Original Research Article

To assess the reduction in bone mineral density among children who completed steroid therapy for nephrotic syndrome

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Abstract

Introduction: Minimal Change Nephrotic Syndrome is the most common type of nephrotic syndrome accounting for 85% of cases. It is the most common primary or idiopathic type of nephrotic syndrome in children. It occurs between 1 to 12 years of age, but most commonly 2 to 6 years. Even though the majority of cases show remission of nephrotic syndrome, the hypocalcemia due to Glucocorticoids are very severe. It reduces the bone mineralization and reducing the bone mineral content and thereby reducing bone density.

Aim of the study: To assess the reduction in bone mineral density among children who have completed the first course of steroid therapy for nephrotic syndrome by measuring biochemical markers of bone.

Materials and methods: This study was done to find out the reduction in the Bone mineral density among children who completed steroid therapy for nephrotic syndrome, by using bone biochemical markers. This study also helped to assess the side- effect of Glucocorticoids on bone density and to prevent bone demineralization and pathological fractures in children.

Results: The results showed there was a reduction in the serum calcium values among children with MCNS. This implied hypocalcemia among children due to GCs and the P value is significant <0.001. This represented the corrected calcium levels among the children after drug effect. It implied the

overall the corrected calcium levels at low levels with MEAN=8.34 mg%. The P value was <0.024 Significant. The total proteins were normal among children after completing the glucocorticoid therapy. The P value was <0.001 and was significant. Mean = 5.68. Standard Deviation (SD) = 0.28. The serum phosphorus was almost normal among remission MCNS Children and at higher levels among defaulters, SDNS and SRNS.

Conclusion: Glucocorticoids is the drug of choice and standard therapy for Minimal Change Nephrotic Syndrome (MCNS), but the drug-induced hypocalcemia and hypovitaminosis D are assessed by our study. Added to the above, the disease itself characterized by hypocalcemia and hypovitaminosis D. So, all children should undergo this assessment to prevent growth failure and pathological fractures. Nutritional supplements are recommended for the quality of life among children.

Key words

Minimal Change Nephrotic Syndrome (MCNS), Calcium, total protein, Low bone mineral density.

Introduction

Nephrotic syndrome is defined "as the clinical manifestation of disease of the glomerular system associated with heavy (nephrotic range) proteinuria". "Nephrotic range of proteinuria is explained as proteinuria >3.5gm/1.73 m^2/24 hours or > 0.01 gm/kg/24 hours or > 2gm/24 hours and the urinary protein: creatinine ratio >2" [1]. The nephrotic syndrome usually affects 1 to 3 /1 Lac children less than16 years of age. Children with the Nephrotic syndrome, are highly prone to death due to Infection, when not taken treatment. But, 80% of the cases with Nephrotic (MCNS) syndrome respond well to corticosteroid regimen. Though GCs (Glucocorticoids-Prednisolone) is the standard drug for Nephrotic syndrome, the Mechanism of action of the drug in treating this disease is not clear [2]. It remains a most common cause of nephrotic syndrome in children less than 16 years. It appears between the ages of 1 and 12 years. Most commonly appears between 2 and 6 years of age. Majority of MCNS lies below 6 years of age. But, it may occur even at six months of age and until adolescence [3]. Although, MCN is often thought of as a pediatric disease, it is one of the most common causes of nephrotic syndrome in adult as well. It is now third most common nephrosis in adults. MCNS also called as a lipoid nephrotic syndrome, "NILL" disease, idiopathic NS. This type of NS will have a good response to steroid therapy. So, it is also termed as steroid-sensitive NS [4]. The initial episodes of nephrotic syndrome usually have 85-90% remission following corticosteroid therapy. But frequent relapses usually occurs following the minor infections and uncommonly to insect bites allergic reactions, reaction to wasp stings or to any poison [5]. Although, most MCNS in children achieve permanent remission of symptoms by the time they reach puberty, some cases have been reported into childhood. Furthermore, new cases have been reported in 12 years [6]. However, the relative incidence of MCN as the etiology of Nephrotic syndrome decreases with age in children. Although no precipitating cause may be apparent in many children, is not unusual for the development of edema and proteinuria to be preceded by an upper respiratory tract infection, an allergic reaction to an insect sting or immunogenic stimuli or the use of certain drugs. In both adult and pediatric age group, malignancies, especially Hodgkin's disease, have been associated with the development of MCNS [7]. Edema formation may begin within a few days of the inciting events. Facial edema (esp. peri-orbital edema) usually is noted first, with few other indications of an ongoing disease process. This can be confused with allergic symptoms, especially if associated with an upper respiratory tract infection. Edema usually increases gradually. It becomes detectable in the adult only when several liters of fluid has accumulated; by the

time medical advice is sought, the children typically have to pit edema involving the sacrum and the lower extremities [8]. When anasarca is present, peri-orbital edema can be severe that the eyelids are swollen shut, scrotal or vulval edema may be marked, and there may be significant abdominal distension. Respiratory embarrassment may occur from accumulation of either pleural or ascitic fluid, although the infrequency of dyspnoea or orthopnoea in the setting of massive fluid retention is striking. This reflects the absence of increased pulmonary capillary wedge pressure needed to generate pulmonary edema. Headaches and irritability are common accompanying complaints of edema. The children may note vague symptoms such as malaise, easy fatiguability, irritability, and depression. Rarely, the development of cellulitis, peritonitis or pneumonia may be the first indication of an underlying nephrotic syndrome [9]. The pallor resulting from edema can be misinterpreted as indicating anemia [10]. On physical examination, dependent edema is the most prominent finding. The retina has a characteristic "wet" appearance. Subungual edema may reverse the usual color pattern on the fingernails –the normally white lunulae may be pink and the rest of the nail bed white. Horizontal white lines that may be seen on both the fingernails and the toenails are referred as Muebercke Bands. Inguinal and umbilical hernias may be present, especially if the children have had severe ascites for a prolonged period. The elasticity of the cartilage in the ear appears to be decreased. Chronic severe ascites may present with Inguinal and Umbilical Hernias in children [11]. Blood pressure in children with MCN usually within normal limits, but elevated systolic pressure has been recorded in 21% and elevated diastolic pressure in 14% of children evaluated by the International Study of Kidney Disease in Children (ISKDC). Growth failure occasionally may be found in children, most often in those who have had multiple relapses of MCNS requiring frequent courses of steroids. Evidence of infection, especially peritonitis, cellulitis or pneumonia, should be sought as part of the physical examination. These infections may be associated with septicemia and shock [12].

Materials and methods

Totally 102 children with the first episode of nephrotic syndrome, who attended at Nephrology OPD, Pediatric OPD and admitted in Nephrology IPD, and Pediatric IPD of Government Mohan Kumaramangalam Medical College, Salem, were included in our study as per the inclusion and exclusion criteria. This study was done to find out the reduction in the Bone mineral density among children who completed steroid therapy for nephrotic syndrome, by using bone biochemical markers. This study also helped to assess the side- effect of Glucocorticoids on bone density and to prevent bone demineralization and pathological fractures in children.

Inclusion criteria: Children with the first episode of the nephrotic syndrome (MCNS variety), who were admitted in the pediatric ward and Nephrology ward and attended pediatric and Nephrology OPD, of age between 2 years and 12 years.

Exclusion criteria: Age less than 2 years, age more than 12 years, primary or idiopathic nephrotic syndrome other than minimal change nephrotic syndrome (MCNS) such as FSCS, membranous nephropathy, membrano-proliferative nephritis, IgA nephropathy, children with sepsis (both urosepsis and blood sepsis), without parents/guardians consent.40 to 60 cases.

In due course of study, as many cases were reported, we extend the load to 100 cases, as many MCNS cases were reported. The reduction in bone mineral density was assessed by evaluating bone biochemical markers such as Serum Calcium, Serum Phosphorus, serum Alkaline Phosphatase, serum Vitamin D3.The investigations were done with parents and guardians consent. The evaluation was done on two occasions as before starting the drug therapy and after completion of drug therapy. According to APN (Association of pediatric Nephrology0, the duration of drug regime was 12 weeks daily

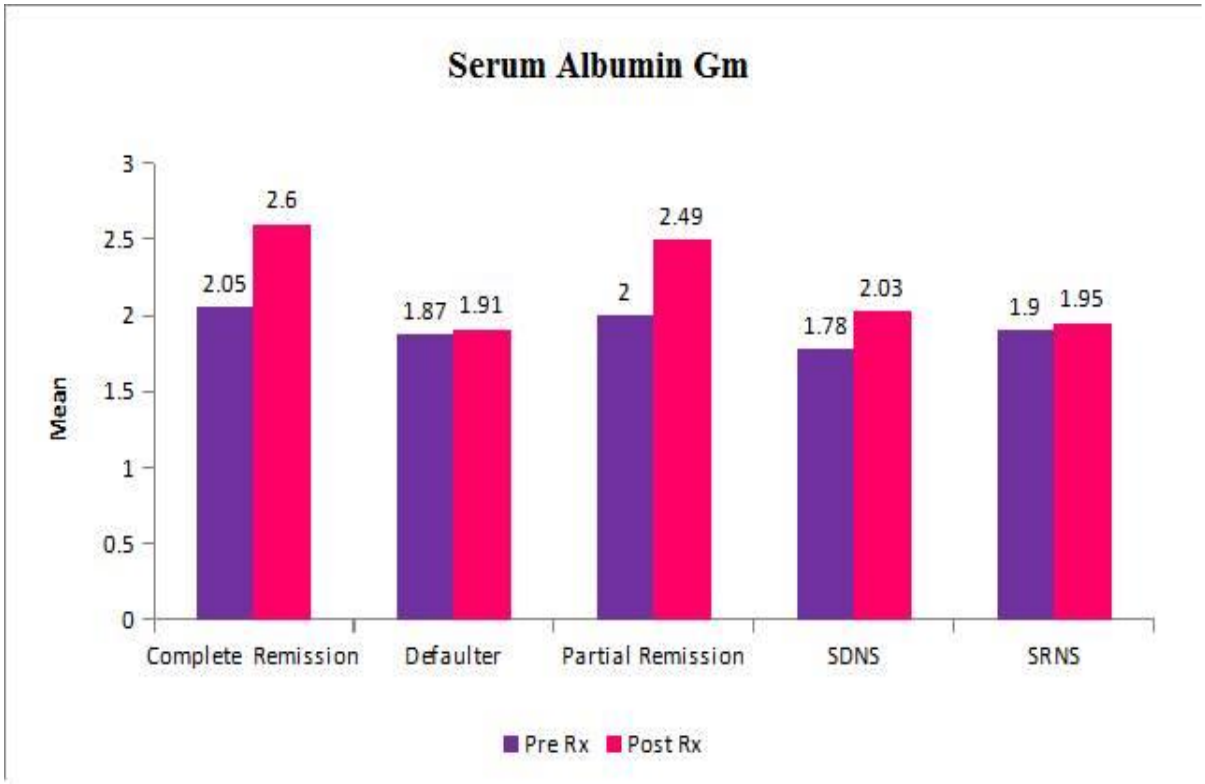
regime 2 mg/kg/day for 6 weeks and alternate day regime 1.5 mg/kg/day for 6 weeks. GCs will be issued for every fortnight at nephrology OPD and all cases had evaluation while getting drugs. Height, weight, Blood pressure and Urine albumin were evaluated every 2 weeks. This helped to found out SRNS and SDNS. Any complications due to NS (minimal change) or GCs (prednisolone) could be picked up at every check-up. The Ethical committee clearance was obtained. The duration of the study was done from July 2015 to June 2016. As per proforma, a detailed history which included the age of onset of disease, duration of the disease, course of the disease, number of Episode, any other drugs intake, any other chronic diseases. History features of sepsis such as persistent fever, burning micturition were also worked out and excluded. Every child underwent a detailed physical examination to find out any other secondary causes of nephrotic syndrome. The Course of disease was assessed by anthropometric evaluation, all systems examination such as CVS, RS, Abdominal and CNS. Under strict aseptic precautions, vena-puncture did and blood was collected in sterile EDTA tubes and shifted immediately to the hospital laboratory. Serum vitamin D3 values were evaluated in outside laboratory with my own expenses. Other investigations such as Chest X-rays and Ultra-sonogram abdomen were done for all children on both occasions (pre and post drug).

Results

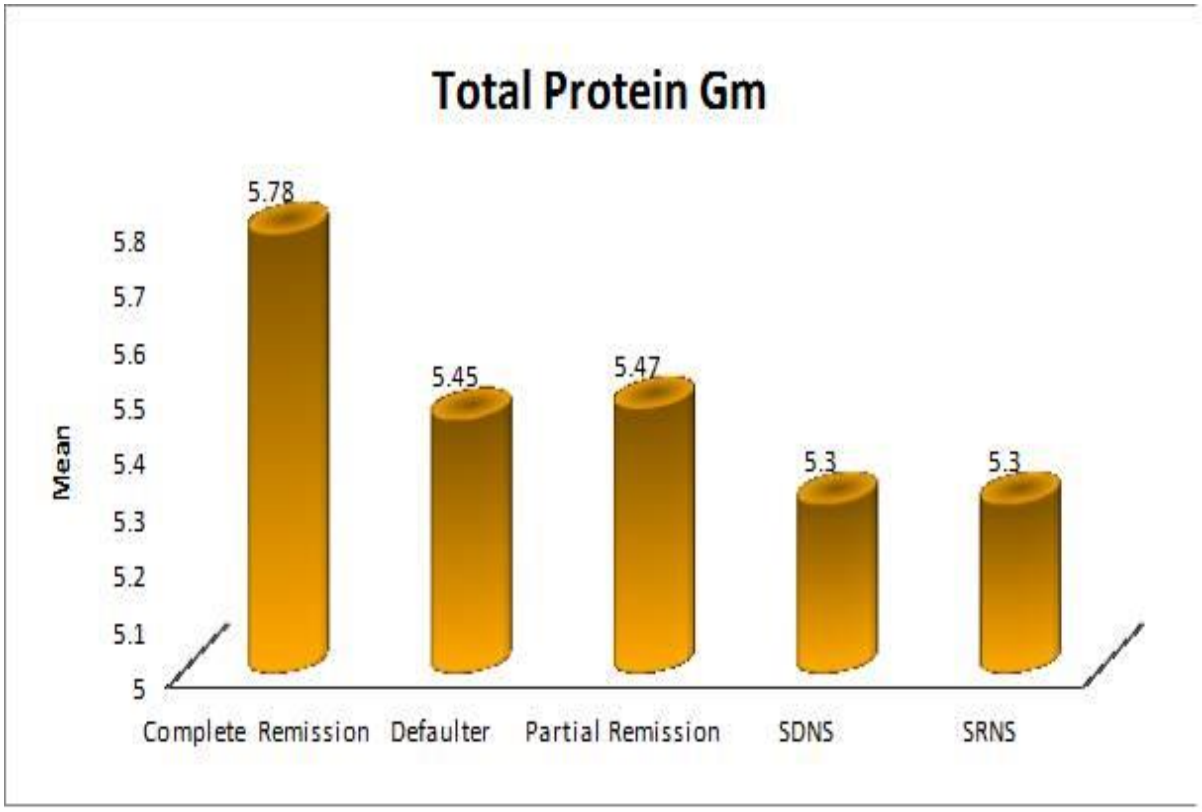
This study was done to find out the reduction in the Bone mineral density among children who completed steroid therapy for nephrotic syndrome, by using bone biochemical markers. This study also helped to assess the side- effect of Glucocorticoids on bone density and to prevent bone demineralization and pathological fractures in children.

The drug's effect on the children showed as pre and post drug effect and the P values were significant ($p<0.001$). This implied that the remission was attained in the majority of MCNS cases (**Graph – 1**).

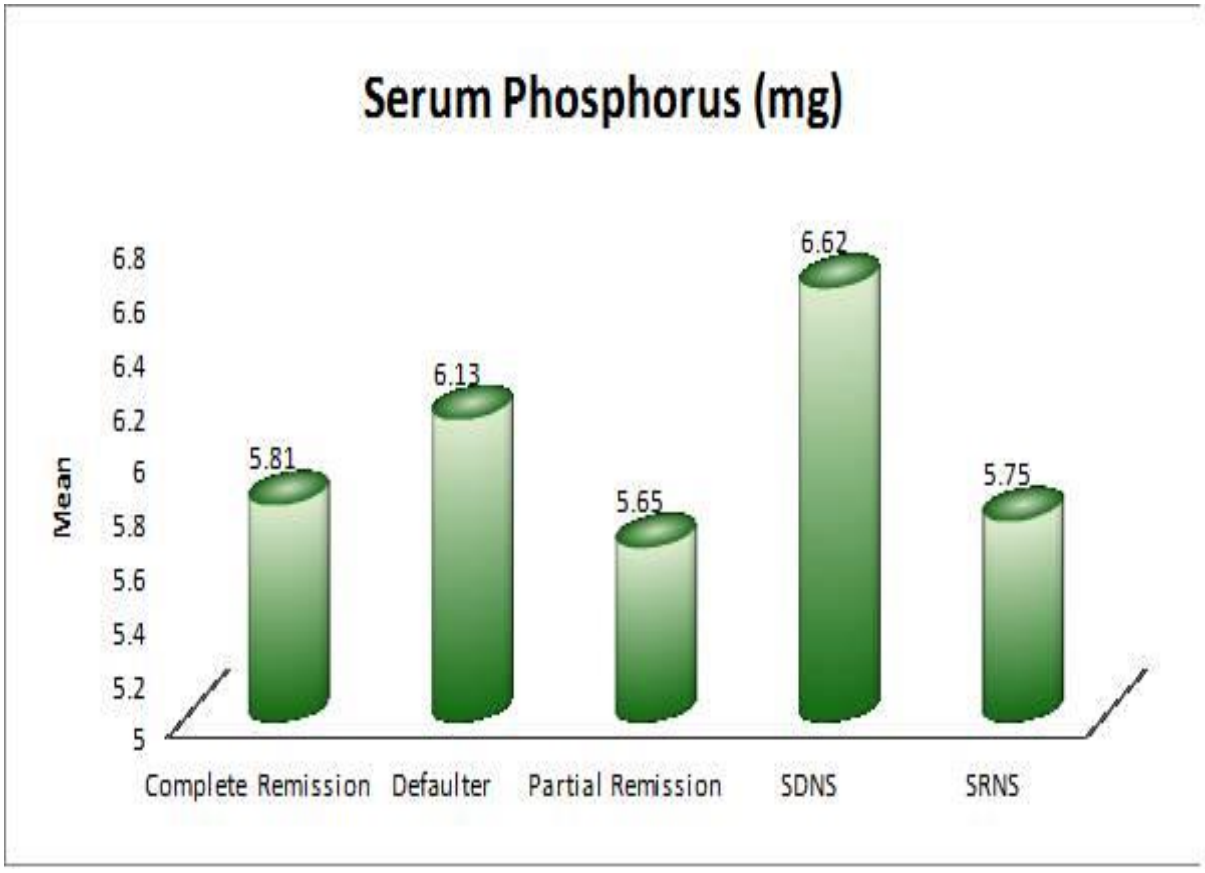
Graph - 1: Comparison of serum albumin among children.



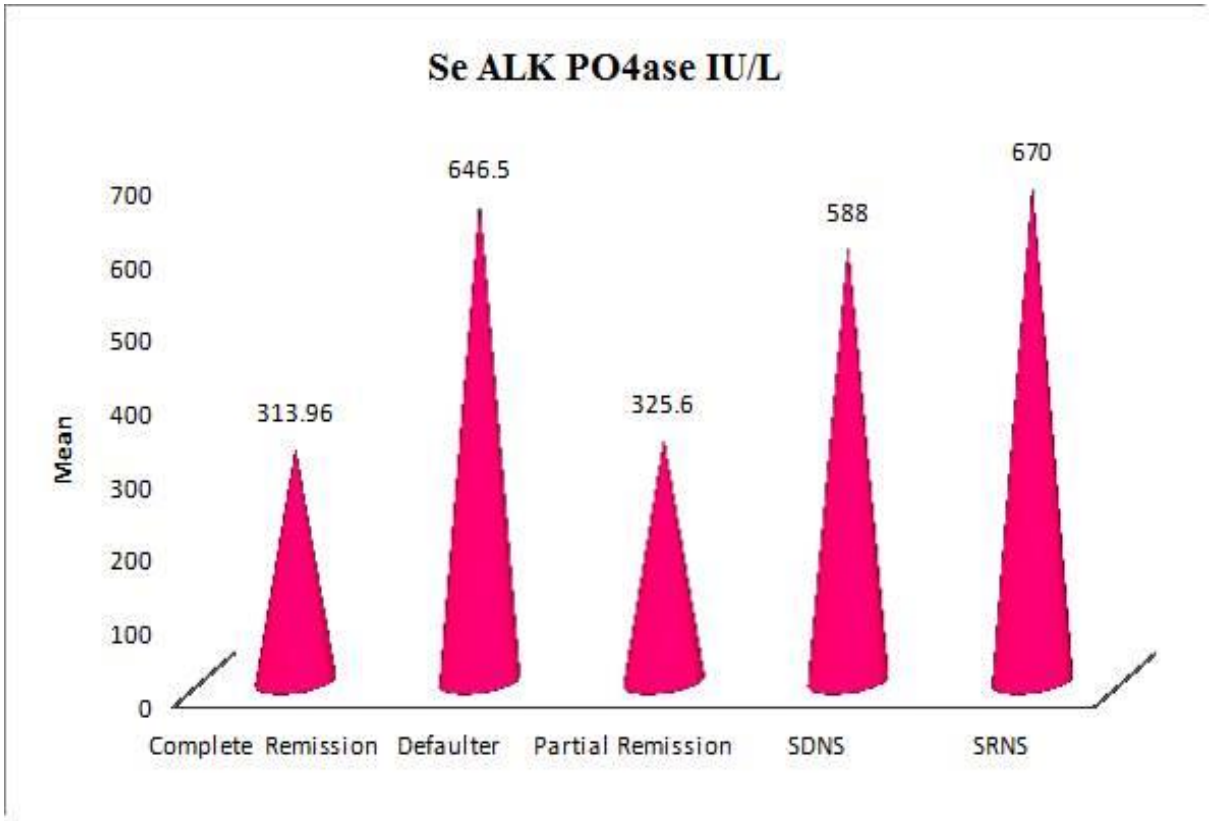
Graph – 2: Mean values of total proteins among the outcome of the study.



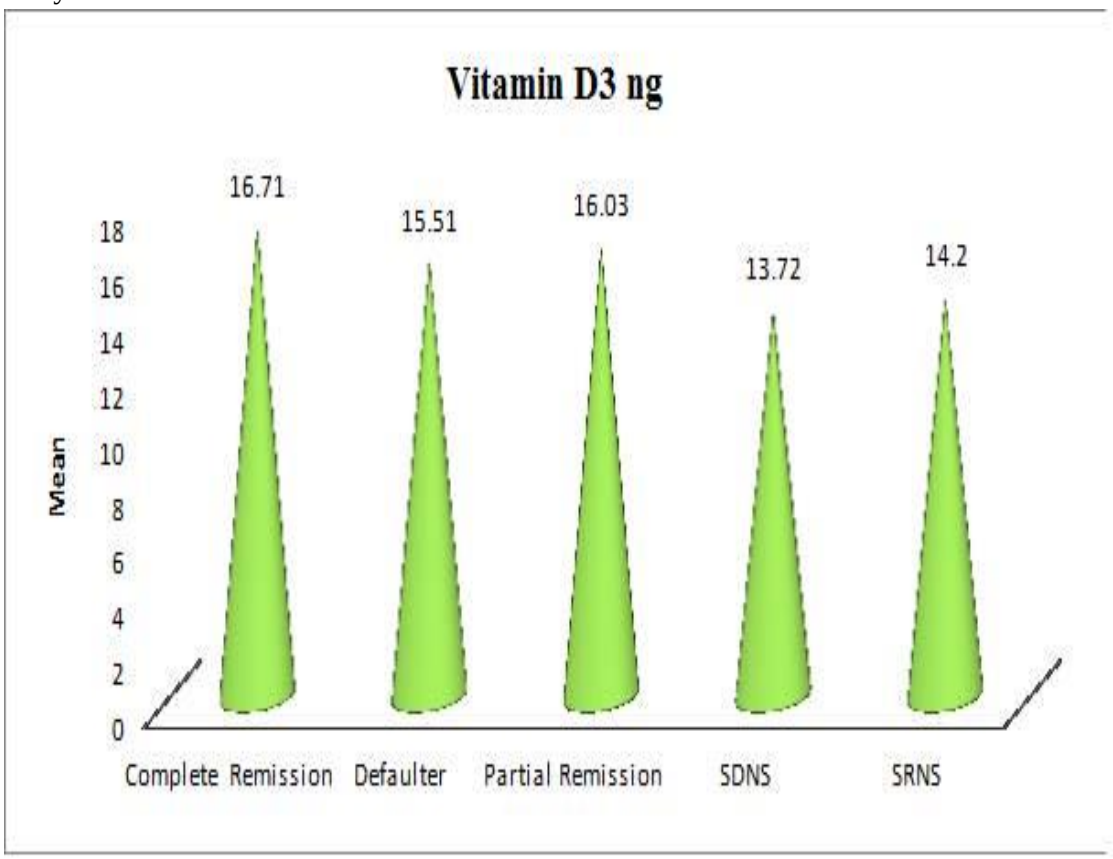
Graph – 3: Graphical representation of post-treatment effect of serum phosphorus among MCNS in this study.



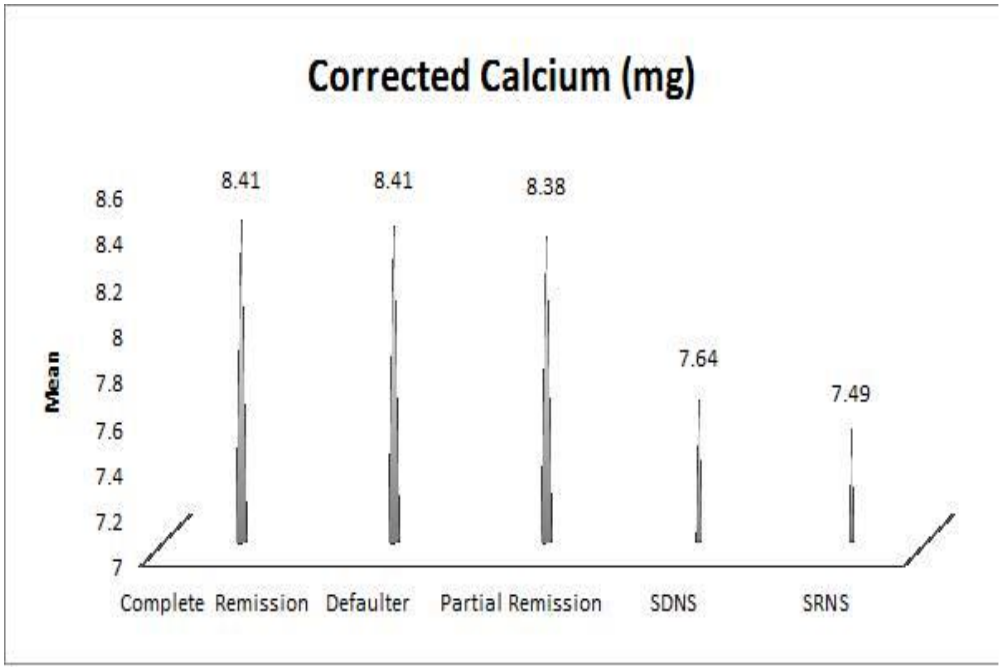
Graph – 4: Post-drug effect of serum alkaline phosphatase among the outcome of the study.



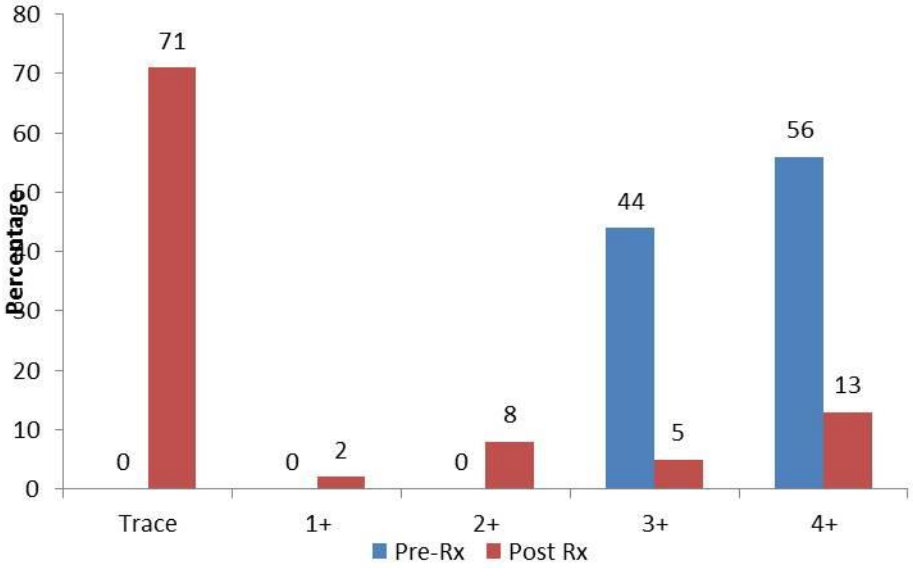
Graph – 5: Graphical representation of post-drug effects on vitamin D3 values among children in this study with MCNS.



Graph - 6: Graphical representation of corrected calcium values in post-drug condition.



Graph – 7: Graphical representation of the outcome of the study (> 80% with remission).



Total proteins were normal among children after completing the glucocorticoid therapy. The P value was <0.001 and was significant. Mean = 5.68. Standard Deviation (SD) = 0.28 (**Graph – 2**). The serum phosphorus was almost normal among remission MCNS Children and at higher levels among defaulters, SDNS and SRNS. The P value was 0.031 and was significant (**Graph – 3**).

Serum Alkaline Phosphatase returns to normal range among the complete and partial remission MCNS children in this study. The serum phosphatase values remained at higher levels among defaulters, SDNS and SRNS. The study was significant with P value <0.001 (**Graph – 4**).

There was the reduction in the Vitamin D3 levels among the study. This implied the post-drug effect reduction in the production of the Vitamin

D3 metabolites. The study was significant with P value <0.001. Mean = 16.28. Standard Deviation (SD) = 1.37 (**Graph – 5**). Lower levels of corrected calcium among SDNS and SRNS were as per **Graph - 6**. Majority of the children with remission of disease in the post-drug state was as per **Graph - 7**.

Discussion

Minimal Change Disease (MCD) is the leading cause of primary childhood Nephrotic Syndrome (NS). So, in childhood nephrotic syndrome, most children beyond the first year of life will be treated with corticosteroids without an initial renal biopsy [13]. Children with NS often have a number of calcium homeostasis disturbances, including hypocalcemia, reduced serum vitamin D metabolites and impaired intestinal absorption of calcium due to drug effect namely GCs [14]. Although the exact biochemical basis for Changes in levels of calcium and vitamin D metabolites in patients with NS remains speculative. Because of the potential adverse effects of these changes among growing children, widespread screening for vitamin D deficiency or routine vitamin D supplementation should be considered. As MCNS (Minimmal changes nephrotic syndrome) is the most common primary type of nephrotic syndrome in children, MCNS was taken exclusively for the study [15]. From the results of the study among 102 children, 5 children did not turn up for the post-treatment review. Among the remaining 97 children, 10 were Defaulters in drug intake i.e., not taken drug according to the regimen or skipped the doses. Among 87 children, 69 children were listed in complete remission and 10 children with partial remission. Excluding the defaulters, approximately 90.8% were in remission, after completing the first course of steroid therapy of 12 weeks for the first episode of nephrotic syndrome [16]. The 8 children were categorized as SDNS-6 Children and SRNS-2 children. As 6 children termed as SDNS, all 6 children had 2 consecutive relapses, when they were in the alternate day and they were admitted and had further followed up. Now those children are under next course of steroid therapy [17]. As all children were reviewed in nephrology OPD for getting drugs (GCs) for every 2 weeks once, Height, weight, Blood pressure and urine albumin will be examined. During that evaluation, 2 children didn't show remission with urine albumin dipstick were 3+ and 4+.These 2 children were admitted and evaluated as SDNS [18]. Among the load, 54% children were male and remaining 46 % were female sex, as MCNS is common in male than female. M>F. Majority of about 55 % children were between 3 years to 6 years. 35 % children were more than 6 years of age. The Height was not affected by the drug, as growth was not affected by the single course of drugs (as P valve was non- Significant). Serum albumin was significant in the study with P values (<0.001), which implies that there was a reduction in serum albumin in pre-treatment. The post-treatment, serum albumin increased with remission [19]. Urine albumin has measured both pre and post-treatment. Urine albumin was 3+ or 4+ in pre-treatment and in complete remission, urine albumin with NIL and TRACE. Partial remission with urine albumin values with 1+ or 2+. The P value was significant (p<0.001). The majority of children attained clinical remission after completing the drug THerapy GCs (glucocorticoids). The outcome of the study was relevant with 90% remission and the drug compliance was also good. The remission was in turn divided as Complete (71%) and partial (10%) remission [20]. Many of defaulter children had developed severe gastritis and discontinued the drug. The results imply that there was a reduction in the serum calcium in the post-drug status among children with MCNS. The hypocalcemia is the main side-effect of the GCs (glucocorticoids) and the values lie below the normal values of serum calcium. As seen earlier, glucocorticoids inhibit the osteoblast differentiation and osteoid formation and the outcome of hypocalcemia was obtained. The Mean of serum Ca 2+ is 7.101 mg% [21]. The mean value of complete remission corrected calcium 8.41 mg% after treatment and this value is at less than the lower limit. These values are even at low levels for SRNS, SDNS and are <7.5

mg%. The P value is <0.024 and is significant. Even though the study group was supplemented with calcium, these children are presented with hypocalcemia. This is due to drug-induced glucocorticoids. The serum phosphorus levels remain high in pre-treatment and stayed at upper limit even in the post-drug effect. But the values were very high in the defaulters, SRNS, and in SDNS. The P value is significant <0.031 [22]. The serum Alkaline phosphatase enzyme remains at the higher levels of defaulters, SDNS and SRNS. The enzymes return to normal levels but at the upper limit for complete and partial remission [13]. The P value is <0.001 and is Significant. The serum phosphorus and serum alkaline phosphatase values in the outcome reflect the post-drug effect of GCs (glucocorticoids) and these imply that the bone biomarkers are increased due to GCs (prednisolone) which favors the study. The Vitamin D3 metabolites are also affected and the values also remain at the lower limit i.e. <20 ng%, which implies the osteoporosis. The lower range of vitamin D3 is believed due to urinary loss of vitamin D3 binding proteins in the nephrotic syndrome [24]. The pretreatment values of vitamin D3 was not less than the osteoporotic range, in due course of the disease, the hypovitaminosis D3 was identified. Glucocorticoids also inhibit the Vitamin D3 metabolism. So, all the children should be supplemented with vitamin D3 according to RDA of 400 IU /day without fail. In this vitamin, D3 was not given [25].

Conclusion

This is to conclude that the GCs (glucocorticoids) is the drug of choice and standard therapy for Minimal Change Nephrotic Syndrome (MCNS), but the drug-induced hypocalcemia and hypovitaminosis D are assessed by our study. Added to the above, the disease itself characterized by hypocalcemia and hypovitaminosis D. So, all children should undergo this assessment to prevent growth failure and pathological fractures. All children should be supplemented with more amount of dietary calcium in addition to oral calcium tablets and also with vitamin D3. Recently, some studies had been done to supplement with bisphosphonate.

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