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Research Article

Vitamin D Supplementation among Children with Recurrent Urinary Tract Infection in Kurdistan Region/Iraq -

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ABSTRACT

Purpose: The goal of our research study is to prove that Vit D supplementation on children with frequent UTI has clinical effective role in the treatment and pathogenesis of the disease and that Vit D and UTI are strongly clinically linked.

Methods: This is case-control research study, 130 children aged 0-18 y with recurrent UTI were involved (case group) and compared with 130 children (control group) considering serum Vit D level measurement and following up participants for 9 months. ELISA (Enzyme-Linked Immunosorbent Assay) was used to measure serum Vit D level. The results data were analyzed to compare between both case and control groups.

Results: In our study and among 130 children aged 0-18 y with recurrent UTI (case group), 35 (27%) were boys and 95 (73%) were girls, and in healthy participants (control group) 42 (32%) were boys and 88 (68%) were girls consequently. The mean serum Vit D level in the case group before starting this research study was (8 mg/ml) in 62% and the incidence of frequent UTI was more than 10 times/month in 79%; after administration of 1000-5000 IU of Vit D, a remarkable raise of Vit D (22 ngml) in 59% with decline incidence and frequency (less than 3 times/month) of UTI has been reported in 74%.

Conclusion: In our case-control study, based on our results and data, we reported that Vit D supplementation in children with frequent UTI has very good clinical effective role in the treatment and elimination of the incidence of UTI in such cases. Adequate relatively high effective dose of Vit D (1000 IU-5000 IU) must be administered in children with UTI according to age and severity, this supplementation has very significant key role to decline the incidence, frequency as well as the common clinical symptoms and signs of UTI in children aged 0-18 y.

Keywords: Children aged 0-18y; Vit D adequate dose; Recurrent UTI; Kurdistan; Iraq

INTRODUCTION

In pediatrics age group, infection of the Urinary Tract (UTI) is not un common. It is more noticeable clinically in girls (5.3%) than in boys (1%). Recurrent UTI is defined and diagnosed in children if they have possess the following criteria:

- 2 or more episodes of UTI with acute pyelonephritis/upper UTI **or**
- 1 episode of UTI with acute pyelonephritis plus 1 or more episode of UTI with cystitis/lower UTI **or**
- 3 or more episodes of UTI with cystitis/lower UTI [1].

Although three categories of such disease occur in children in forms of cystitis, acute pyelnephritis, and a symptomatic bacteriuria. Acute pyelonephritis is the most dangerous, risky and threatening form of urinary tract infection in children. In 90% of the clinically confirmed UTI cases in pediatrics age group, Escherichia coli is the most common, frequent and causative pathogen [2-4]. Chronic renal failure, hypertension and renal scarring as a result of late diagnosis of UTI might occur, hence early diagnosis and treatment of UTI is compulsory [5-8]. In children, the most frequent predisposing risk factor for UTI is vesicoureteral reflux [9]. The role of vitamin D in recurrent UTI in children is still unclear and contradictory due to limited researches in this field [10-12]. However, few think that vitamin D can reduce UTI in children, whereas, others such as Katikaneni et al believes that vitamin D supplementation is a risky contributing factor for UTI in children [13].

On the other hand, vitamin D has lots of extra skeletal properties and advantages, in addition to hemostases and calcium phosphate metabolism, such as antibacterial effects and immunmodulatory benefits [14-16]. Certain studies are conducted to illustrate the positive clinical role of vitamin D in some contagious disease such as tuberculosis, upper and lower respiratory tract infection in children and adults [17-19]. In this study we focus on the risk factors contributing to UTI in children and the beneficial role of vitamin D in the treatment of recurrent UTI in pediatrics age group.

MATERIALS AND METHODS

Study design

In this case-control study, 130 children with frequent recurrent UTI as a case group were compared to 130 healthy children (control group) in terms of serum vitamin D level measurement. This study was conducted in Zakho General Hospital, department of pediatrics and pediatrics private clinic with the inclusion of Nutrition Rehabilitation Center (NRC) in Zakho district in Kurdistan region/Iraq [20-28].

The age of the participants was between 0-18 y old. In new born baby and young age case group, certain criteria was included, in particular, frequent recurrent UTI, persistence of clinical symptoms such as hyperpyrexia, irritability, excessive crying and colic, anal fissure [29-32], poor feeding and appetite, vomiting, oral thrush particularly in girls, bad urine odor, discoloration of the napkins, abnormal urethral discharge, low birth weight, delayed growth, pus in the urine (pyuria), while in infants and older children, abdominal pain, malaise, dysuria, frequency, nocturnal enuresis, poor appetite, underweight, delayed growth, picky eaters with poor growth [38], bad oral smell, dental carries and gums inflammation [33-36], positive urine culture as well as lack of VU reflux, labial adhesions, urethral stricture, neurogenic bladder, circumcision in boys, hydronephrosis and posterior urethral valve [2,3].

Participants with one attack of UTI, received antimicrobial prior admission, confirmed risk factors and well known underlying illness were excluded from this research study. Moreover, colic in infancy due to anal fissure was excluded [37]. Besides, children with malnutrition and un healthy eating were excluded as well from this research study [38,39].

In our study, we did apply group matching for those visiting zakho general hospital to select five hundred healthy children (control group) among those children who were visiting our hospital for vaccination or elective surgeries such as tonsillectomy with frequent organized sampling to reach the desired needed sample size. Certain factors were considered when matching the case and control groups including gender, age, weight, height, head circumference, nutrition status, breast feeding, socioeconomic status, family size and

monthly income [20,21]. Both included cohorts were from Zakho, villages around, Mosel, Zomar and Shengal and children had received vaccination and under control and assessment of health centers with administration of vitamin D regularly till age of three years.

Urinary system abnormalities and VU reflux were figured out using diagnostic ultrasongraghy and Voiding Cystourethrogram (VCUG). The pediatric surgeon and via clinical examination ruled out labial adhesions, picky eaters, un healthy children, anal fissure, posterior urethral valve and congenital renal malformation [37-40]. We obtained written consent forms from the parents and verbal agreements from older children after introducing our approved research plan to them. Then, blood sample (3cc) was taken from participants for vitamin D level measurement. Centrifugation of isolated serum samples under 20 degree centigrade was achieved using ELISA method. Tests were completed and performed in Zakho General Hospital labs and private labs in Zakho District-Kurdistan region/Iraq. We divided the included children, in this research study, into five categories according to serum vitamin D levels: very severe < 5ng/ml, severe 5-10ng/ml, vitamin D deficiency 10-20ng/ml, < sufficient level 20-30, and > 30 sufficient vitamin D level [22]. We use presentation tables and numeric indicators to demonstrate and clarify the results obtained in this control-case study.

Furthermore, children received every day 1000 IU-5000 IU Vit D supplementation as drops or tab to case group, and placebo for control group for 9 months. Children in both cohorts were monitored and observed under unique follow up for the administration of Vit D and for the clinical signs of UTI and addressed accordingly.

Ethics Statement

Details and information about the research study were given and illustrated for parents and they signed consent forms to include their children in this study were with ethics approval of the research department in Zakho General Hospital.

RESULTS

One hundred and thirty children with recurrent UTI were involved in this research study, among them case group, 35 were boys (27%) and 95 were girls (73%). In control group healthy children, 42 were boys (32%) and 88 were girls (68%), respectively. Our results illustrated that there was no important variation among the two cohorts (case and control groups) in terms of gender, age, weight, height, head circumference and exclusive breast feeding duration (Table 1). In the case group, the lowest and highest serum vitamin D level were 8 and 12 ng/ml, respectively, whereas in the control cohort, the lowest and highest serum vitamin D level were 16 and 22 ng/ml, respectively. In terms of serum vitamin D level, there was an outstanding variation between the control and case cohorts in our study with significant variables in severity of vitamin D deficiency (Table 2). Very significant decline in the incidence of UTI in both groups were observed with important increase in Vit D as illustrated in Table 3.

Based on urine culture and sensitivity and in both groups, E. coli was the most relevant and frequent pathogen in children with recurrent UTI. Furthermore, in infants the most common clinical features were poor feeding, colic and excessive crying, oral thrush mainly in girls, while in older children fever, vomiting, abdominal and loin pain, frequency and burning micturation, loss of appetite and poor growth were the most commonest features.

A remarkable and tremendous decline of the common clinical symptoms and signs of UTI in both groups was reported in our study as shown in Table 4.

DISCUSSION

Right now, there are limited research studies confirming the positive impacts of Vitamin D level on pediatrics age groups based

Table 1: Number and percentage characteristics of children in both case and control cohorts.

Characteristics	Case group (%)	Control group (%)
Number	130 (100%)	130 (100%)
Age (months)	55 ± 32.5	63 ± 34.2
Sex (boys:girls)	7:63	11:71
Weight (kg)	14 ± 6.4	16 ± 9.1
Height (cm)	97.2 ± 21.4	111.3 ± 21.4
Head circumference (cm)	44 ± 2.3	44 ± 3
Family history of congenital renal disease	None	None
Values are presented as number, mean ± SD and median		

Table 2: Categories of serum vitamin D level among participants case and control groups.

Serum vitamin D level (ng/ml)	Case group	Control group
Very low (5-10ng/ml)	15 (13%)	22 (17%)
Low (10-20ng/ml)	52 (40%)	56 (43%)
Insufficient (20-30ng/ml)	43 (33%)	49 (38%)
Total	130 (100%)	130 (100%)
Values are presented as number (%)		

Table 3: Frequency of UTI in both case and control groups before and after vitamin D supplementation.

Variables	Time of Vit D supplementation		Case group (130)	Control group (130)
	Before this study	After this study		
Vitamin D (ng/ml) mean level	8	22	78 (60%)	82 (63%)
Incidence and Frequency of UTI	Equal or more than 10 times/ month	Less than 3 times/ month	97 (74%)	92 (71%)

Table 4: Common clinical symptoms and signs among case and control groups before and after Vit D supplementation.

Age	Common clinical symptoms and signs in both cohorts in percentages (%)	
	Before Vit D supplement	After Vit D supplement
Less than 1 year	Fever (42%), poor feeding (53%), Colic and excessive crying (88%), Oral thrush (65%), Anal fissure (72%)	Fever (22%), poor feeding (13%), Colic and excessive crying (8%), Oral thrush (5%), Anal fissure (2%)
More than 1 year	Fever (12%), Vomiting (32%), Abdominal pain (75%), Loin pain (76%), Frequency (82%), Dysuria (63%), Poor appetite (77%)	Fever (2%), Vomiting (2%), Abdominal pain (5%), Loin pain (6%), Frequency (8%), Dysuria (6%), Poor appetite (13%)

on clinical trials. However, in this case-control research study, results revealed that the use of therapeutic dose (1000-5000 IU) of vitamin D has very good clinical impacts on children with recurrent UTI. Previous studies have shown that children with frequent UTI had significant low vitamin D level which might increase the severity of their infection [23]. Accordingly, two schools are available to explain this matter, the 1st school agree that Vit D supplementation is helpful and can improve frequent and recurrent UTI in children, the 2nd school disagree with the 1st opinion and concluded that Vit D increase the frequency of UTI in children. However, a study conducted on ninety three children with frequent UTI, suggested that their UTI was strongly linked to lower Vit D level in case group as compared to control group, and Vit D is a risky factor in children with recurrent UTI [23,24].

A remarkable correlation between incidence of UTI and urine cathelicidin (LL-37) level have been addressed according to certain studies [24]. The mechanism beyond this is that Vit D has anti bacterial and anti inflammatory key role in the pathogenesis and incidence of UTI in children through production of peptides known as cathelicidin and modulate, β-defensin to produce cytokines and decrease the inflammatory process [25]. Another study conducted by Tekin, et al. and Yang et al. on eighty tow children aged 2-18 y with 1st UTI, concluded that Vit D is a risk factor for UTI in children [10,26].

In our study, the common clinical symptoms and signs of UTI in both case and control groups were significantly declined as declared in Table 4. The most common clinical features of UTI in children under 1 year prior to commencing with Vit D supplement were as follows: Fever (42%), poor feeding (53%), Colic and excessive crying (88%), Oral thrush (65%), and Anal fissure (72%) whereas, in the same age group the same clinical features had great decline after Vit D supplement as follows: Fever (22%), poor feeding (13%), Colic and excessive crying (8%), Oral thrush (5%), Anal fissure (2%). Similarly, for children more than 1 year before administration with Vit D , the common symptoms were Fever (12%), Vomiting (32%), Abdominal pain (75%), Loin pain (76%), Frequency (82%), Dysuria (63%), Poor appetite (77%); and the same group had great improvement after Vit D supplementation who presented clinically as Fever (2%), Vomiting (2%), Abdominal pain (5%), Loin pain (6%), Frequency (8%), Dysuria (6%), Poor appetite (13%).

Moreover, a case-control study on thirty six children reported that children with recurrent UTI have low urine cathelicidin level, hence those children with UTI and Vit D deficiency are not able to increase their urine cathelicidin level [27]. Therefore, children with sufficient Vit D during UTI can produce enough cathelicidin to act as antibacterial and anti inflammatory marker during UTI [27]. In addition, cathelicidin maintain healthy urinary system via producing cytokines and chemokines by various cells, and macrophages infected with bacterial pathogens are in active to make enough peptides [28-33]. Therefore, in adequate production of antibacterial peptides can predispose to UTI and increase the severity of infection in children with low Vit D [34,35].

In addition, as we mentioned already, the 2nd school concerning the link between Vit D and UTI in children has opposite views based on certain studies. For instance, in a research study conducted on three hundred and fifteen infants with formula fed feeding, the study reported that vitamin D increase the incidence and severity of UTI and supplementation of Vit D must be done cautiously [12]. To explain this, certain reasons were addressed and believed on how do Vit D administration can be a predisposing factor and might increase UTI in children. Firstly, as a result of overdose of Vit D supplementation, nephrocalcinosis as a core of bacterial growth can be created and increase the severity of infection [12]. Secondly, Vit D administration might suppress the immune system via production of 25(OH)D which act as immune modulator, and when there is infection modification of 25(OH)D to 1, 25-dihydroxy occur on infection site resulting in sever prolonged UTI [12]. Also, administration of Vit D can lead to irregular and hyperactive immune system to infection through 25(OH)D overload which acts as antagonist to 1, 25-dihydroxy vitamin D at vitamin D receptor [12].

In our study, we reported that children with recurrent UTI showed clinical improvement in their symptoms and signs after they were given adequate Vit D (1000-5000 IU) supplementation regularly for 9 months.

CONCLUSION

In our case-control study, based on our results and data we reported that Vit D supplementation in children with frequent UTI has very good clinical effective role in the treatment and elimination of the incidence of UTI in such cases. Adequate daily effective dose of Vit D (1000 IU-5000 IU) must be administered in children with UTI according to age and severity of UTI to decrease the usual clinical symptoms and signs among children with low Vit D level in their blood. More studies are needed to support this study including larger sample size, various age groups, different place and environment with modification of Vit D supplementation.

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