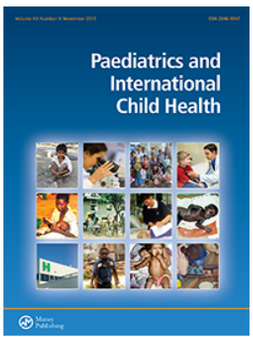

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Relationship between low serum vitamin D status and urinary tract infection in children: a case–control study

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ABSTRACT

Background: A link between vitamin D deficiency and susceptibility to bacterial and viral infections has recently been suggested.

Aim: To investigate a possible association between vitamin D deficiency and urinary tract infection (UTI).

Methods: A case–control study was undertaken comprising 75 children aged 2–7 years with UTI (cases) compared with 75 healthy controls in terms of serum 25 hydroxyvitamin D [25(OH) D] levels. Serum 25(OH)D levels were measured using a chemiluminescence assay. For cases, dimercaptosuccinic acid (DMSA) renal scan was used as the gold standard to distinguish between acute lower UTI (cystitis) and acute pyelonephritis.

Results: Median (IQR) 25(OH)D levels were lower in the UTI group [14.5 ng/mL (9.4–18.8)] than in the controls [27 ng/mL (22.4–39.0)] ($p < 0.001$). In addition, the prevalence of 25(OH)D levels <20 ng/mL was higher in the children with UTI than in the controls (68% *vs* 18%) ($p < 0.001$). There was a statistically significant difference between the cystitis and pyelonephritis groups in mean (SD) serum 25(OH)D levels—18.76 (9.35) ng/mL *vs* 13.94 (6.97) ng/mL, $p < 0.05$, respectively.

Conclusion: Low serum vitamin D is associated with UTI and supports the hypothesis that children with low vitamin D levels could be at greater risk of UTI.

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25-hydroxyvitamin D; urinary tract infection; pyelonephritis; cystitis

Introduction

Urinary tract infection (UTI) is one of the most common bacterial infections in children [1]. Causative pathogens vary but *Escherichia coli* is still the most predominant in 80–90% of cases. An important factor in the predominance of *E. coli* is its ability to attach to the urinary tract endothelium [2,3]. Genetic predisposition, chronic constipation, diabetes mellitus and immune deficiency also increase the risk of UTI [1,4]. Vitamin D is a pleiotropic hormone that plays an important role in bone health, calcium homeostasis, the cardiovascular system and immunity [5–8]. In recent years, vitamin D status and its potential effect on health has received considerable attention. Vitamin D and vitamin D receptor (VDR) expression and activity are associated with immunity against various infections and auto-immune disorders [9,10]. The secosteroid hormone which is mainly produced in the skin after exposure to ultraviolet radiation stimulates antibacterial peptide expression in macrophages and monocytes, including b-defensin and cathelicidin. These peptides are directly involved in killing intracellular bacteria [11]. There is increasing evidence that vitamin D deficiency plays an important role in susceptibility to infections [12,13]. Vitamin D deficiency has been reported in children with community-acquired pneumonia, recurrent tonsillitis, influenza and sepsis [14–17].

Cross-sectional studies [18,19] have demonstrated that serum vitamin D levels in children with UTI are lower than in healthy children, whereas a limited number of studies have suggested that increased serum vitamin D levels may be a risk factor for UTI [20,21].

This study was undertaken to determine the relationship between serum 25-hydroxyvitamin D [25(OH) D] levels and UTI.

Methods

Brief counselling regarding vitamin D deficiency together with clarification of the aims and methods of the study was provided and parents were informed of their children's vitamin D status in due course.

Serum 25(OH)D levels in 75 children with UTI were compared with 75 healthy controls. The study was undertaken in Motahari Children's Hospital affiliated to Urmia University of Medical Sciences, west Azerbaijan province.

Inclusion criteria for the cases were as follows. Children aged 2–7 years with a first UTI with clinical signs and symptoms which included fever (≥38°C), dysuria, abdominal pain, malaise, anorexia and nausea; pyuria (≥5 white blood cells/high-power field on spun urine), a positive urine culture (>10^5 colony-forming units (CFUs)/ml of a single pathogen in a midstream

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clean-void urine sample or 10^4 CFUs/ml of a single pathogen in a sample obtained via urinary catheterisation] [22,23]; nutritional status with no obesity or malnutrition, no renal disorders and no history of vitamin D supplementation during the last 12 months.

Excluded children were those with current or previous renal disorders, diabetes mellitus or immune deficiency, and those with coexisting morbidity of septicaemia, urine culture positive for more than one organism or clinical signs of rickets. The control group was selected randomly from children aged 2–7 years attending a well-child paediatric clinic. The study was undertaken in the autumn.

Laboratory analysis

After obtaining written informed consent from each participant's parents, 3 ml of venous blood was drawn. Serum 25(OH)D levels were measured by chemiluminescent assay [24]. Dimercaptosuccinic acid (DMSA) renal scan (as the gold standard) was used to distinguish between acute pyelonephritis and acute lower UTI (cystitis). It was undertaken immediately after UTI was diagnosed. Acute pyelonephritis was confirmed by determining diffuse or focal areas of diminished uptake associated with preservation of renal cortical outline in DMSA renal scan [25]. The United States Endocrine Society criteria for classification of vitamin D status were applied. Vitamin D deficiency was defined as 25 (OH)D levels <20 ng/mL, vitamin D insufficiency when 25(OH)D levels were 20–29 ng/mL and vitamin D sufficiency when 25(OH)D levels were ≥30 ng/mL [26,27]. The tests were performed in Motahari Hospital laboratory, Urmia.

Statistical analysis

Statistical analyses were performed using IBM SPSS software version 16.0 (SPSS Inc., Chicago, IL, USA). Data were summarised using number and percentage for qualitative variables, mean (SD) for normally distributed quantitative variables and median (IQR) for non-normally distributed quantitative variables. The Kolmogorov–Smirnov test was used to analyse the normality of the distribution of the measured parameters. The baseline characteristics of each group were compared using Student's *t*-test or the Mann–Whitney U-test for continuous variables and the χ^2 test for categorical variables. Correlation between serum 25(OH)D level and inflammatory and non-inflammatory variables in the cases were assessed by Spearman and Pearson analysis and Spearman's correlation coefficients for the association between continuous variables. $p < 0.05$ was considered statistically significant.

Ethics approval

The study was approved by the Ethics Committee of Urmia University of Medical Sciences (IR.UMSU.REC.1398.158) and was undertaken in accordance with the principles of the Helsinki Declaration.

Results

Seventy-five children with UTI and 75 healthy controls were enrolled in the study, and age and sex were successfully matched in both groups. Nine of the 75 (12%) cases of UTI and 15 (20%) controls were boys. In the cases, 32 had pyelonephritis (42.7%) and 43 (57.3%) had cystitis.

E. coli was the most commonly cultured bacterium in the children with UTI (89.5%). There was no statistically significant difference in age, sex, height or weight between the groups (Table 1). The most common clinical symptoms of UTI were dysuria, abdominal pain, fever and malaise. The minimum and maximum serum 25(OH)D levels in the cases were 4 and 40 ng/mL, respectively, and in the controls were 10 and 65 ng/mL, respectively ($p < 0.001$) (Figure 1). The severity of 25(OH)D deficiency in the cases and

Table 1. Comparison of variables in cases and controls.

Variable	Cases	Controls	*p*-value
Boys (%)	9 (12)	15 (20)	NS[a]
Girls (%)	66 (88)	60 (80)	
Age, yrs, mean (SD)	4.5 (1.6)	4.2 (1.6)	NS[b]
Deficient 25(OH)D < 20 ng/mL (%)	51(68.0)	18 (24.0)	**<0.001**[a]
Insufficient 25(OH)D 20–30 ng mL (%)	17 (22.7)	30 (40.0)	
Normal 25(OH)D > 30 ng/mL (%)	7 (9.3)	27 (36.0)	**<0.001**[a]

[a]χ^2 test; [b]*t*-test.
Statistically significant *p*-values are in bold.

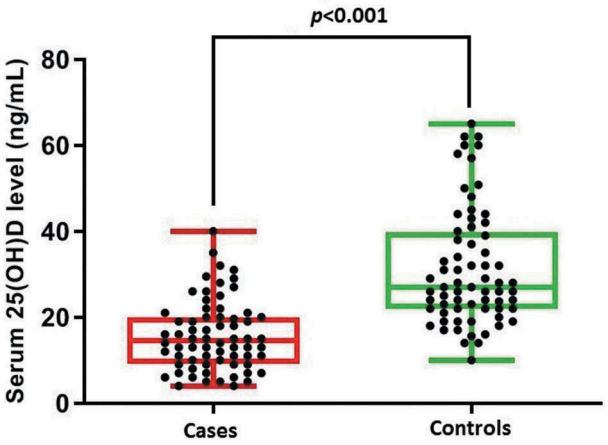

Figure 1. 25(OH)D concentrations in UTI cases and healthy controls. Data are represented as box-plots showing median (IQR). The whiskers represent the range of the data. The black circles are the results for individual children. Cases with UTI had significantly lower levels of 25(OH)D than healthy controls. Median (IQR) 25(OH)D level, 14.5 ng/ml (9.4–18.8) *vs* 27 ng/ml (22.4–39.0), respectively, $p < 0.001$. Probability was determined by the Mann–Whitney U-test.

controls is shown in Table 1. Levels were deficient (<20 ng/mL) in 68% of cases and in 18% of controls ($p < 0.001$) (Table 1).

There was a negative correlation between serum 25(OH)D levels and white blood cell count, neutrophil percentage and duration of disease (Table 2). Serum 25(OH)D levels were sufficient (>30 ng/mL) in 27 (36%) of the 75 controls and in 7 (9.3%) of the 75 patients with UTI. Median (IQR) vitamin D levels were significantly lower in cases [14.5 ng/mL (9.4–18.8)] than in controls [27 ng/mL (22.4–39.0)] ($p < 0.001$) (Figure 1). In the cases, there was no correlation between serum 25(OH)D levels and age, body temperature, platelet count, ESR and CRP (Table 2).

Mean (SD) 25(OH)D levels were 13.9 ng/mL in the children with acute pyelonephritis and 18.7 ng/mL in the children with cystitis ($p < 0.05$) (Table 3). Vitamin D deficiency was diagnosed in 26 (81.25%) of 32 children with pyelonephritis, and in 25 (58.1%) of 43 with cystitis ($p < 0.05$) (Table 4).

Table 2. Correlation analysis between serum 25(OH)D level and inflammatory and non-inflammatory variables in the cases.

Variable	Serum 25(OH)D level *r*	*p*-value
Age, yrs	−0.01	0.92
Temperature, °C	−0.04	0.74
WBCs $\times 10^9$/L	−0.31	**<0.001**
Neutrophils, %	−0.24	**0.04**
Platelets, 10^9/L	0.13	0.28
ESR, mm/hr	−0.12	0.30
CRP, mg/L	−0.07	0.57
Duration of disease, days	−0.26	**0.02**
Type of organism (*E. coli*/other organisms)	0.19	0.49

Spearman and Pearson analysis. WBC, white blood cell count; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein. *p*-values in bold are statistically significant.

Table 3. Comparison of serum 25(OH)D levels and inflammatory variables between children with cystitis and those with acute pyelonephritis.

Variable	Cystitis *n* = 43	Acute pyelonephritis *n* = 32	*p*-value
Serum 25(OH)D level, ng/mL	18.76 (9.35)	13.94 (6.97)	**<0.05**
ESR, mm/hr	25.98 (8.63)	32.13 (6.45)	**<0.01**
CRP, mg/L	28.75 (11.40)	37.53 (13.81)	**<0.01**

Values are presented as mean (SD); *p*-values in bold are statistically significant.

Table 4. Distribution of patients with cystitis and acute pyelonephritis according to 25(OH)D levels.

25(OH)D level	Cystitis *n* = 43 (%)	Acute pyelonephritis *n* = 32 (%)	*p*-value[a]
Deficient, <20 ng/mL	25 (58.13)	26 (81.25)	**0.03**
Insufficient, 20–30 ng/mL	12(27.90)	5(15.62)	
Normal, >30 ng/mL	6 (13.95)	1(3.12)	

[a]χ^2 test; values presented as mean (SD).

Discussion

In recent years, the effects of vitamin D apart from on the skeletal system have been increasingly recognised and many studies provide evidence of its role in susceptibility to infection [10,28–30].

This case–control study aimed to investigate the relationship between serum 25(OH)D levels and UTI. The results demonstrate that the proportion of children with vitamin D deficiency in the UTI group was significantly greater than in the controls, confirming an association between vitamin D deficiency and UTI. Furthermore, serum 25(OH)D levels were significantly lower in patients with acute pyelonephritis than in those with cystitis.

Vitamin D is critical in immune regulation and is thought to have a systemic effect on pathogens [31–33] with a cardinal role in different acute and chronic illnesses. Also, hypocalcaemia as a result of vitamin D deficiency further reduces lymphocyte and neutrophil functions [34]. Based on this evidence, studies have examined a link between vitamin D and UTI. The findings of this study are consistent with a similar study in Egypt of children aged 2 months to 6 years which demonstrated a significant difference in mean serum vitamin D level between cases and controls. It was suggested that the beneficial effects of vitamin D are related to the production of antibacterial peptides such as cathelicidin and β-defensin, modulating cytokines production and suppressing inflammation [30]. A study in Turkey of 82 children aged 2–18 years with a first UTI showed that vitamin D deficiency was a risk factor for UTI [1]. A study in China of 132 infants aged 1–12 months with a first UTI and 106 healthy infants (controls) showed that serum 25(OH)D levels in the cases were significantly lower than in the controls. Furthermore, the incidence of UTI in the infants supplemented with vitamin D was less than in the infants who were not supplemented. According to these results it was concluded that the risk of UTI is higher in children with vitamin D deficiency [19]. A study in Turkey of 38 healthy children and 36 children with UTI demonstrated that patients with vitamin D deficiency were unable to enhance their urine cathelicidin levels during infection and it was suggested that vitamin D can prevent the occurrence of UTI by increasing urine cathelicidin levels [35].

In contrast with the above studies, a study in the USA of 315 infants under 3 months of age reported that vitamin D supplementation increased the risk of UTI in formula-fed infants and it was suggested that vitamin D supplementation of formula-fed infants should be undertaken with caution [20].

It has been proposed that when there is vitamin D deficiency, macrophages infected with bacterial pathogens are unable to provide adequate antibacterial peptides [36]. This secosteroid hormone stimulates innate (macrophage) immunity by enhancing bacterial killing but it also modulates adaptive (lymphocyte)

immunity to minimise inflammation and auto-immune disease. Specific genes which are targets of 1,25-dihydroxyvitamin D in mature T-helper cells have been identified [37].

The main limitation of this study was the small number of subjects and lack of serum vitamin D level re-measurement after the UTI had been treated.

In conclusion, vitamin D deficiency was found to be associated with UTI in children. Also, serum levels of 25 (OH)D were significantly lower in patients with acute pyelonephritis compared with those with cystitis. These results suggest that vitamin D deficiency may be a risk factor for UTI in children. However, studies with a larger number of subjects are required to validate these data and assess whether correction of serum 25(OH)D levels might prevent UTIs.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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Notes on contributor

Sarvin Pashapour collected and analysed the data, reviewed the literature and wrote the manuscript; Hashem Mahmoudzadeh supervised the study and data collection; Ahmad Ali Nikibakhsh supervised the patient management and data collection; Morteza Ghasemnejad-Berenji planned the study, supervised the data collection and analysis, the literature review, critically reviewed the manuscript and approved the final version.

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