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Original Article

The Evaluation of Serum Vitamin D Levels in Pediatric Patients With Vesicoureteral Reflux

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ABSTRACT

Background and Aim:: Vesicoureteral Reflux (VUR) refers to the pathological return of urine from the bladder to the ureter and then to the kidney in some patients. Vitamin D deficiency is associated with some renal diseases. This study examines the relationship between vitamin D deficiency and urinary reflux.

Methods: In this cross-sectional study, 200 children referred to Amir Kabir Hospital in Arak, Iran, were divided into 2 groups of patients with VUR (n=100) and another group of pediatric participants considered healthy and had no findings of VUR (n=100). Confirmation of diagnosis was performed via voiding cystourethrogram. Serum vitamin D levels were evaluated by the Enzyme-Linked Immunosorbent Assay (ELISA) method in all participants.

Results: The results showed that the rate of vitamin D deficiency was 38% and 42% in the case and control groups, respectively. Therefore, no significant correlation was observed between the two study groups in terms of vitamin D deficiency. This finding was regardless of VUR complications affecting vitamin D metabolism.

Conclusion: We assume that VUR is a complicated condition with several complications, and the relationship of each complication with vitamin D deficiency has been determined to some extent in previous studies; however, this condition cannot be considered an independent factor leading to vitamin D deficiency.

Keywords: Vitamin D deficiency, Vesicoureteral reflux, Complications, Pediatrics

Introduction

Vesicoureteral Reflux (VUR) is a pathological retrograde regurgitation of urine from the urinary bladder to the ureter progressing into the kidney in some patients with a higher grade of reflux [1]. Accordingly, VUR is one of the most common urinary tract disorders among children; its genetic origin is based on the fact that 30% of siblings of children with VUR are affected by VUR [1, 2]. The most common form of VUR may be caused by congenital insufficiency of the ureterovesical junction [1]. Moreover, reflux can lead to Urinary Tract Infections (UTIs), resulting in reflux nephropathy, focal segmental glomerulosclerosis, and renal scarring [1-5].

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Depending on the severity of reflux grade, its prognosis is mainly different. Although some patients with reflux also have a renal injury, their renal function is never significantly impaired. If one kidney is only involved, the other kidney can continue to work normally. However, renal injury can sometimes be overwhelming insofar as causing renal failure in children or adults [5].

Vitamin D, a fat-soluble vitamin, is naturally found in scarce foods; therefore, it can currently be used as a dietary supplement. Also, it is endogenously produced by exposure to sunlight on the skin surface. Notably, vitamin D obtained from dietary supplements or supplements made in the skin are endogenously inactive, and to be activated, it must undergo two hydroxylation reactions in the liver and kidney. In the liver, vitamin D is converted to 25-hydroxyvitamin D called calcidiol. Then, the second stage of hydroxylation occurs in the kidney, in which the physiologically active form of vitamin D, 1, 25-dihydroxy vitamin D, also called calcitriol, is formed [4].

Vitamin D absorbs calcium from the gastrointestinal tract and then maintains adequate concentrations of calcium and phosphate, thereby normalizing bone mineralization. Accordingly, these actions are essential for bone growth and regeneration [6]. Vitamin D deficiency occurs when the intake is less than the prescribed level; there is insufficient sunlight exposure, the kidneys cannot hydroxylate vitamin D, or the gastrointestinal tract cannot absorb vitamin D [7]. In case of vitamin D deficiency, the bones become weak, fragile, and malformed. Adequate vitamin D levels prevent rickets and osteomalacia in children and adults, respectively.

Vitamin D also plays other roles in the body, such as regulating cell growth, neuromuscular function, immune function, and reducing inflammation. Many protein-coding genes regulating proliferation, differentiation, and cell death are partly regulated by vitamin D [8]. A serum concentration of 25 (OH) D is the best indicator of vitamin D status. It shows the type of vitamin D made in the skin and taken through food and supplements, and its half-life is 15 days; however, the serum level of 25 (OH) D does not show the amount of vitamin D stored in body tissues. Unlike 25 (OH) D, 1,25 (OH) 2 D has a short half-life (less than 15 hours), and its concentration is controlled by parathyroid hormone and phosphate concentration [9].

Vitamin D metabolism is regulated enzymatically. Filtration and tubular reabsorption of 25-hydroxy vitamin D is a part of renal vitamin D metabolism, which is firmly regulated by parathyroid hormone, fibroblast growth factor-23, and 1,25-dihydroxy vitamin D. A significant reduction exists in the production of 1,25-dihydroxy vitamin D from 25-hydroxy vitamin D in patients with renal dysfunction, such as patients with Chronic Kidney Disease (CKD). Decreased production of Cytochrome P450 family 24 subfamily A member 1 (CYP24A1) (which is the main remnant of 25 (OH) D catabolism) also confirms the above finding [10]. According to the findings, a relationship may exist between low serum vitamin D levels and patients with VUR who may have some levels of renal impairment.

Moreover, UTI is a common complication of the VUR. Recent studies have shown a correlation between vitamin D and a broad spectrum of actions against autoimmune diseases and infections, such as UTIs [11-13]. Also, a significant relationship was observed between vitamin D receptor gene polymorphism and susceptibility to UTI in children with UTI [14]. Furthermore, a recent meta-analysis has shown that vitamin D insufficiency is associated with an increased risk of UTI in the pediatric age group [15]. These findings show that considering the infectious complications of VUR, such as UTI, vitamin D levels may be altered in patients with VUR, especially those who have developed infectious complications. In this study, we aimed to investigate the prevalence of vitamin D deficiency in pediatric patients with VUR.

Materials and Methods

In a cross-sectional study, a group of pediatric patients with VUR without other chronic diseases referred to Amir Kabir hospital, Arak, Iran, were randomly selected as the case group. Their condition was confirmed with voiding cystourethrogram by a pediatric nephrologist. Written consent was obtained from parents/legal guardians for participation in this study. The exclusion criteria included patients with other diseases or those who did not consent to laboratory tests, or patients receiving vitamin D supplements. Another group of healthy children of similar age and sex was randomly selected as the control group. The Enzyme-Linked Immunosorbent Assay (ELISA) technique was utilized to assess the serum vitamin D levels in all participants. This study included 100 children with urinary reflux in the case group and 100 healthy children in the control group. No costs were imposed on patients, and the researchers adhered to the Helsinki Declaration during the study.

In addition, the children with VUR underwent a Dimercaptosuccinic Acid (DMSA) scan to evaluate the extent of reflux nephropathy and possible renal scarring.

The data were entered into the SPSS software, version 20. To measure the mean of a quantitative variable between two groups, the Mann-Whitney U-test was used, and the P<0.05 was significant.

Results

The results showed the Mean±SD age values in healthy children (control group) and patients with VUR (case group) were 4.0±1.77 and 4.34±1.81 years, respectively. In addition, the age range of the control and case groups were 2-7 and 1-7 years, respectively (Table 1).

In the control group, 46 children (46%) were boys, and 54 (54%) were girls, while in the case group, 37 children (37%) were girls, and 63 (63%) were boys. Age and sex were not significantly different between the two groups (P=0.28, P=0.15, respectively). Furthermore, DMSA results indicated that 31 patients (31.7%) with VUR had reflux nephropathy of the left kidney, 25 patients (23.2%) had reflux nephropathy of the right kidney, and 44 patients (45.1%) had bilateral reflux nephropathy. Also, in the control group, vitamin D level in 58 cases (58%) was in the normal range, and 42 cases (42%) had vitamin D deficiency, while in the case group, 62 cases (62%) had a normal range of vitamin D and 38 cases (38%) had vitamin D deficiency. A comparison of vitamin D levels in healthy children and children with VUR using the Mann-Whitney test showed no statistically significant relationship between the two groups (P=0.66) (Table 2).

Discussion

Studies have been conducted on the relationship between serum vitamin D levels and UTI and CKD. However, this study is the first one that examines the relationship between serum vitamin D levels and VUR in children. In this novel study, we aimed to compare serum vitamin D levels between children with VUR and healthy children to determine the relationship between serum levels of Vitamin D and VUR and its complications. Considering confirmatory investigation and assessment of VUR sequelae, the DMSA scan showed 25% reflux nephropathy in the right kidney, 31% in the left kidney, and 44% in both kidneys. The main result showed that 42% of the control subjects (healthy children) and 38% of the patients (children with urinary reflux) had vitamin D deficiency. Therefore, no significant difference was observed in serum vitamin D levels between the patients with reflux (case group) and healthy subjects (control group).

Aslan et al. examined the relationship between vitamin D receptor gene expression and UTI and concluded that the vitamin D receptor gene polymorphism has a relationship with UTI and subsequent renal scar formation [14]. Additionally, Katikaneni et al. evaluated the effects of breastfeeding and vitamin D supplements on urinary tract infections in children less than 3 months and showed that vitamin D supplementation led to increased infection [16]. Moreover, Tekin M. et al. assessed the relationship between vitamin D levels and UTIs in children. They selected 82 children with the first episode of UTI and then examined their vitamin D levels and concluded that vitamin D deficiency could be considered a risk factor for UTI [17]. Also, Serra Sürmeli Döven et al. examined the relationship

Table 1. Prevalence of age, sex, and status of vitamin D in the case and control groups

Groups	Age (y), (Mean±SD)	Vitamin D	State (%)
Case	4.34±1.81	Normal=62	62
	Min-max=1-7	Deficit=38	38
Control	4.0±1.77	Normal=58	58
	Min-max=2-7	Deficit=42	42

Table 2. Comparison of vitamin D levels in two groups

Groups	Mean±SD	P
Case	2.13±0.86	0.46
Control	2.11±0.37	

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between renal scarring after recurrent UTIs and vitamin D deficiency. They proposed that vitamin D deficiency can be a crucial risk factor for scarring in recurrent UTIs, and vitamin D supplements can greatly help these patients [18]. Finally, Yang et al. investigated the relationship between low levels of vitamin D with the risk of UTI and compared vitamin D levels between the two study groups, and concluded that vitamin D deficiency was associated with an increased risk of UTI [19]. VUR is the most common underlying etiology for febrile UTIs or pyelonephritis in the pediatric population [20]. Thus, the vitamin D level may be altered in pediatric patients with VUR. Despite the mentioned studies, our research did not show such a correlation. Hence, preventive measures for vitamin D supplementation in patients with VUR are not required. However, this inconsistency with previous studies can be due to the small sample size or lack of division of the case group according to VUR patients with or without UTIs.

Also, VUR is a critical cause of Reflux Nephropathy (RN). This condition is renal scarring that mainly occurs in association with UTIs. However, it can occur in VUR patients without UTIs [21]. RN is a leading cause of CKD in children requiring dialysis or renal transplantation [22]. Vitamin D deficiency is common in pediatric patients with CKD. Several studies have been conducted to assess the prevalence of vitamin D deficiency in children with CKD. In this population, vitamin D deficiency ranges from 30% to 50% [23-27]. In this study, we also showed the prevalence of vitamin D deficiency (38%) in patients with VUR who had RN. However, the rate of vitamin D deficiency in the control group was 42%, which could not show a significant relationship between VUR and vitamin D deficiency. Thus, VUR cannot be considered an individual factor for vitamin D deficiency regardless of complications associated with urinary reflux.

Conclusion

In conclusion, we assume that VUR is a complex condition with several complications, and the relationship of each complication with vitamin D deficiency has been determined to some extent in previous studies. However, this condition cannot be considered an independent factor, leading to vitamin D deficiency. Further studies are suggested with a concise division of VUR patients into groups with and without complications.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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