for prevention of recurrent UTI as well as its related complications, possibly the risk of microbial resistance would be increased also. Thus, there are recommendations for other alternative medications such as mannose, cranberry, and probiotics to prevent recurrent UTI.^[15,16]

Considering the anti-inflammatory, immune protective, and anti-infectious effects of Vitamin D^[8-10] and the evidences which indicated lower level of Vitamin D in both adults and children with UTI,^[17,18] we have suggested that using Vitamin D as a supplement or alternative therapy to antibiotics could have protective effect for prevention of recurrent UTI in children.

Some studies reported the effectiveness of Vitamin D with mentioned dose for preventing recurrent acute otitis media and pneumonia.^[19,20]

Reviewing of published papers in this field, we have found some studies regarding the low level of Vitamin D, but there was not any interventional study regarding using of Vitamin D for preventing recurrent UTI.

For the first time, Nseir *et al.* have indicated the association between recurrent UTI in premenopausal women and Vitamin D deficiency.^[17]

In a recent study in the Netherlands, van der Starre *et al.* have indicated that most of adults patients with UTI had insufficient Vitamin D and the level of Vitamin D was lower in patients than the control group.^[18]

Javadi Nia *et al.* in Tehran-Iran, in a cross-sectional study, have compared the level of Vitamin D in 25 children with UTI with 40 healthy children. Level of Vitamin D was lower in children with UTI than control group,

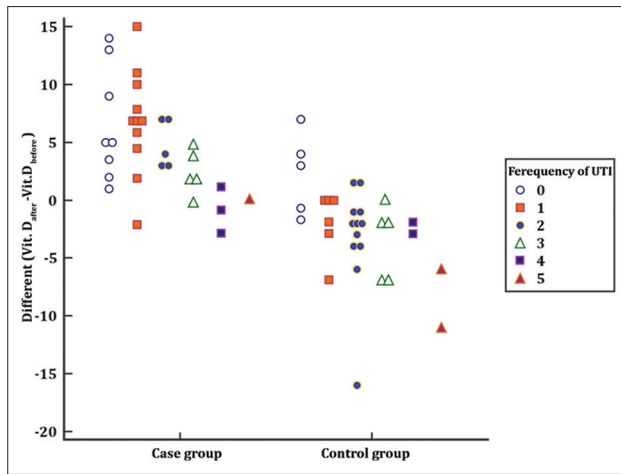


Figure 2: The mean of vitamin changes in terms of the urinary tract infection frequencies in the two groups

Table 2: Comparison of mean level of Vitamin D before and after the study and frequency of urinary tract infection during the study in two groups

Variables	Time	Case group (n=33)	Control group (n=32)	P*
Vitamin D (ng/ml)	Before	15.80±8.74	19.43±13.28	0.196
	After	20.56±8.30	17.43±9.99	0.041
P**		<0.001	0.004	
Frequency of UTI during trial, n (%)				0.72
0		8 (24.2)	5 (15.6)	
1		11 (33.3)	6 (18.8)	
2		5 (15.2)	12 (37.5)	
3		5 (15.2)	5 (15.6)	
4		3 (9.1)	2 (6.3)	
5		1 (3)	2 (6.3)	

*Significant level of the independent sample *t*-test for comparison between the two groups, **Significant level of the paired sample *t*-test for comparison before and after intervention in each group. UTI: Urinary tract infection

but the difference was not statistically significant. They concluded that Vitamin D deficiency may have a role in the vulnerability of children to UTI but for more accurate results more studies are needed.^[21]

More recently, Tekin *et al.* in Turkey, in an observational study, have compared the level of serum Vitamin D concentration among children with and without UTI. The level of Vitamin D was significantly lower in patients than healthy children (11.7 [3.3] vs. 27.6 [4.7] ng/ml). They showed that occurrence of UTI in children with Vitamin D levels below 20 ng/ml is 3.5 times higher than those with normal level of Vitamin D.^[22]

The underlying mechanisms which could explain the association between Vitamin D and recurrent UTI are unknown, but there are some evidence which could explain the link. *In vitro* studies have been demonstrated that

bladder epithelium of women who have under treatment of Vitamin D supplement has the capacity to produce larger amount of cathelicidin during infection. According to that findings, higher level of Vitamin D might have protective effect in preventing UTI and bacteremia through the production of cathelicidin.^[23]

To the best of our knowledge, this study was the first trial which investigated the effectiveness of Vitamin D in prevention of recurrent UTI in pediatric population.

El-Mazary *et al.* in Egypt have evaluated the effect of Vitamin D supplementation (400 IU/daily) for 6 months on the immunity and risk of infections including UTI during the 1st year of life among 99 full-term infants. Their results showed no differences in the frequency of UTI in infants supplemented with Vitamin D and those who have not received.^[24]

In our study, though the level of Vitamin D had tended to be increased significantly, the rate of recurrent UTI was not different in intervention and placebo group. The proportion of Vitamin D deficiency and insufficiency had trend to be improved to Vitamin D adequacy in intervention group, but the difference was not significant statistically. The frequency of UTI during the study was not different between studied groups.

Obtained findings could be explained as follows: As mentioned, the level of Vitamin D had increasing trend, but it is suggested that the protective effect of Vitamin D would be more appropriate in higher or normal level of Vitamin D. Moreover, it seems that the possible immune protective effect of Vitamin D through cathelicidin and β -defensin would be more effective in normal or higher level of Vitamin D. In this study, the proportion of patients with Vitamin D deficiency or insufficiency decreased after the study, but the rate of Vitamin D adequacy was still low. However, further studies should be designed in this regard. It is also recommended to evaluate the effectiveness of higher level of Vitamin D in this field or compare its effectiveness among patients with normal, low, and high level of Vitamin D.

Our study was conducted during autumn and winter, so considering the seasonal variation of Vitamin D level^[25] and its related factors, it seems that environmental factors had influence on effectiveness of Vitamin D supplementation and its serum level. Trials with longer duration (at least 1 year period) would provide us more conclusive results.

There are also some explanations which have mentioned in prior studies and should be investigated. The ascending nature of UTI infections and weakness of local urinary track immune system were the explanations suggested by El-Mazary *et al.*^[24]

There are possibilities that the immunoprotective effect of Vitamin D is superior in viral infections for children than for bacterial ones.^[25]

The limitations of this study were small sample size and short duration of the trial. In addition, though we have not any limitation in selecting patients regarding their gender, after excluding patients with anatomical abnormalities which were mainly boys and given that UTI is more prevalent in girls, many selected patients were girls, and we have obviously low number of the boys in the samples. It seems that increasing sample size would be helpful for resolving such a problem.

The strength of this study was that it was the first clinical trial study conducted for evaluation of Vitamin D supplement in the prevention of recurrent UTI.

Conclusion

Results of this interventional trail among pediatrics population demonstrated that Vitamin D supplement, with a dose of 1000 IU/daily, have not significant impact on preventing recurrent UTI. It seems that the protective effect of Vitamin D on recurrent UTI of pediatric patients would be more appropriate in higher or normal level of Vitamin D which could be achieved by using higher dose or longer duration of it. Suggested explanations for the obtained results should be investigated in the future interventional studies with consideration of mentioned limitations.

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Conflicts of interest

There are no conflicts of interest.

References

1. Awais M, Rehman A, Baloch NU, Khan F, Khan N. Evaluation and management of recurrent urinary tract infections in children: State of the art. *Expert Rev Anti Infect Ther* 2015;13:209-31.
2. Frankul FA, Tawaige ZH, AL-Janabi AA. Urinary tract infections in febrile children. *J Fac Med (Baghdad)* 2003;45:41-50.
3. Salo J, Ikäheimo R, Tapiainen T, Uhari M. Childhood urinary tract infections as a cause of chronic kidney disease. *Pediatrics* 2011;128:840-7.
4. Williams G, Craig JC. Long-term antibiotics for preventing recurrent urinary tract infection in children. *Cochrane Database Syst Rev*. 2011 Mar 16;(3):CD001534. doi: 10.1002/14651858.CD001534.pub3.
5. Nickavar A, Sotoudeh K. Treatment and prophylaxis in pediatric urinary tract infection. *Int J Prev Med* 2011;2:4-9.
6. Paintsil E. Update on recent guidelines for the management of urinary tract infections in children: The shifting paradigm. *Curr Opin Pediatr* 2013;25:88-94.
7. Yang SS, Chiang IN, Lin CD, Chang SJ. Advances in non-surgical treatments for urinary tract infections in children. *World J Urol* 2012;30:69-75.
8. Walker VP, Modlin RL. The Vitamin D connection to pediatric infections and immune function. *Pediatr Res* 2009;65:106R-13R.
9. Wu S, Sun J. Vitamin D, Vitamin D receptor, and macroautophagy in inflammation and infection. *Discov Med* 2011;11:325-35.
10. Science M, Maguire JL, Russell ML, Smieja M, Walter SD, Loeb M, *et al.* Low serum 25-hydroxyvitamin D level and risk of upper respiratory tract infection in children and adolescents. *Clin Infect Dis* 2013;57:392-7.
11. Yin K, Agrawal DK. Vitamin D and inflammatory diseases. *J Inflamm Res* 2014;7:69-87.
12. Aslan S, Akil I, Aslan G, Onay H, Ozyurt BC, Ozkinay F, *et al.* Vitamin D receptor gene polymorphism in children with urinary tract infection. *Pediatr Nephrol* 2012;27:417-21.
13. Kelishadi R, Ardalan G, Motlagh ME, Shariatinejad K, Heshmat R, Poursafa P, *et al.* National report on the association of serum Vitamin D with cardiometabolic risk factors in the pediatric population of the Middle East and North Africa (MENA): The CASPIAN-III study. *Nutrition* 2014;30:33-8.
14. National Collaborating Centre for Women's and Children's Health (UK). *Urinary Tract Infection in Children: Diagnosis, Treatment and Long-term Management*. London: RCOG Press; 2007.
15. Gurley BJ. Cranberries as antibiotics? Comment on "Cranberries vs. antibiotics to prevent urinary tract infections: A randomized double-blind noninferiority trial in premenopausal women". *Arch Intern Med* 2011;171:1279-80.
16. Head KA. Natural approaches to prevention and treatment of infections of the lower urinary tract. *Altern Med Rev* 2008;13:227-44.
17. Nseir W, Taha M, Nemarny 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.
18. van der Starre WE, van Nieuwkoop C, Thomson U, Zijderveld-Voshart MS, Koopman JP, van der Reijden TJ, *et al.* Urinary proteins, Vitamin D and genetic polymorphisms as risk factors for febrile urinary tract infection and relation with bacteremia: A case control study. *PLoS One* 2015;10:e0121302.
19. Marchisio P, Consonni D, Baggi E, Zampiero A, Bianchini S, Terranova L, *et al.* Vitamin D supplementation reduces the risk of acute otitis media in otitis-prone children. *Pediatr Infect Dis J* 2013;32:1055-60.
20. Das RR, Singh M, Panigrahi I, Naik SS. Vitamin D supplementation for the treatment of acute childhood pneumonia: A systematic review. *ISRN Pediatr* 2013;2013:459160.
21. Javadi Nia S, Noorbakhsh S, Izadi A, Soheyli Pour F, Tabatabaei A, Shokrollahi M. Comparison of Vitamin A, D & zinc serum levels between children with urinary tract infection and control group in two university hospital. *Tehran Univ Med J* 2013;71:244-9.
22. 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.
23. Hertting O, Holm Å, Luthje P, Brauner H, Dyrdak R, Jonasson AF, *et al.* Vitamin D induction of the human antimicrobial peptide cathelicidin in the urinary bladder. *PLoS One* 2010;5:e15580.
24. El-Mazary AM, Maaboud MA, Momen MM, Nasef KA. Vitamin D supplementation and the risk of infections in full term infants: Correlations with the maternal serum Vitamin D. *Egypt J Pediatr Allergy Immunol* 2012;10:87-94.
25. Perret JL, Lodge CJ. Seasonality and total 25-hydroxyvitamin D levels as sources of potential misclassification of Vitamin D deficiency. *Ann Am Thorac Soc* 2014;11:1336-7.