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An Observational Study of Urinary Calcium Excretion in Nephrotic Children

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Abstract

Background: Hypocalcemia is a known entity in nephrotic syndrome. Does hypercalciuria contribute to this state, is investigated in our study.

Aims: To study the urinary calcium excretion during nephrotic range proteinuria and during remission in nephrotic children.

Design & Setting: This observational-cohort study was carried out in a tertiary care hospital in Northern India from July 2015 to June 2016.

Material & Methods: Eighty consecutive nephrotic patients (aged 2-14 years) with new onset nephrotic syndrome or relapse were enrolled. Eight patients were lost to follow up and 3 were excluded due to addition of calcium to their treatment. Urinary and blood samples of the patients were sent at initial enrollment, at remission and at completion of alternate day therapy. Urinary calcium to urinary creatinine ratio (UCa/UCr) at onset (of patients with initial episode) or relapse (in known cases of nephrotic syndrome) and during remission was compared.

Statistical Analysis: Analysis of variances (ANOVA) was applied for comparison among groups showing normal distribution and Kruskal-Wallis Test was used for parameters having non-Gaussian distribution.

Results: No statistically significant difference in the value of UCa/UCr was observed during onset/relapse, after remission and after stopping steroid therapy.

Conclusion: Urinary calcium excretion does not statistically vary during nephrotic range proteinuria and after it.

Keywords: Calciuria; Relapse; Remission; UCa/UCr ratio.

Introduction

Nephrotics characterized by heavy proteinuria, hypoalbuminemia, hyperlipidemia and edema, show a number of calcium homeostasis disturbances leading to abnormal bone histology such as hypocalcemia, reduced serum vitamin D metabolites, impaired intestinal absorption of calcium and elevated level of immunoreactive parathyroid hormone [2]. Total plasma calcium concentration is low, parallel to reduction of albumin level as calcium is partly albumin bound [9]. Serum calcium is reduced proportionately to fall in

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concentration of serum albumin during early stages and true hypocalcemia becomes evident later in course of disease [7]. Later is mainly attributed to loss of plasma proteins and mineral in urine and to steroid therapy [8]. Levels of both vitamin D binding protein and 25 hydroxy D_3 is lost in urine in patients with nephrotic syndrome (NS) [5]. Blood levels of 25 hydroxy D_3 has direct and significant relationship with levels of serum albumin and an inverse significant relationship with degree of proteinuria [10]. Systemic corticosteroids reportedly cause hypercalciuria by inhibiting osteoblastic activity and increasing osteoclastic activity in bone, as well as by increasing urinary calcium excretion from kidney [6]. However, exact biochemical basis for changes in levels of calcium in patients with NS remains speculative.

In this study we evaluated urinary calcium excretion during proteinuric and non proteinuric phases to observe the contribution of calciuria in causing decrease in level of calcium in these patients. We aimed to establish how much does the loss of ionic calcium which forms 45% of total calcium and is freely filtered contributes to decrease in calcium levels.

Material and Methods

The prospective cross sectional study was conducted at tertiary level hospital in Northern India over 12 months from July 2015 to June 2016. Eighty consecutive patients of nephrotic syndrome attending the hospital were enrolled for the study. The eligible candidates were 2-14 year old nephrotics with normal renal function. Those excluded were children with clinical evidence of malnutrition, systemic disease and inflammatory renal disease or those taking calcium or vitamin D supplementation 3 months prior to enrollment and during study period and those who received diuretics or any other drug altering calcium or vitamin D metabolism.

Written informed consent was obtained from all parents/guardian before enrolling the patients in study. The study protocol was approved by institutional ethical committee.

Detailed history and physical examination of each case was recorded systematically on a standard performa. Spot urine sample was tested by reagent strip to test for proteinuria. Blood and urine sample was obtained in morning following an overnight fasting at relapse/initial episode, remission and on stopping of steroid treatment. Three milliliter blood in and 10 ml sterile urine was sent to lab for serum albumin, lipid profile (total cholesterol, VLDL, HDL), serum urea, creatinine and serum ionized calcium. Non fasting second urine passed in the morning as collected in hydrated state for UP/UC and UCa/UCr estimation. Hypocalcemia was defined as ionized calcium level <4.5 mg/dl and hypercalciuria was defined as UCa/UCr >0.2.

Patients were treated according to ISPN protocol [8]. UCa/UCr was used to assess calcium excretion during relapse/first episode, remission and after stoppage of steroid. If any patient developed features of hypocalcemia during the study period then calcium was added to his treatment and he was excluded from the study. Data was entered in Microsoft Excel sheet and analyzed by Epi Info 7 software. Analysis of variances (ANOVA) was applied for comparison among groups showing normal distribution and Kruskal-Wallis Test was used for parameters having non-Gaussian distribution.

Results

Of 80 patients of nephrotic syndrome aged 2 to 14 years were enrolled, 8 patients were lost to follow up and 3 excluded from the study due to administration of calcium during follow up leaving 69 children whose data was analyzed (Fig. 1). There were 48 male and 21 female patients with 37 children between 2-5 years of age, 29 between 6-10 years and 3 patients between 11-14 years of age. Thirty patients were from rural background and 39 were from urban area. Mean ± SD height of the patients was 103.9 ± 23 cm, weight was 17 ± 6.3 kg and BMI was 15 ± 3.3 kg/m^2.

Forty three patients had prior steroid exposure and 26 were cases with no prior exposure to steroids. Out of 69 patient 35 did not require hospitalization and 34 required hospitalizations for causes like massive edema, infection and oliguria. Mean time to attain remission was 7.84 days. Fifty nine patients remitted on prednisolone alone but 10 patients required alternative drugs (7 were on levamisole, 1 on cyclophosphamide and 2 on calcineurin inhibitors). One patient was on long term alternate day therapy. Nine patients re-relapsed in the study period.

There was highly significant difference in the mean value of serum albumin during onset/relapse, remission and after stoppage of steroid therapy ($p < 0.001$). There was significant difference in mean value of VLDL, HDL and TG in initial episode/ relapse of nephrotic syndrome and after stopping steroid therapy ($p < 0.05$) and the corresponding

difference in value of total cholesterol was highly significant (p<0.001). There wasn't any significant difference in the mean value of serum urea and creatinine during onset/relapse, remission and after stopping steroid therapy (p>0.05). There was highly significant difference in the mean value of UP/UC during onset/relapse, remission and after stoppage of steroid therapy (p<0.001) (Table 1).

In patients with initial episode of nephrotic syndrome there was no significant difference in the mean value of UCa/UCr during onset, remission and after stopping steroid therapy (p >0.27). There was significant difference in the mean value of UCa/UCr during relapse, remission and after stopping steroid therapy in frequent relapsing and steroid resistant nephrotic syndrome (p value 0.022 and 0.016 respectively). However, with the combined data of all the subgroups, there was no significant difference in the mean value of UCa/ UCr during onset/relapse, remission and after stopping steroid therapy (p>0.05) (Table 1). No correlation was foundbetween changes in values of serum albumin and UCa/UCr levels.

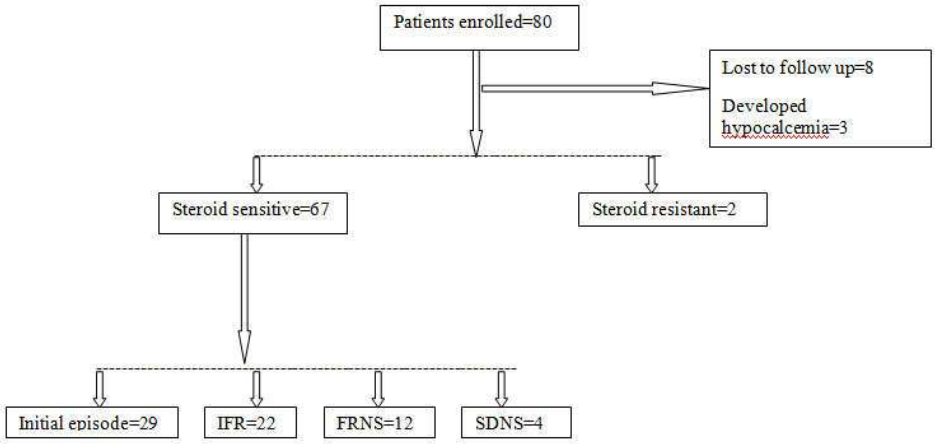

Fig. 1: Study cohort

IFR = Infrequent relapsers

FRNS = Frequently relapsing nephrotic syndrome

SDNS = Steroid dependant nephrotic syndrome

Table 1: Biochemical parameters in mean ± SD during onset/relapse (a), at remission (b) and after steroid therapy(c).

	(a)	(b)	(c)	p value
S.Albumin(g/dL)	2.4 ± 0.58	3.35 ± 0.52	3.85 ± 0.55	a vs. b <0.001 a vs. c <0.001
VLDL(mg/dL)	67 ± 39.7	55 ± 36.2	51.1 ± 29.9	a vs. b >0.05 a vs. c <0.05
HDL(mg/dL)	90.2 ± 33	77.2 ± 31	70.15 ± 33.3	a vs. b >0.05 a vs. c<0.01
Total cholesterol (mg/dL)	374 ± 179	304 ± 159	209 ± 86	a vs. b<0.05 a vs. c<0.001
S.Urea(mg/dL)	36 ± 26	32 ± 16	34 ± 16	a vs. b >0.05 a vs. c>0.05
S.Creatinine(mg/dL)	0.71 ± 0.18	0.72 ± 0.19	0.72 ± 0.18	a vs. b >0.05 a vs. c>0.05
UP/UCr	11.44 ± 6.7	2.28 ± 3.2	1.5 ± 2.6	a vs. b<0.001 a vs. b<.001
S.calcium(mg/dl) (ionized)	1.04 ± 0.16	1.23 ± 1.0	1.09 ± 0.56	a vs b >0.05 a vs c >0.05
UCa/UCr	0.55 ± 1.1	0.60 ± 1.68	0.53 ± .77	a vs. b>0.05 a vs. b>0.05

Discussion

We found no significant difference in the mean value of UCa/UCr during relapse, remission and after stopping steroid therapy ($p>0.05$). Also there was no significant difference in mean value of serum ionized calcium during relapse, remission and after completion of steroid therapy. Although blood calcium level was lower than normal it failed to reach statistically significant level. However, we did not find the calciuria significant.

Limitation of the study was that though we excluded the patients on calcium supplementation but the dietary intake of calcium and duration of sun exposure of different patients could have been different. Secondly although we aimed to measure urinary excretion but what proportion of it was due to corticosteroid therapy and what proportion was due to disease per se is difficult to demarcate. Thirdly vitamin D levels in patients at baseline and in remission were not available.

A number of studies have pointed out the presence of hypocalcemia in nephrotic patients. Dasitania et al. in their study mention that hypocalcaemia is due to hypoalbuminemia, loss of vitamin D-binding protein in the urine and the use of steroid therapy [3]. Goldstein et al. studied Vitamin D metabolites and calcium metabolism in patients with nephrotic syndrome and normal renal function and found low ionized calcium [4]. The mechanism of hypocalcaemia is not evident. It is possible that low value of 25OHD results in low blood levels of other vitamin D metabolites, such as 1, 25-dihydroxyvitamin D [l,25-(OH)2D] and 24,25-(OH)2D3; a deficiency of these compounds may cause defective intestinal absorption of calcium (α) and resistance to the calcemic action of parathyroid hormone (PTH), resulting in hypocalcaemia [4].

But what contribution did hypercalciuria have in this state of hypocalcemia is to our knowledge seldom studied. Akil et al. did find increased renal calcium excretion with usage of oral prednisolone but their comparison group was patients with bronchial hyperactivity using inhalational steroids [1]. In another study Ayi Dilla et al. did a prospective study on calcium and vitamin D supplementation in children with frequently relapsing and steroid dependent nephrotic syndrome. In their study they found that urinary calcium/creatinine ratio progressively increased [11].

A state of hypocalcemia exists in patients of nephrotic syndrome. Calcium supplementation is still not recommended in asymptomatic patients on short term steroid therapy. Since there is no significant increase in calciuria during state of proteinuria, vitamin D deficiency may be the major contributor. Whether targeted Vitamin D supplementation is required in nephrotic during phase of heavy proteinuria may be investigated in further larger studies.

Conclusion

We know nephrotic patients during state of heavy proteinuria are hypocalcemic. However urinary excretion of calcium is not significantly altered during and after the state of proteinuria.

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References

1. Akil I, Yuksel H, Urk V, Var A, Onur E. Biochemical markers of bone metabolism and calciuria with inhaled budesonide therapy. Pediatr Nephrol. 2004;19(5):511-15.
2. Bagga A, Mantan M. Nephrotic syndrome in children. Indian J Med Res. 2005;122(1):13-28.
3. Dasitania V, Chairulfatah A, Rachmadi D. Effect of calcium and vitamin D supplementation on serum calcium level in children with idiopathic nephrotic syndrome. Paediatr Indones. 2014;54(3):162-67.
4. Goldstein DA, Haldimann B, Sherman D, Norman AW, Massry SG. Vitamin D metabolites and calcium metabolism in patients with nephrotic syndrome and normal renal function. J Clin Endocrinol Metab. 1981;52(1):116-21.
5. Goldstein DA, Oda Y, Kurokawa K and Massary SG. Blood levels of 25 hydroxy vitamin D in patients with nephrotic syndrome. Ann Internal Med. 1977;87:664.
6. Gungor SS, Sonmez F, Yilmaz D. Effect of corticosteroids on urinary calcium excretion. A pilot study. J Clin Anal Med. 2016;7(4):524-8.
7. Hooft CA, Vermassen and Van Belle M. On calcemia and phosphatemia in the nephrotic syndrome. Comparative study of the periods before and after the introduction of hormone therapy. Helv Paediat Acta. 1960;15:437.
8. Indian Pediatric Nephrology Group. Indian Academic of Pediatrics. Management of steroid sensitive nephrotic syndrome. Revised guidelines. Indian Pediatr. 2008;45:203-14.
9. Salvesen HA and Linder GC. Observations on the inorganic bases and phosphates in relation to the protein of blood and other body fluids in Bright's disease and in heart failure. J Biol. Chem. 1924; 58:617.

10. Schmidt-Gayk H, Schmitt W, Grawunder C, Ritz E, Tschope W, Pietsch V et al. 25 hydroxy vitamin D in nephrotic syndrome. Lancet. 1977;2:105.

11. Septarini AD, Tambunan T, Amalia P. Calcium and vitamin D supplementation in children with frequently relapsing and steroid-dependent nephritic syndrome. Paediatr Indones. 2012; 52(1):16-21.