IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 18, Issue 4 Ser. 8 (April. 2019), PP 45-50
www.iosrjournals.org

Study on Effect of Steroid on Calcium and Vitamin D in Children with Nephrotic Syndrome in a Tertiary Care Hospital in Jharkhand

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Abstract: *Minimal Change Disease is the leading cause of childhood Nephrotic Syndrome . Therefore in nephrotic syndrome, most children beyond the first year of life will be treated with corticosteroids .Children with Nephrotic syndrome often display a number of calcium homeostasis disturbances causing abnormal bone histology,including hypocalcemia, reduced serum vitamin D metabolites, impaired intestinal absorption of calcium.This study aims to analyse the level of calcium and vitamin D in patients of nephrotic syndrome on steroids in the tertiary care hospital of Jharkhand.This is a prospective observational hospital based case-control study which includes 75 cases and controls of children of age 2-12 years diagnosed with nephrotic syndrome and admitted to hospital for steroid therapy. Hypovitaminosis D waspresent in both cases and controls in the study cohort. However, children with Steroid sensitive nephrotic syndrome had worse Vitamin D status than healthy controls. Mean serum calcium levels were found to be significantly lower (p value-<0.0001)than those at the beginning of the therapy. Thus we conclude that Corticosteroiod treatment causes a decrease in bone formation, as shown by the changes in vitamin D levels which remain lower than control subjects after Corticosteroid therapy. Children with steroid sensitive nephrotic syndrome may benefit from routine measurement of vitamin D and prophylactic supplementation with calcium and Vitamin D.*

Date of Submission: 27-03-2019 Date of acceptance: 12-04-2019

I. Introduction

Nephrotic Syndrome is the clinical manifestation of glomerular diseases associated with heavy (nephrotic range) proteinuria. The triad of clinical findings associated with nephrotic syndrome arising from the large urinary losses of protein are hypoalbuminemia[1] (<2.5g/dl), edema and hyperlipidemia (cholesterol >200mg/dl)[2]. Corticosteroids are the mainstay of therapy for MCNS. Nephrotic syndrome often occurs as a part of a systemic illness with an inflammatory state. The increased osteoclastic bone resorption accompanying inflammation is thought to be mediated by TNFα and other cytokines rather than by the RANKL, RANK, OPG pathway. On the other hand, it was reported that both 25(OH) vitamin D and calcitriol are transported by vitamin D binding globulin and albumin, which are depleted by heavy proteinuria-albumin losses. These changes contribute to secondary hyperparathyroidism and increased bone turnover[3,4]. A reduced bone mineral density is common, particularly in the first several months of treatment. Glucocorticoid use is associated with reduced osteoblastic bone formation, increased apoptosis of both osteocytes and osteoblasts . Glucocorticoids also indirectly affect bone. It causes reduced intestinal calcium absorption and increased urinary calcium losses. Only a very few studies have been undertaken among Indian population. The presence study is an attempt to determine the level of biochemical bone marker in Nephrotic syndrome patients.

II. Material And Methods

The present study was conducted in the Department of Pediatrics ,Rajendra Institute of Medical Sciences, Ranchi, Jharkhand. This hospital is 1000 bedded multi disciplinary teaching hospital with advance diagnostic tools.

Study Design: Prospective observational hospital based case-control study.

Study Location: The present study was conducted in the Department of Pediatrics ,Rajendra Institute of Medical Sciences, Ranchi, Jharkhand.

Study Duration: This study was carried out from April 2017 to September 2018.

Sample size: A total of 75 children and adolescent diagnosed with nephrotic syndrome were enrolled in the study and 75 controls were taken.

Study population: The study population constituted patients who are children and adolescent admitted in Department of Pediatrics in RIMS Ranchi diagnosed with Nephrotic syndrome. The study participants who fulfilled inclusion criteria were included in this studies.

Subjects & selection method: Taking into consideration of availability of patients during data collection period, a total of 75 children and adolescent diagnosed with nephrotic syndrome were enrolled in the study and 75 controls were taken.

Inclusion criteria:

1. Children between 2-12 age group of years.
2. Diagnosed case of nephrotic syndrome.
3. Idiopathic nephrotic syndrome.
4. On steroid therapy.
5. Steroid sensitive Nephrotic Syndrome

Exclusion criteria:

1. Children <2 years and >12 years.
2. Children with secondary causes of nephrotic syndrome.
3. Children who are steroid resistant (defined as failure to achieve Remission after 8 wk of corticosteroid therapy) or steroid dependent (Occurrence of 2 consecutive relapses during alternate days steroid therapy or within 2 weeks of its discontinuation).
4. Children on alternative therapies to corticosteroids.
5. Short stature due to other causes excepting steroid therapy.
6. Very sick children.
7. Unwilling for study.
8. On any calcium, phosphorus or vitamin-D containing preparations.

Procedure methodology :

Full detailed history and thorough clinical examination was done on all cases and control.

Height was measured at the point of entry then every six months till the end of study. Treatment history with steroid and steroid sparing agents was meticulously noted in the proforma during follow up. End of recruitment of new patients six months prior to completion of the study. Minimum two height measurement data six months apart was essential criteria to remain included as study subject in this study. Contact number was taken and were asked to come to prevent loss of patient during study.

Height was measured by a stadiometer (3years to 12 years). Children younger than three years were measured on a firm horizontal platform that contains three essential components: an attached yardstick, a fixed headplate, and a movable footplate. One adult held the child's feet steady while another adult obtained the measurement.

Relevant laboratory investigations were done as mentioned below and records were maintained in a Proforma sheet.

Laboratory investigations:

•Serum calcium will be estimated using arsenazo iii complex method (spectrophotometry).

•Serum levels of vitamin D by CMIA (chemiluminiscentmicroparticle immunoassay).

Statistical analysis :

For statistical analysis data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS 24.0. and GraphPad Prism version 5. Data has been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. Two-sample t-tests for a difference in mean involved independent samples or unpaired samples. Unpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate. p-value ≤ 0.05 was considered statistically significant.

III. Result

The mean age of cases was 6.6 years, whereas that of controls was 6.4 years. The mean age at diagnosis of patients was 5.4 years. Although hypovitaminosis D was universal in the study cohort; cases had worse Vitamin D status than controls. The mean Vitamin D of cases was 12.6 ng/ml and in controls, the mean Vitamin D was 17.8 ng/dl.

In cases, the mean serum Ca was 6.8 mg/dl and in controls, the mean serum was 9.6mg/dl. Difference of mean serum Ca among groups was statistically significant ($p<0.0001$).

Table no 1 Shows , the mean age (mean± s.d.) of patients was 6.6867 ± 2.7751 years. In control, the mean age (mean± s.d.) of patients was 6.4533 ± 2.8119 years. Difference of mean age vs. group was not statistically significant (p=0.6098).

Table no 1 Distribution of Mean Age (years)

		Number	Mean	SD	Minimum	Maximum	Median	p-value
Age(years)	Case	75	6.6867	2.7751	2.5000	12.0000	6.0000	0.6098
	Control	75	6.4533	2.8119	1.5000	12.0000	6.0000	

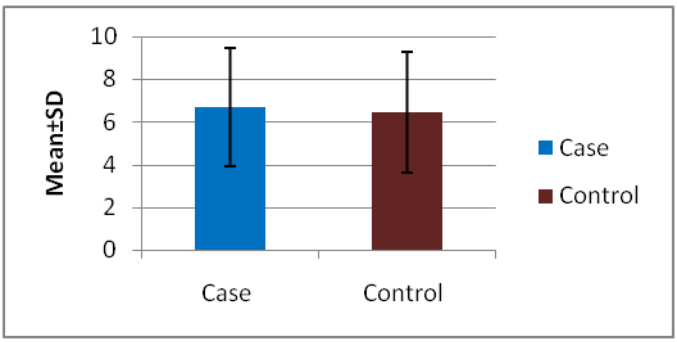

Table no 2 shows the mean age at diagnosis (mean± s.d.) of patients was 5.4067 ± 2.4143 years.

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Table no2: Distribution of Mean age at diagnosis in cases

	Number	Mean	SD	Minimum	Maximum	Median
Age at Diagnosis	75	5.4067	2.4143	2.0000	10.5000	5.0000

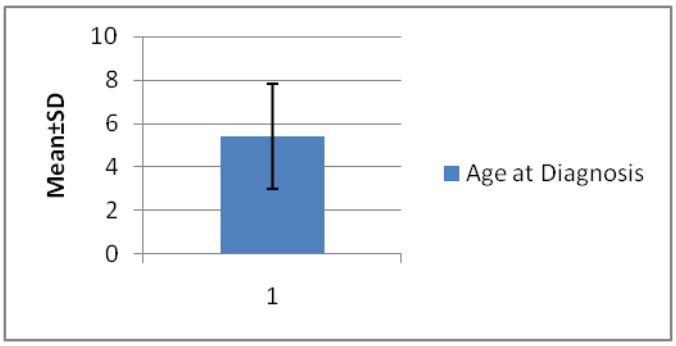


Table no3: Shows in cases, 30(40.0%) patients were female and 45(60.0%) patients were male. In control, 25(33.3%) patients were female and 50(66.7%) patients were male. Association of sex vs. group was not statistically significant (p=0.3968).

Table no 3 : Distribution of Association of SEX

	GROUP		
SEX	**Case**	**Control**	**TOTAL**
Female Row % Col %	30 54.5 40.0	25 45.5 33.3	55 100.0 36.7
Male Row % Col %	45 47.4 60.0	50 52.6 66.7	95 100.0 63.3
TOTAL Row % Col %	75 50.0 100.0	75 50.0 100.0	150 100.0 100.0

Chi-square value: 0.7177**; p-value:** 3968

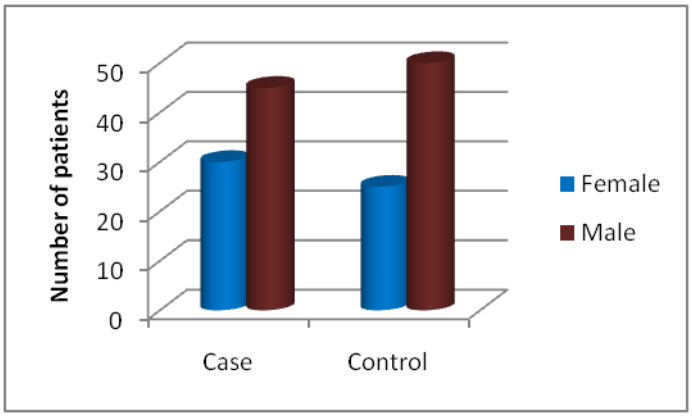


Table no 4 shows in case, 59(78.7%) patients had Hindu, 11(14.7%) patients had Muslim and 5(6.7%) patients had Christian. In control, 57(76.0%) patients had Hindu, 10(13.3%) patients had Muslim and 8(10.7%) patients had Christian. Association of religion vs. group was not statistically significant (p=0.6790).

	GROUP		
Religion	**Case**	**Control**	**TOTAL**
Hindu Row % Col %	59 50.9 78.7	57 49.1 76.0	116 100.0 77.3
Muslim Row % Col %	11 52.4 14.7	10 47.6 13.3	21 100.0 14.0
Christian Row % Col %	5 38.5 6.7	8 61.5 10.7	13 100.0 8.7
TOTAL Row % Col %	75 50.0 100.0	75 50.0 100.0	150 100.0 100.0

Chi-square value: .7744**; p-value:** 0.6790

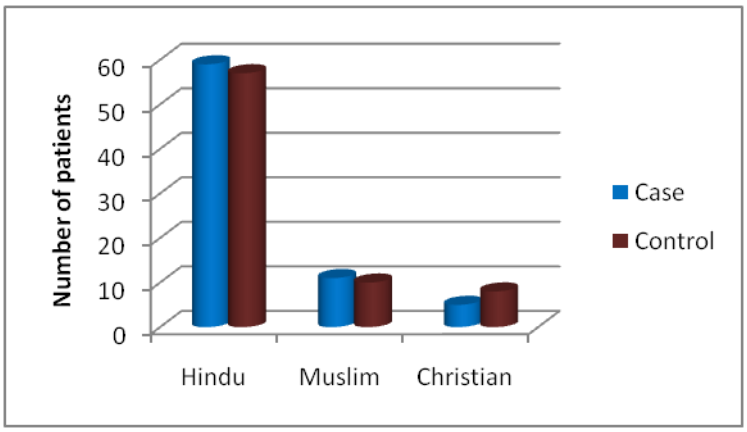


Table no 5 Shows in case, the mean Vitamin D (mean± s.d.) of patients was 12.6293 ± 3.4974. In control, the mean Vitamin D (mean± s.d.) of patients was 17.8907 ± 4.6069. Difference of mean Vitamin D vs. group was statistically significant (p<0.0001).

Table no 5: Distribution of Mean Vitamin D

		Number	Mean	SD	Minimum	Maximum	Median	p-value
Vitamin D	Case	75	12.6293	3.4974	4.2000	22.0000	12.4000	<0.0001
	Control	75	17.8907	4.6069	8.8000	32.0000	17.9000	

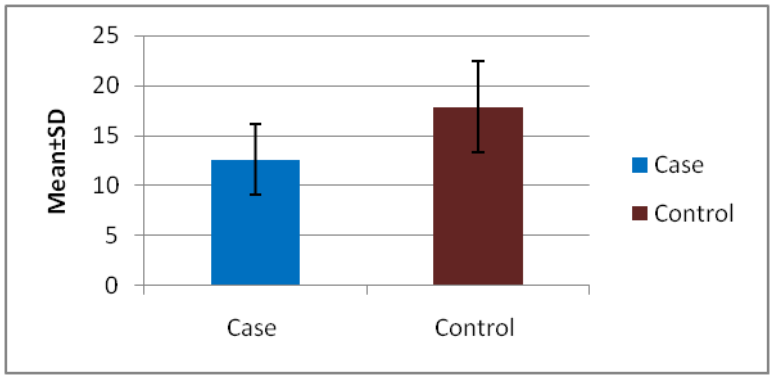
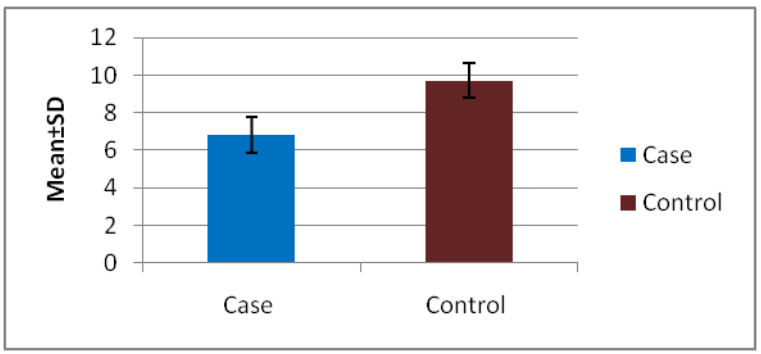


Table no 6 shows in case, the mean serum Ca (mean± s.d.) of patients was 6.8000 ± .9672. In control, the mean serum Ca (mean± s.d.) of patients was 9.6907 ± .9218. Difference of mean serum Ca vs. group was statistically significant (p<0.0001).

Table no 6: Distribution of Mean Serum Ca

		Number	Mean	SD	Minimum	Maximum	Median	p-value
Serumo Ca	Case	75	6.8000	.9672	5.0000	9.6000	6.7000	<0.0001
	Control	75	9.6907	.9218	7.8000	11.6000	9.6000	



IV. Discussion

Children with NS often display a number of calcium homeostasis disturbances causing abnormal bone histology, including hypocalcemia, reduced serum vitamin D metabolites, impaired intestinal absorption of calcium, and elevated levels of immunoreactive parathyroid hormone (PTH). These are mainly attributed to the loss of a variety of plasma proteins and minerals in the urine as well as steroid therapy[5-9]. Children with idiopathic nephrotic syndrome are at risk for metabolic bone disease such as reduced Bone Mineral Density (BMD) and abnormal bone histology, including osteomalacia as well as excessive bone resorption resembling secondary hyperparathyroidism. Early diagnosis and management of these abnormalities, could prevent the growth retardation and renal osteodystrophy that affects children with nephrotic syndrome.

Hypocalcemia seems to be a common feature in NS patients although some studies reported normal serum calcium levels. In a study conducted by Thomas *et al*. in 1998 nephrotic syndrome, was among significant univariate predictors of hypovitaminosis D. The Plasma concentration of 25-hydroxyvitamin D [25(OH) D] is low in patients with NS because of a loss of vitamin D-binding protein in the urine . 1,25(OH)2D levels, which shares the same plasma binding protein, have been found to have decreased or to have been unchanged in patients with nephrotic syndrome. Osteoporosis is a well-known serious side effect of long-term treatment with glucocorticoids. GCs (GlucoCorticoids) are associated with decreased gastrointestinal calcium absorption and increased urinary Ca excretion by decreasing its reabsorption in the renal tubule, resulting in a negative calcium balance. Furthermore, GCs stimulate bone resorption directly by enhancing osteoclast activity and indirectly via increasing parathormon (PTH) production. Glucocorticoids also inhibit osteoblasts through

reduction of osteoblast differentiation and increasing apoptosis of the mature osteoblasts resulting in reduce in reduce the total number of osteoblasts, and an inhibition of the synthesis of osteoid by these cells, which results in significant reductions in bone formation. Reduced Bone mineral content (BMC) also has been reported in short term, high dose applications of GCs. children may display preserved bone mineral mass even shortly after the cessation of intermittent high dose glucocorticoid therapy, suggesting the capability of the young skeleton to rapidly regain previous steroid-induced bone losses[10].

In the present study we found that in case, the mean age (mean± s.d.) of patients was 6.6867 ± 2.7751 years. In control, the mean age (mean± s.d.) of patients was 6.4533 ± 2.8119 years. Difference of mean age vs. group was not statistically significant (p=0.6098). Present study found that the mean age at diagnosis (mean± s.d.) of patients was 5.4067 ± 2.4143 years. Present study found that in case, 30(40.0%) patients had female and 45(60.0%) patients had male. In control, 25(33.3%) patients had female and 50(66.7%) patients had male. Association of sex vs. group was not statistically significant (p=0.3968). We found that in case, the mean Vitamin D (mean± s.d.) of patients was 12.6293 ± 3.4974. In control, the mean Vitamin D (mean± s.d.) of patients was 17.8907 ± 4.6069. Difference of mean Vitamin D vs. group was statistically significant (p<0.0001). Present study found that in case, the mean serum Ca (mean± s.d.) of patients was 6.8000 ± .9672. In control, the mean serum Ca (mean± s.d.) of patients was 9.6907 ± .9218. Difference of mean serum Ca vs. group was statistically significant (p<0.0001). It is noteworthy that the net effect of corticosteroids is highly variable. Therefore, steroids side effects have to be monitored individually.

V. Conclusion

Mean values of Serum Calcium was significantly altered in patients of nephrotic syndrome on steroid therapy. Vitamin D levels were significantly altered in patients of nephrotic syndrome, which suggests Vitamin D levels assesement in every nephrotic syndrome patient. Vitamin D level should be evaluated before starting the steroid treatment with regular follow for early detection of Vitamin D insufficiency and supplementation with Vitamin D and calcium should be done at the earliest.

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