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Original Article

Comparison of calcium metabolism in different subgroups of nephrotic syndrome in children

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ABSTRACT

Background: Children with nephrotic syndrome are at risk of altered calcium metabolism because of the disease *per se* as well as steroid therapy even before fall in glomerular filtration rate (GFR). **Objective:** To compare the pattern of alteration in calcium metabolism in different subgroups (infrequent relapser [IFR], frequent relapser or steroid-dependent nephrotic syndrome [FR/SDNS], and patients in remission) of nephrotic syndrome in children. **Methods:** We conducted a cross-sectional study in the Department of Pediatrics, PGIMS, Rohtak. Children between 1 and 8 years of age were divided into three groups, viz., IFR (Group I), FR/SDNS (Group II), and patients in remission (Group III). Serum total calcium, ionized calcium, phosphate, parathormone (PTH), albumin levels, and urinary calcium and phosphate were measured, and X-rays of both lower limbs were done. **Results:** 10 patients in each group were compared. Serum total calcium, ionic calcium, and urinary calcium levels were decreased in patient with nephrotic syndrome during active disease. No difference was noted in serum phosphate, urinary phosphate, and GFR in all the three groups ($p>0.05$). Serum calcium and urinary calcium were significantly lower in Group II as compared to Group I ($p<0.05$), whereas serum PTH levels were significantly higher in Group II as compared to Group I ($p<0.05$). None of the patients with IFR and in remission had changes of osteopenia while 50% patients with FR/SDNS had features of osteopenia in their X-rays. **Conclusion:** Hypocalcemia is a common finding in children with nephritic syndrome. These children especially those with FR or SDNS should undergo careful monitoring of calcium, phosphorus, and PTH to prevent bone mineral disease.

Key words: *Children, Hypocalcemia, Nephrotic*

Alteration in the calcium metabolism in patients suffering from nephrotic syndrome is not uncommon. These include hypocalcemia, reduced serum vitamin D metabolites, elevated levels of immunoreactive Expansion parathormone (PTH), and normal serum phosphate levels [1-6]. Metabolic studies have demonstrated intestinal malabsorption of calcium [5] as well as excessive urinary losses of various vitamin D metabolites and their binding proteins [2,7] which, in turn, leads to decrease in bone mineral density [3,8] and put these patients at risk of osteomalacia of varying degree [9] as well as excessive bone resorption [10]. As glucocorticoids are the mainstay of treatment, they may further decrease the bone mineral density. Hence, early identification and management of these abnormalities, even before the decline of glomerular filtration rate (GFR), could ameliorate the growth retardation. However, there have been different schools of opinion regarding the incidence of hypocalcemia, hyperparathyroidism, osteomalacia, calcium, and vitamin D supplementation among the subgroups of nephrotic syndrome [11-14]. The present study was designed to study the calcium metabolism in different subgroups of nephrotic syndrome.

METHODS

This cross-sectional study was carried out on 30 children diagnosed with steroid sensitive nephrotic syndrome between the age of 1 and 8 years, who presented to Pediatric Medicine Department at Pt. B. D. Sharma, PGIMS, Rohtak. The children were divided into three groups of 10 each as per the standard clinical definitions and criteria [15]. Group 1 comprises 10 patients who presented with the first episode or were infrequent relapser (IFR); Group 2 comprises 10 patients who were FR or steroid-dependent nephrotic syndrome (FR/SDNS), and Group 3 comprises 10 patients in remission. Patients who had <2 relapses in the initial 6 months or <3 relapses in any 12-month period were categorized as IFR. Those presented with two or more relapses in initial 6 months or more than three relapses in any 12 months were categorized as FR. Patients who had two consecutive relapses while on alternate day steroids or within 14 days of its discontinuation were categorized as SDNS. Patients who remain in remission for 6 months were taken as patients in remission. The following patients were excluded: (i) Chronic kidney disease, (ii) rickets, (iii) patients already on calcium supplementation, and (iv) patients with malabsorption syndrome.

The study was approved by the Ethics Committee of the Institute. Following informed parental consent, all patients were evaluated including detailed history suggestive of nephrotic syndrome, history of similar episodes in the past, response to steroids, periods of remission, and cumulative dose of steroids used. The biometric data and the clinical findings were recorded for all the patients. The following laboratory investigations done: Hemoglobin, total and differential leukocyte count, and serum creatinine, calcium ionic calcium, and phosphorus, serum total protein, albumin, alkaline phosphatase, intact PTH level, urine examination, 24 h urinary protein, 24 h urinary calcium, and phosphorus. X-rays of both lower limbs were also done. GFR was calculated using the Schwartz formula. Serum ionic calcium levels were computed from the level of total serum calcium and total plasma proteins utilizing the McLean and Hastings Nomogram. Intact PTH levels were measured by chemiluminescence enzyme immunoassay. Investigations were done during relapse in Group I and Group II.

Statistical Analysis

Results were analyzed using STATA software version 11 (College Station, TX, USA). Continuous data were expressed as mean±standard deviation and categorical variables as number (%). Results were analyzed for statistical significance using Student's test for continuous variables and Chi-square test for discrete variables. The $p<0.05$ was considered statistically significant.

RESULTS

The present study was carried out on 30 children of nephrotic syndrome aged 1-8 years. 20 were male and 10 were female. Each group, i.e. IFR, FR/SDNS, and remission group comprised 10 patients. The majority of children were of 3-6 years of age. The majority had up to 2 weeks duration of symptoms before reporting to the hospital. All patients who came in relapse received oral prednisolone; however, among patients with SDNS, two patients received levamisole and one patient received cyclophosphamide in addition to steroids. The baseline characteristics of the study population are shown in Table 1. Among 10 patients in Group I, five patients came with the first episode of nephrotic syndrome, four patients with first relapse, and one came with the second relapse. Among the 10 patients in Group II, two came with 5th relapse, one with 6th, two with 7th, and one with 8th relapse and two each with 9th and 10th relapse.

The mean total serum calcium was 7.97±0.349 mg/dl in Group I, 7.40±0.664 mg/dl in Group II, and 8.84±0.544 mg/dl in Group III patients, respectively. Among subgroups, serum calcium levels were significantly lower in patients in Group II as compared to Group III ($p<0.01$) and Group I ($p<0.05$) (Table 2). In patients with active disease, serum ionic calcium was also found to be decreased. Serum ionic calcium levels in Group II (FR/SDNS) patients were significantly lower than Group I patients ($p<0.01$) and Group III patients ($p<0.05$). Similarly, ionic calcium in Group I patients were significantly lower than Group III patients ($p<0.05$) (Table 2).

Table 1: Baseline characteristics of the patients

Baseline characteristics	Group I (N=10) (%)	Group II (N=10) (%)	Group III (N=10) (%)
Age (years)			
1-3	3 (30)	1 (10)	1 (10)
3-6	5 (50)	7 (70)	7 (70)
6-8	2 (20)	2 (20)	2 (20)
Duration of symptoms			
Up to 2 weeks	5 (50)	6 (60)	-
2 weeks to 1 month	3 (30)	2 (20)	-
1 month to 3 months	1 (10)	2 (20)	-
3 months to 4 months	1 (10)	-	-

As shown in Table 2, serum PTH levels were significantly higher in Group II (FR/SDNS) as compared to Group III ($p<0.001$) and Group I ($p<0.05$). Similar results were obtained while comparing Group I patients with Group III ($p<0.001$). Serum phosphate levels were found to be normal in all groups. No significant difference was noted in urinary phosphate levels and GFR between all groups ($p>0.05$). Serum proteins were found significantly higher in Group III than in Group I and Group II patients ($p<0.001$); however, no significant difference was noted between Group I and Group II ($p>0.05$). In our study, Group I and Group III patients had no changes of osteopenia; however, 5 out of 10 patients of Group II had radiological features of osteopenia in their X-rays.

DISCUSSION

This cross-sectional study revealed that hypocalcemia is a common finding in patients with nephrotic syndrome during active disease which is in accordance to previous studies [16-20] and in contradiction to studies which have reported normal calcium levels [2,21,22]. On subgroup analysis, serum calcium levels were found to be significantly lower in FR/SDNS patients as compared to IFR patients. This lower calcium levels may be due to longer courses of steroid in FR/SDNS and which, in turn, leads to decreased gastrointestinal calcium absorption and increased urinary calcium excretion by decreasing its reabsorption in the renal tubule, resulting in a negative calcium balance.

These results are also in accordance with a study by Gulati et al. [12], in which symptomatic hypocalcemia was observed in 6 of 70 (8.6%) children with FR/SDNS as compared to compared with none of 30 children with IFR. Same study [12] also found corrected mean serum calcium level significantly lower in FR as compared with IFR. However, a recent study by Naglaa et al. [14] found no difference in serum calcium in two groups of nephrotic syndrome. We found normal serum calcium levels in the patients in remission, which is in accordance with the study by Huang et al. [18].

Earlier it was thought that hypocalcemia in nephrotic syndrome is due to the reduction in the protein bound calcium

Table 2: Comparison of biochemical parameters between patients of three groups

Biochemical parameters	Group I	Group II	p value[a]	Group III	p value[b]	p value[c]
Serum calcium (mg/dl)	7.97±0.349	7.40±0.664	<0.05	8.84±0.544	<0.001	<0.01
Serum IONIC calcium	3.98±0.204	3.59±0.303	<0.01	4.25±0.246	<0.05	<0.05
Serum PO_4	4.92±0.792	5.01±1.192	>0.05	5.09±1.683	>0.05	>0.05
Serum PTH	80.5±13.77	94.66±13.9	<0.05	28.1±23.3	<0.001	<0.001
Urinary calcium	4.61±2.00	2.83±1.52	<0.05	24.61±20.5	<0.01	<0.001
Urinary phosphate	1.00±0.646	1.01±0.402	>0.05	1.14±0.569	>0.05	>0.05
GFR	91.36±13.24	92.63±14.04	>0.05	96.91±28.10	>0.05	>0.05
Serum proteins	5.37±0.64	5.41±0.49	>0.05	6.43±0.54	<0.001	<0.001

[a]Difference between Group I and Group II, [b]Difference between Group I and Group III, [c]Difference between Group II and Group III. PTH: Parathormone, GFR: Glomerular filtration rate

fraction secondary to heavy proteinuria [23,24] and serum ionized fraction was not thought to be affected [25]. However, subsequent studies showed that the reduction in serum calcium concentration was not only in the protein bound fraction but also in ionized calcium [6,10,26-28]. These changes cannot be attributed to renal insufficiency because most nephrotic patients with this alteration showed normal or slightly reduced GFR [6,10,26-28]. Serum ionic calcium levels were found to be lower in patients during active disease than patients in remission which can be explained by frequent urinary losses of vitamin D metabolites and calcium during relapse [3,29].

In our study, ionic calcium levels were lower in FR/SDNS patients than IFR patients in contrast to the study by Nurmalia et al., where no differences were seen between these two groups [13]. 24 h urinary calcium was observed to be decreased during active disease, and it was significantly lower in FR/SDNS patients than IFR patients ($p<0.05$). Similar findings were found in other studies also [5,30]. Our study found normal serum phosphate levels in all the three groups, which are in accordance with previous studies [17,19,21,22,29,31,32]. However, in a study by Feinstein et al., serum phosphate levels were found to be elevated during relapse which normalized in remission in patients with SSNS [33].

The majority of the previous studies showed that despite low ionized serum calcium and histological evidence of secondary hyperparathyroidism in some patients, PTH levels were not consistently elevated in nephrotic syndrome (NS) patients [2,3,9,19,21,22]. On the other hand, some studies reported high PTH levels [1,18,29]. Our study also showed raised PTH levels during active disease and FR patients were found to have significantly higher PTH levels than IFR patients ($p<0.05$) that can be explained by the longer duration of disease and higher doses of steroids received by the FR children. This result is consistent with a recent study by Mohamed and Abdel-Latif [11] but is in contrast to that reported by Gulati et al. [12]. Our study also showed similar results as shown by Freundlich et al. that biochemical abnormalities related to NS normalized during remission [29].

There have been discrepancies in studies regarding bone mineralization and steroid therapy in patients with nephrotic syndrome. In our study, patients with IFR/first episode and patients in remission had no changes of osteopenia in their X-rays. However, 50% of FR/SDNS patients had these changes. Similarly, Gulati et al. revealed the incidence of osteoporosis up to 22% of patients with nephrotic syndrome, 28% of FRNS/SDNS/SRNS, and 7% of IFR patients [12]. Greater dose and longer courses of steroids in these patients have been implicated as the reason behind this. Although some studies have related defective bone mineralization with dose of corticosteroids in children with NS [8,34-36], others found no difference in bone mineral content in children receiving corticosteroids compared with those who were off steroids [37]. Similar discrepancies are regarding the role of supplementation with calcium and vitamin D in these patients with some studies favoring supplementation [17,38,39] while others do not [40].

Limitations of our study include that we have not measured vitamin D levels and bone mineral density in these patients which is the new area of interest and could help us in learning the calcium metabolism in a better way. Second, sample size was small, and it was not calculated as we cater less number of patients with SDNS/FRNS. Furthermore, the dietary intake of calcium and duration of sun exposure was not taken into account in our study. Finally, we have not included patients with the steroid-resistant nephrotic syndrome. Our results suggest that children with the active nephrotic syndrome, especially those with FR/SDNS should undergo careful monitoring of calcium, 25(OH)D, phosphorus, and PTH to prevent renal osteodystrophy, low turnover bone disease. However, studies with larger samples are still required to confirm these findings.

CONCLUSION

Changes in calcium levels in patients with nephrotic syndrome are considered to be due to urinary losses of these metabolites or their carrier proteins or secondary to corticosteroid therapy, but the exact biochemical basis for these changes remains speculative. Because of the potential adverse effects of calcium and vitamin D deficiency on the skeleton and other organ systems in these patients, especially growing children, widespread screening with serum calcium levels and supplementation of calcium should be considered.

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