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Vitamin D3 Supplementation Reduces the Frequency of UTI and Relapses in Children with Idiopathic Nephrotic Syndrome

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Abstract: ***Background: NS is the commonest kidney disease in children and may be complicated by frequent relapses, thrombosis and infections. UTI is the most common infectious complication of NS. Patients with nephrotic syndrome have low serum levels of vitamin D due to urinary loss vitamin D together with the vitamin D binding protein Vitamin D deficiency has been reported in children with many infections, including recurrent tonsillitis, sepsis, community-acquired pneumonia, and influenza. Aim of the study: The aim of this study was to evaluate the role of vitamin D supplementation in preventing recurrent UTI in pediatric patients with nephrotic syndrome. Methodology: 100 children with idiopathic nephrotic syndrome were included in the study and were divided into identical groups : group 1 received vit D3 supplementation at dose of 1000 IU/day, group 2 received placebo and both groups were followed up for 24 months during which the attacks of UTI and relapses were recorded. Results: The odd ratio (OR) of patients with UTI in group 2 was 3.1 times the patients in group 1 (95% CI 1.1-8.9, p =.03). Patients in group 2 a relative risk (RR) to develop UTI of 2.5 times the patients in group 1 (95% CI 1.05 - 5.9, p=.03) with incidence rate to develop UTI of 1:2 in group 1 while it was 1:1 in group 2 (p <.001). Conclusions: The incidence of recurrent UTI was significantly lower in nephrotic children who received vit D supplementation (p=.03), also, the incidence rate to develop relapses was higher in placebo group but statistically insignificant.***

Keywords: nephrotic syndrome; urinary tract infection; vitamin D3

1. Introduction

NS is the commonest kidney disease in children. It is characterized by (proteinuria, edema, hyperlipidemia and hypo- albuminemia. [1] The most common complications are frequent relapses,, thrombosis and infections. [2] These patients are susceptible to different types of infections that may trigger the disease relapse or cause steroid resistance [3]. The common infections seen in NS are pneumonias, urinary tract infections (UTI), peritonitis and cellulitis. [4] Some studies have shown that UTI is the most common infectious complication of NS [5]. However, some others suggest that the incidence of UTI is low in the first episode than in relapsing NS [6, 7]. The infectious episodes result from multiple factors that increase the patients' susceptibility to infections. These factors include low serum levels of immunoglobulins, predominantly IgG, due to renal losses, defects in the opsonization of bacteria; and immunosuppressive therapy [8, 9]. Patients with nephrotic syndrome have low serum levels of vitamin D due to urinary loss vitamin D together with the vitamin D binding protein [10].Vitamin D has a crucial role in immune regulation, and is thought to have a systemic effect on pathogens [11]. In addition, hypocalcemia as a result of vitamin D deficiency further reduces both lymphocyte and neutrophils functions [12]. Vitamin D deficiency has been reported in children with many infections, including recurrent tonsillitis, sepsis, community-acquired pneumonia, and influenza [13]. The aim of this study was to evaluate the role of vitamin D supplementation in preventing recurrent UTI in pediatric patients with nephrotic syndrome.

2. Patient and Methods

100 pediatric patients with nephrotic syndrome (75 with steroid dependent or frequent relapsing NS and 25 with steroid resistant nephrotic syndrome) where divided into 2 groups matched for age and sex and response to steroids. Group 1 (50 patients) received vitamin D_3 at dose of 1000 IU/ day. Group 2 (50 patients) received placebo. The 2 group were followed up for 24 months and attacks of UTI in both groups are recorded. UTI is diagnosed by the following characters (fever, abdominal pain, ± lower urinary tract symptoms and positive urine culture with colony count >100.000). Recurrent UTI is defined by either 2 attacks of UTI within 6 months or 3 attacks within 1 year. Exclusion criteria were: 1) Age < 1 year or > 18 years at the onset of the disease. 2) Patients with severe hypocalcemia. 3) patients with secondary NS 4) Impaired eGFR. 5) Patients with underlying anomalies of the urinary tract.

3. Statistical Analysis

Statistical analysis was done using statistical package for social sciences (SPSS), computer software (version22), IBM software, USA. Data were described in the form of mean ± standard deviation for quantitative data, and frequency and proportions for qualitative data. A p value <0.05 was considered statistically significant. Differences were analyzed between the groups by Student t test as regards normally distributed data. Calculation of Odds ratio and relative risk (RR) with 95% confidence interval (CI) was used to determine the association between UTI and patients clinical characters.

4. Results

Both groups were matched for age, sex, anthropometric measures, response to steroid therapy (table 1). The odd ratio (OR) of patients with UTI in group 2 was 3.1 times the patients in group 1 (95% CI 1.1-8.9, p =.03). Patients in group 2 who did not receive vit. D supplementation had a relative risk (RR) to develop UTI of 2.5 times the patients in group 1 (95% CI 1.05 - 5.9, p=.03). The incidence rate to

develop UTI in group 1 was 1:2 while it was 1:1 in group 2 (p <.001). On stratification of patients according to sex both relative risk and odds ratio were insignificant (p=.3). When comparing patients who are developed UTI while receiving immune-suppressive therapy with those only on steroids the RR in patients on immune-suppressive therapy was 3.5 times patients on steroids only (95% CI 1.35- 9.53, P = 0.01).(table 2). The number of patients who experienced relapses during the study duration was larger in group 2 but statistically insignificant (p=.06).

5. Discussion

Our study had proved that vit. D supplementation markedly reduced the incidence of recurrent UTI in patients with nephrotic syndrome. UTI is a major risk of relapsing of proteinurea and may cause poor response to steroid therapy. Besides that, recurrent UTI can cause renal scaring and deterioration of kidney functions [14]. UTI also accounts for repeated hospital admissions as well as the cost of treatment. Causes of UTI in nephrotic syndrome include the urinary losses of immunoglobulin G, decreased bactericidal activity of the leukocytes, immunosuppressive therapy and urinary loss of complement factors (mainly C3 and C5) leading to impaired opsonization of microorganisms. [15]. Nephrotic patients are reported to have vit D deficiency even during remission due to repeated attacks of proteinurea, lack of exposure to sunlight and insufficient dietary intake of vit D [16]. Several studies had documented the role of Vit D and its receptor in the regulation and induction of the immune system through several pathways including regulation of CAMP gene expression, modulation of T-cell proliferation and cytokine production, decreases the Th1 development, inhibition of Th17 development and enhancement of the frequency of Th2 and regulatory T-cell production. [13, 17-22]. Multiple studies had highlighted the relation between vit D deficiency and incidence of several infections in pediatric populations [23-26] but no previous studies documented the relation between vit D supplementation and the frequency of UTI in nephrotic patients or its effect on the frequency of relapses in those patients. Our study had revealed that the frequency of UTI was significantly higher in patients who did not receive vit D supplementation indicating the crucial role of vit D in improving the immune function especially in high-risk population as in nephrotic patients. Despite it was statistically insignificant; the percentage of SDNS patients who experienced relapses in group 2 was almost double that in group 1 (23% versus 42%) concomitant with the risk of poor response to steroids and relapsing of proteinurea during the attacks of UTI and may be due an immune modulatory mechanism that needs further studies to clarify it.

In conclusion: the incidence of recurrent UTI was significantly lower in nephrotic children who received vit D supplementation (p=.03), also, the incidence rate to develop relapses was higher in placebo group but statistically insignificant.

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Table 1: Comparison of the demographic data of the study groups

		Mean ± Std. Deviation		P
		Group 1	Group 2	
Age (years)		7.71± 3.51	9.26± 3.10	>.05
Age at onset (years)		5.26 ± 2.76	3.91± 2.18	>.05
Weight (kg)		29.02 ± 13.39	31.1± 9.71	>.05
Height (cm)		114.96 ± 34.19	127.30± 24.03	>.05
BMI		19.78 ± 5.490	19.92± 5.11	>.05
Relapses in SDNs	Yes	7(23%)	15(42%)	>.05
	No			
Steroids response	SDNS	30	35	>.05
	SRNS	20	15	
Immune suppressive ttt	Yes (no)	20	18	>.05
	No (no)	30	32	
Sex	Male (no)	32	34	>.05
	Female (no)	18	16	

Table 2: Comparison between the relative risk (RR) and odds ratio (OR) in the study groups

		UTI		RR	95% CI	p	OR	95% CI	p
		Yes	No						
Group	1	6	44	2.5	1.05- 5.91	0.03	3.14	1.104-8.94	0.03
	2	15	35						
Sex	M	12	54	0.68	0.321- 1.46	0.3	0.61	0.23 - 1.65	0.33
	F	9	25						
Immune suppressive Therapy	Yes	11	27	3.58	1.35- 9.53	0.01	4.64	1.46 - 14.6	.009
	No	**5**	**57**						