OPEN RANDOMISED CONTROLLED INTERVENTIONAL PROSPECTIVE STUDY TO EVALUATE THE ROLE OF PROPHYLACTIC CALCIUM AND VITAMIN D IN PREVENTING SHORT TERM STEROID INDUCED BONE LOSS IN NEW ONSET NEPHROTIC SYNDROME

A dissertation submitted in partial fulfillment of the rules and regulations for the award of MD (Branch VII – Paediatrics) degree of The Tamil Nadu Dr. MGR Medical University, Chennai to be held in March 2009

CERTIFICATE

This is to certify that the dissertation entitled **"Open Randomized Controlled Interventional Prospective study to evaluate the role of prophylactic Calcium and Vitamin D in preventing short term steroid induced bone loss in children with new onset Nephrotic Syndrome "** is a bonafide, original work done by **Dr. Surabhi Choudhary**, during her academic term – **March 2006 to February 2009**, at the Christian Medical College, Vellore, in partial fulfillment of the rules and regulations for the award of MD (Branch VII – Paediatrics) degree of The Tamil Nadu Dr. MGR Medical University , Chennai to be held in March 2009

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ACKNOWLEDGEMENTS

First and foremost, I would like to thank all my patients and their families for their cooperation, eager willingness to participate in the study and their efforts to return regularly for the scheduled hospital visits.

I am grateful to Dr. Jana (Head of the Department, Child Health) and Dr. Anand Job (Principal) and the members of the research committee for permitting me to do this study.

I thank Dr. Indira Agarwal, my thesis guide and my teacher for her support, able guidance and encouragement as also for her painstaking endeavor of revising and rerevising my work.

My gratitude to Dr. M S Seshadri, co guide for my thesis, for his initiative, suggestions and guidance as also for being kind enough to provide free use of the DEXA machine for the study.

I am grateful to Dr. Prabhakar Moses and Dr. Anna Simon for permitting me to include their unit children in the study.

I would like to extend my gratitude to all my teachers and colleagues in the department of Child Health for their interest and help in recruiting patients.

Many thanks to my statistician, Ms Nithya for her prompt and efficient work.

My sincere thanks to all the technicians in the DEXA room who performed the DEXA test at the appropriate dates.

I would like to acknowledge the efforts taken by Mr. Kumar, the Medical Records Officer of the Paediatric Nephrology OPD, and the staff in Child Health treatment room in coordinating the study.

This study would not have been possible without the support of my friends and well wishers.

Most of all I would like to thank my parents for taking care of me and nurturing every sphere of my life. Wherever I am today is solely because of them.

Surabhi Choudhary

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INTRODUCTION

Nephrotic Syndrome is a common glomerular disorder affecting children. It is characterized by heavy proteinuria, hypoalbuminemia, edema and hypercholesterolemia. The incidence is 2-3 per 1, 00,000 children per year (1).

Approximately 90% of children with Nephrotic Syndrome have some form Idiopathic Nephrotic Syndrome. This includes 3 histological types:

- Minimal Change Disease
- Mesangial Proliferative Glomerulonephritis (MesPGN)
- Focal Segmental Glomerulosclerosis

Corticosteroids like Prednisolone are the recommended first line treatment for nephrotic syndrome. Majority of children have Steroid Sensitive Minimal Change Disease. Most children with Steroid Sensitive Nephrotic Syndrome (SSNS) have repeated relapses, which generally decrease in frequency as the child grows older (1).

Glucocorticoids are used in myriad other pediatric diseases. It is estimated that 10% of children may require some form of glucocorticoids at some point in their childhood (2). Prolonged steroid use is known to cause osteoporosis. Decreased bone mineral density (BMD) has been described in various pediatric disorders that require glucocorticoids, including asthma, juvenile rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, and organ transplantation (3-6). Impairment of childhood growth with an approximate cortisone dose of 1.5 mg/kg/day was first described over 40 years ago; osteopenia in children receiving a Prednisolone dose of less than 0.16 mg/kg/day has also been reported (7, 8).

37,000 children were studied in UK by Van Staa et al (9), to evaluate the incidence of fractures among pediatric glucocorticoid users .Results showed that the risk

of fracture was increased in children who received four or more courses of oral corticosteroids for a mean duration of 6.4 days. Fracture risk was also increased among children using 30 mg Prednisolone or more each day.

Childhood Steroid sensitive nephrotic syndrome provides a clinical model of chronic glucocorticoid therapy in the absence of significant underlying disease activity. The course of SSNS is characterized by relapses which result in protracted, repeated courses of glucocorticoids**.** The standard Prednisolone dose for new onset disease and relapses is 2 mg/kg per day which far exceeds the 5 mg/day that is considered a risk factor for Glucocorticoid induced osteoporosis in adults (3).

While osteoporosis has long been considered a disease of the aging, there is increasing awareness that children are not exempt from developing the disease. Threats to bone health that are operative during the pediatric years may be particularly costly long-term, since growth and development of the skeletal system play a critical role in determining bone strength and stability in later years (10).

Although the deteriorative effect of steroid treatment on children's bones has been well known for years, no recommendations have been suggested for the prevention of diminished BMD and BMC in children with nephrotic syndrome. There are no clear cut guidelines as to when bone protective strategies must be instituted. This study was thus undertaken to determine the protective efficacy of Calcium and Vitamin D supplementation in children with Nephrotic Syndrome on short term steroids. Using Bone Mineral Density (BMD) and Bone Mineral Content (BMC) as tools, those receiving supplementation were compared with those not receiving it.

The results will enable us to draw protocols / guidelines for institution of bone protective therapy for children on short term steroids.

AIM

To study the effect of short term corticosteroid therapy and the prophylactic role of Calcium and Vitamin D on bone health in children with nephrotic syndrome

OBJECTIVES

PRIMARY OBJECTIVES

- To study the effect of short term steroids on bone in children with nephrotic syndrome using serial measurements of Bone Mineral Density (BMD) & Bone Mineral Content (BMC)at the Lumbar spine.

- To evaluate the role of prophylactic Calcium and Vitamin D in preventing short term steroid induced bone loss in children with new onset Nephrotic Syndrome

SECONDARY OBJECTIVE

- To study the adverse effects of steroid therapy

LITERATURE REVIEW

NEPHROTIC SYNDROME

Childhood Nephrotic syndrome is a chronic glomerular disorder. It is a disorder of glomerular capillary wall permeability that may be primary, or secondary to an overt systemic disease.

Nephrotic syndrome is characterized by heavy proteinuria, hypoalbuminemia (<2.5 g/dl), edema & hypercholesterolemia (>200 mg %) (1). Proteinuria is considered to be in the nephrotic range when the urine protein is 3+/4+ on a dipstick , Spot Urine Protein / Creatinine ratio is > 2 or Urine Albumin > 40 mg / m2/ hour (on a timed sample) (11).

The International Study of Kidney Disease in Children (ISKDC) reported the following distribution by histology in children with nephrotic syndrome (12):

Glomerular Histology	% distribution
Minimal Change Disease (MCD)	77 %
Focal Segmental Glomerulo Sclerosis (FSGS)	10 %
Proliferative Glomerulonephritis	
Membranoproliferative (MPGN)	5 %
Diffuse Mesangial (DMP)	3 %
Crescentic (CGN)	3 %
Membranous Nephropathy (MN)	2 %

Idiopathic nephrotic syndrome is the most common form of nephrotic syndrome in children, representing more than 90 percent of cases before 10 years of age and 50 percent after 10 years of age (13). Idiopathic nephrotic syndrome is characterized by diffuse foot process effacement on electron microscopy and Minimal changes (called minimal change disease (MCD), Focal segmental Glomerulosclerosis (FSGS), or Mesangial proliferation on light microscopy.

Patients with histological findings of MCD are generally responsive to steroid

therapy. Because clinical findings are highly predictable in differentiating MCD from other forms of nephrotic syndrome, steroid therapy is initiated in patients who are likely to have MCD based upon clinical criteria without histological confirmation by renal biopsy. One third of patients with FSGS will also initially respond to steroid therapy.

Clinical experience has demonstrated that the response to steroid therapy rather than the histological features seen on renal biopsy is better at predicting long-term prognosis. Patients with nephrotic syndrome can be defined by their response to steroid therapy as follows:

Steroid-sensitive nephrotic syndrome - More than 90 percent of patients who respond to steroid therapy have MCD, and FSGS is seen in the remaining patients (14). Steroid sensitive NS is considered to be a relatively benign condition; progression to end stage renal failure is extremely rare and over 80 % achieve spontaneous remission in later childhood.

Steroid-resistant nephrotic syndrome - One-fourth of the patients who fail to respond to steroids have MCD (14). Patients who fail an initial course of steroids should undergo renal biopsy to determine the underlying diagnosis to guide further therapeutic choices.

Some of the terms that help define the course of the disease are as follows:

REMISSION: Urine Albumin nil or trace (or proteinuria < 40 mg / m2 / h) for 3 consecutive days

RELAPSE: Urine Albumin 3+ or 4+ (or Proteinuria > 40 mg/m2/hr) for 3 consecutive days, having been in remission previously

FREQUENT RELAPSES: 2 or more relapses in 6 months of initial response, or more

than 3 relapses in any 12 months.

STEROID DEPENDENCE: Occurrence of 2 consecutive relapses during steroid therapy or within 2 weeks of cessation.

STEROID RESISTANCE: Absence of remission despite therapy with daily prednisolone in a dose of 2 mg/ kg /day for 8 weeks.

The aim of management of Nephrotic Syndrome in children is to induce and maintain remission with complete resolution of proteinuria and edema without encountering serious adverse effects of therapy.

STEROID THERAPY

Empiric steroid therapy can be initiated in patients with a high probability of having minimal change (MCD) without confirmation of the diagnosis by renal biopsy because more than 90 percent of patients with MCD will respond to corticosteroid therapy within eight weeks (14, 15). Initial steroid therapy is given to patients who fulfill all of the following criteria.

- Age older than 1 year and younger than 10 years of age
- None of the following findings: hypertension, gross hematuria and a marked elevation in serum creatinine
- Normal complement levels
- No extra-renal symptoms such as malar rash or purpura

Idiopathic nephrosis is steroid-responsive in most children (14). Approximately 30 percent of treated patients will not have a relapse and are therefore cured after the initial course of therapy (15). Ten to 20 percent will relapse several months after steroid treatment is discontinued, but will have less than four steroid-responsive episodes before permanent remission occurs. However, 30 to 40 percent of patients will have frequent

relapses, and some patients will relapse while on steroid therapy.

Patients who are frequent relapsers or steroid dependent often require multiple and/or prolonged courses of steroid therapy and are at risk for steroid toxicity. A longer duration of the initial course of steroids, which includes periods of daily and alternate day steroids, appears to reduce the risk of relapse and decreases the cumulative dose of steroids (16-19).

This is illustrated by a meta-analysis that included 12 trials (17). The following findings were noted:

- In a pooled analysis from six trials, treatment with Prednisolone for three to seven months reduced the risk of relapse at 12 to 24 months post-therapy versus that observed with a two-month regimen (RR of 0.70 95% CI 0.58 to 0.84). There was no difference in cumulative steroid dose.
- In a pooled analysis of four trials of 382 children, the risk of relapse was lower with six versus three months of therapy (RR of 0.57, 95% CI 0.45 to 0.71). There was no difference in cumulative steroid dose.
- A reduced risk of relapse was associated with both an increase in the duration and an increase in the dose of steroid therapy.

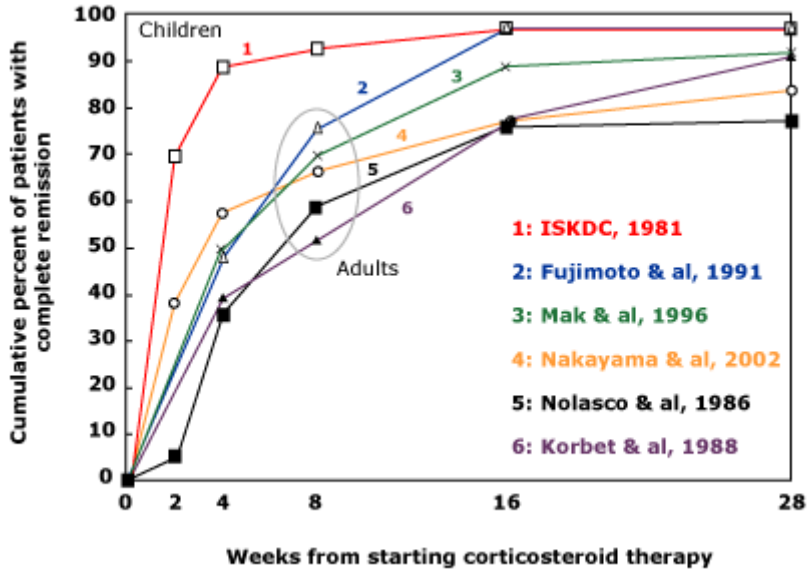
Similar findings were seen in a randomized controlled trial from the Arbeitsgemeinshaft für Pädiatrische Nephrologie (APN) that compared a standard initial treatment of Prednisolone 60 mg/m2 per day for four weeks, to a longer initial regimen of six weeks of continuous prednisone 60 mg/m2 followed by six weeks of alternate day prednisone of 40 mg/m2 (18). The subsequent relapse rate within 12 months after

discontinuation of continuous therapy was lower with the prolonged course of therapy compared to the standard treatment (36 versus 61 percent).

Increasing initial immunosuppression by adding Cyclosporine to steroid therapy had been proposed as a way to reduce the relapse rate. However, the addition of cyclosporine does not alter the two-year relapse rate and the combination of cyclosporine and Prednisone compared to prednisone alone results in a greater number of side effects (20, 21). As a result, steroids alone are used as the initial therapy for childhood nephrotic syndrome.

Time to response

In a report from the International Society of Kidney Disease in Children (ISKDC), approximately 90 percent of patients who will respond to steroids do so within four weeks after starting steroids, with the remaining 10 percent going into remission after two to four more weeks of a daily steroid therapy (12).



Options in those who are not in remission after four weeks of daily steroid therapy

include the following:

- 3 pulses of Methyl Prednisolone (1000mg/1.73 m2) on alternate days. Patients who have persistence of proteinuria one week after this treatment are considered steroid resistant and a renal biopsy is performed.
- Biopsy patients without administering the three pulses of Methyl Prednisolone, as there is an increased likelihood that they have another glomerular disease that may not be responsive to additional steroid therapy.
- Continue daily steroid therapy for another four weeks because an additional 10 percent of steroid responsive patients will respond after four weeks of therapy (12).

Patients who fail to respond to a maximum eight weeks of daily steroid therapy are considered steroid resistant and require a renal biopsy to determine the underlying glomerular disease (12).

Outcome based upon steroid response

- A report from the ISKDC evaluated the outcome of 389 children with minimal change disease who were followed for a mean of 9.4 years based upon their response to initial steroid therapy (13). Following results were noted:
- Ninety-two percent of patients responded to steroids. Of this group of 334 patients, 41 percent did not relapse within six months after the initial course of steroid therapy, 28 percent relapsed frequently, 20 percent had a single relapse within the six month time period, and 3 percent failed to respond to subsequent courses of steroid therapy.
- Prognosis was best in the steroid-responsive patients who did not relapse in the first six months. Approximately 75 percent either continued in remission during follow-up or relapsed rarely. Only 4 percent became frequent relapsers.

- Patients with persistent proteinuria after eight weeks of steroid therapy (steroid-resistant) had a 21 percent risk of progression to end-stage renal disease (ESRD). This risk rose to 35 percent among the 60 percent of initial steroid-resistant patients who had persistent proteinuria six months after the initial course of steroid therapy.
- Overall, 95 percent of children did well, 4 to 5 percent died from complications (eg, peritonitis) or progressed to ESRD.

EFFECTS OF CORTICOSERROIDS

Glucocorticoids are important regulators of diverse physiological systems and are often used in the treatment of a number of renal, chronic inflammatory, autoimmune, and neoplastic diseases. It is estimated that 10% of children may require some form of corticosteroids at some point in their childhood (2).

At physiological levels, glucocorcorticoids are involved in negative feedback modulation of corticotrophin releasing factor and Adrenocorticotropic hormone, maintenance of blood glucose and liver glycogen levels, maintenance of cardiovascular function, blood pressure and muscle work capacity, excretion of a water load and protection against moderate stress. They are unique among pharmacological agents in that being synthetic analogues of chemicals produced by the body they have physiological and pharmacological activities.

Two categories of adverse effects occur with the therapeutic use of systemic glucocorticoids: those resulting from prolonged use of large doses and those resulting from withdrawal of therapy.

The adverse effects of Glucocorticoids include:

1. Effects on Bone

a. Osteopenia / Osteoporosis

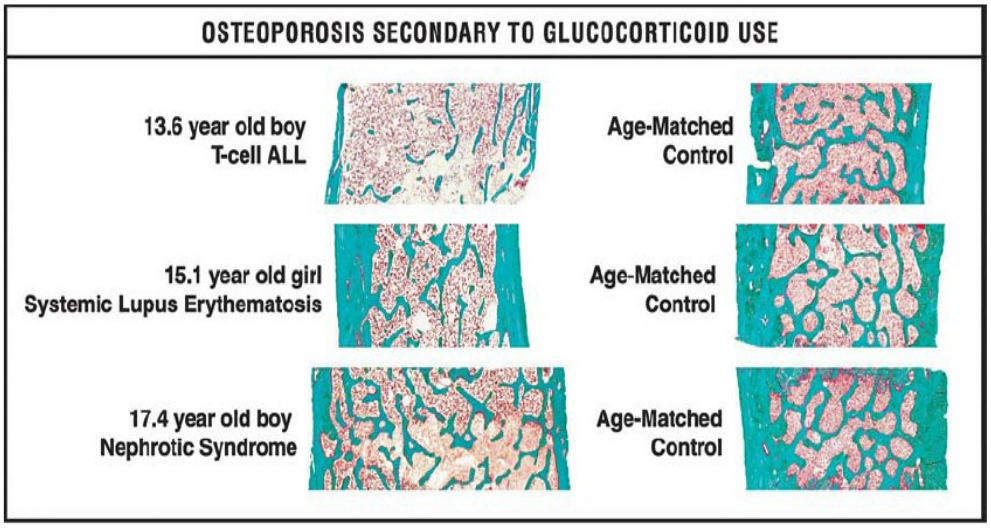
b. Avascular Necrosis

Infancy and childhood are important periods of life for bone development. Prolonged steroid use is known to cause osteoporosis. Impairment of childhood growth with an approximate cortisone dose of 1.5 mg/kg/day was first described over 40 years ago; Osteopenia in children receiving a prednisolone dose of less than 0.16 mg/kg/day has also been reported (7, 8).

Loss of bone and deterioration in short term growth are dependent on the type and dose of glucocorticoids. Moderate to high dose glucocorticoid therapy is associated with loss of bone and increased risk of fracture (22).

Studies have shown that the greatest reduction in bone mineral content (BMC) and BMD among children with leukemia occurred during the first 6–8 months of chemotherapy (23 – 26), similar to the potent Glucocorticoid effect on bone seen in the adult population**.** The temporal pattern of bone mass changes in adults with Glucocorticoid-induced osteoporosis appears to be biphasic, with a precipitous drop observed in the first 6–12 months of therapy, followed by a gradual, but sustained, loss in subsequent years (27, 28).

GCs toxicity appears to have a predilection for trabecular bone, which has a higher metabolic activity than cortical bone, and thus may be more sensitive to the deleterious effect of steroids (29). This is supported by the propensity of GCs to affect the spine.



Qualitative ilial histomorphometry in children with glucocorticoid- induced osteoporosis, with results compared to healthy controls

The mechanisms by which steroids affect bone are many:-

Glucocorticoids have a suppressive effect on osteoblastogenesis in the bone marrow and promote the apoptosis of osteoblasts and osteocytes, thus leading to decreased bone formation (30). Accumulation of apoptotic osteocytes may also explain the so called "osteonecrosis", also known as aseptic or avascular necrosis. There is some evidence to suggest that Glucocorticoids may also increase bone resorption by extending the lifespan of pre-existing osteoclasts (31).

Glucocorticoids may also promote calcium loss through the kidney and gut, and this negative calcium balance can itself lead to increased bone remodeling and osteoclastic activity due to secondary hyperparathyroidism (32).

Glucocorticoids may also impair the attainment of peak bone mass and delay growth through alterations in gonadal function at the level of the pituitary and through direct effects on the gonads. Studies in adults show that glucocorticoid therapy may be associated with testosterone deficiency as well as reversible gonadotrophin deficiency (33, 34). Levels of other sex steroids such as androstenedione and estrogen may also be

depressed due to adrenal inactivity following chronic glucocorticoid therapy (35). In addition, there is in vitro evidence suggesting that glucocorticoids impair FSH action, thus reducing estrogen secretion (36).

According to Wolff's law, bone grows in response to the magnitude and direction of the forces to which it is subjected (37). Glucocorticoids are also well known to cause muscle wasting (38). Therefore, glucocorticoid-induced myopathy may contribute to bone deficits via the functional muscle-bone unit.

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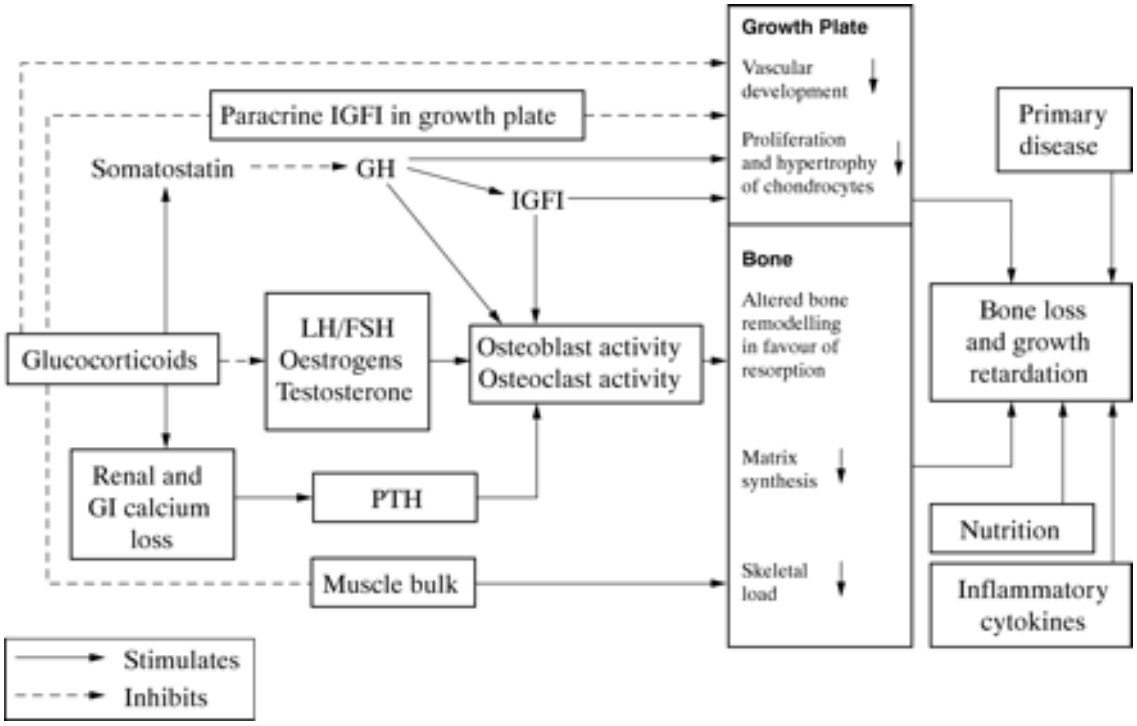


Mechanisms of Glucocorticoid induced bone loss and growth retardation

2. Growth Suppression: Growth suppression is a long term adverse effect of Glucocorticoid therapy. High dose glucocorticoid therapy can attenuate physiological growth hormone (GH) secretion via an increase in somatostatin tone, and the GH response to GH stimulation tests may be reversibly impaired in some cases of steroid exposure (39, 40). However, glucocorticoid induced growth failure may also be due to direct effects on the growth plate. Infusion of glucocorticoids into the growth plate leads to a temporary

reduction in the growth rate of that leg and may disrupt the growth plate vasculature (41, 42). Glucocorticoid exposed chondrocytes show reduced proliferation rates and a reversible, prolonged resting period. In vitro studies suggest that local somatotrophic action of GH and IGF-1 may be affected by a number of different mechanisms, including alterations in the activity of the GH binding protein, down regulation of GH receptor expression and binding capacity, and a reduction in local IGF-1 production and activity (43-46).

3. **Cushing's Syndrome:** Cushing's syndrome was the term originally used to characterize the effects of idiopathic hypercorticism and may be induced by prolonged administration of glucocorticoids. The clinical features include hypertension, truncal obesity, osteoporosis and thinning of subcutaneous tissues. The distribution of fat is predominantly in the subcutaneous tissues of the upper back and abdomen and produces a characteristic 'buffalo hump'. Skin changes include striae (on the lower abdomen, legs, arms and chest), hirsutsm and acne. Hypertension is mild, but may require glucocorticoid dose modification. Biochemically, the illness is characterized by high plasma glucocorticoid levels and suppression of the hypothalamic pituitary axis.

4. **Immunosuppression**

Lymphopenia and neutropenia: Glucocorticoids act as immunosuppressive agents and anti-inflammatory agents. They mask the signs and symptoms of inflammation. Glucocorticoids profoundly affect cell – mediated immune reactions, including delayed hypersensitivity and allograft rejection. Children receiving high dose glucocorticoid over a prolonged period are prone to infections that are associated with defects of delayed hypersensitivity like tuberculosis.

Glucocorticoids decrease the number of circulating lymphocytes, monocytes, basophils and eosinophils, but increase the number of circulating neutrophils. Excess glucocorticoids may also cause polycythemia (47).

5. CNS Effects: The glucocorticoid effects on the central nervous system are mediated by changes in CNS concentration of plasma glucose and electrolyte balance (47).

a. Psychosis:

This is more common in idiopathic Cushing's syndrome than in iatrogenic disease

b. Mood and behavioural disturbances:

In a prospective study on children receiving high dose IV intermittent glucocorticoids, behavioural abnormalities like altered mood, hyperactivity, sleep disturbances and psychosis were noticed.

6. CVS effects:

a. Hypertension: Glucocorticoids can cause hypertension by influencing renal sodium excretion

b. Dyslipoproteinemia

7. Cataracts and glaucoma

8. Metabolic Effects

a. Impaired carbohydrate tolerance

b. Protein wasting

c. Metabolic acidosis

9. Proximal Myopathy

When considering the use of systemic corticosteroids, one must weigh the risks against the benefits of the drug. Though extremely potent and effective against a variety of diseases, they are associated with significant toxicity. Therefore, in using

corticosteroids for treatment of chronic illnesses, it is imperative to monitor for the adverse effects of the drugs

SSNS AS A MODEL FOR STUDYING EFFECTS OF STEROIDS ON BONE HEALTH

Childhood Steroid sensitive nephrotic syndrome provides a clinical model of chronic glucocorticoid therapy in the absence of significant underlying disease activity. The nephrotic state is clinically quiescent as long as high-dose glucocorticoid therapy is continued. Unfortunately, SSNS relapses in the majority of children when the glucocorticoids are reduced, which results in protracted, repeated courses of glucocorticoids. The standard prednisone dose for relapses is 2 mg/kg per day (18) which far exceeds the 5 mg/day that is considered a risk factor for Glucocorticoid induced osteoporosis in adults(3). Although SSNS relapses are associated with transient increases in cytokines, these abnormalities promptly resolve with glucocorticoid therapy and disease remission (48). Therefore, SSNS is proposed as a clinical model without significant systemic inflammatory involvement to examine the effects of glucocorticoids on the growing skeleton (49).

RESEARCH INSTRUMENT: DEXA

Dual energy x-ray absorptiometry (DEXA) is a cheap, easily accessible method with high precision and accuracy for the measurement of mineral content that employs low levels of radiation. DEXA was developed in the late 1980s and was introduced for use in adults to diagnose and monitor the course of osteoporosis, especially in post menopausal women.

DEXA is based on the attenuation of two standardized X-ray beams with differing energy levels as they pass through different types of body tissue. DEXA makes it possible

to differentiate between several body tissues and divide the organism into its content of mineral, fatty and lean mass (50).

DEXA determines the mineral quantity in g (bone mineral content - BMC) contained in a given projection of bone. Dividing this mineral content by the bone area (BA) of the location obtains what is conventionally known as bone mineral density (BMD) in g/cm2.

A DEXA scan report shows the following measurements:

a) **Bone Mineral Content (BMC)**

b) **Bone Area (BA)**

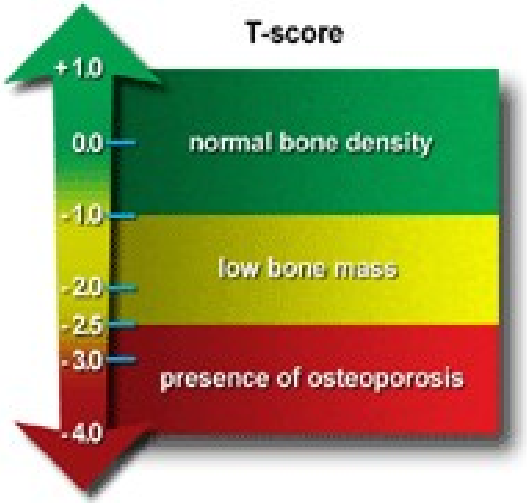
c) **Bone Mineral Density (BMD) = BMC / BA**

d) **Z score:** the difference between the measured BMD and the age-sex matched average

e) **T score:** the difference between the measured BMD and the sex matched average young adult standard

WHO criteria for diagnosing osteoporosis in adults are based on DEXA BMD measurements (51):

- A T-score within 1 SD (+1 or --1) of the young adult mean indicates normal bone density.
- A T-score of 1 to 2.5 SD below the young adult mean (--1 to -- 2.5 SD) indicates low bone mass (osteopenia).
- A T-score of 2.5 SD or more below the young adult mean (> -- 2.5 SD) indicates the presence of osteoporosis



DEXA USE IN CHILDREN – PROBLEMS

Special considerations are involved in the use of DEXA to assess bone mass in children

1. Comparing the bone mineral density (BMD) of children to the reference data of adults (to calculate a T-score) will underestimate the BMD of children, because children have less bone mass than fully developed adults. This would lead to an over diagnosis of osteopenia for children. Thus, T – scores are meaningless in children. To avoid an overestimation of bone mineral deficits, BMD scores are commonly compared to reference data for the same gender and age (by calculating a Z-score).
2. There are very few patterns of normative (reference) data available for BMD / BMC in children. Horlick et al (52) in a recent study concerned themselves with developing a model for evaluating bone mass by DEXA in children and adolescents, and concluded that the variables ethnic origin, weight, height and bone area accounted for 89 to 99% of BMD. Furthermore, they pointed out that the behavior of BMD was specific to different clinical conditions, suggesting that, in addition to all the variables quoted above, the patient's diagnosis must also be taken into account when the results of bone densitometry are interpreted.
3. In addition to age, children pose a unique problem because as time progresses the measured subject changes in shape and volume. An important confounding variable in BMD measurements is bone size. Because the density obtained is based on area and not volume and because the area does not increase in the same proportion as the volume during growth, large bones are overestimated and small bones are underestimated in terms of BMD. Infancy and adolescence are periods

during which the organism is growing rapidly and, therefore, the size of bones vary intensely. Therefore a proportion of the change observed in area-based BMD during these periods is not a real increase in mineralization, but, in fact reflects the volumetric growth of the skeleton (53).

DEXA overestimates the BMD of taller subjects and underestimates the BMD of smaller subjects. Two recent studies by Wren et al (54), and Gafin & Baron (55), illustrated that failure to consider the confounding effect of height results in an overestimation of bone deficits in children with chronic disease.

BMC VS BMD AS A MEASURE FOR GROWTH STUDIES

Bone mineral content, not bone mineral density, is the correct bone measure for growth studies (56).

Areal Bone Mineral Density (aBMD) obtained by dividing BMC with BA is not an accurate measurement of true volumetric bone mineral density, which is mass divided by a volume. The confounding effect of differences in bone size is due to the missing depth value in the calculation of bone mineral density. It is assumed that BMC and BA are directly proportional to one another, such that a 1% change in BA is matched by a 1% change in BMC. This is rarely the case, and the exact relationship depends on the population group, skeletal site, body size, instrumentation, and scanning conditions (57).

There is no mechanical reason why true density should change appreciably with growth, and Matkovic et al (58), showed that, in fact, it did not.

BMD is the wrong measurement during growth, because it factors out most of the component of bone accumulation that is associated with change in bone size (57, 59). What is important in a growth experiment is bone mass (measured as bone mineral content, BMC). Despite DEXA's problems with estimating volume, it is still a fairly

accurate measure of bone mineral content.

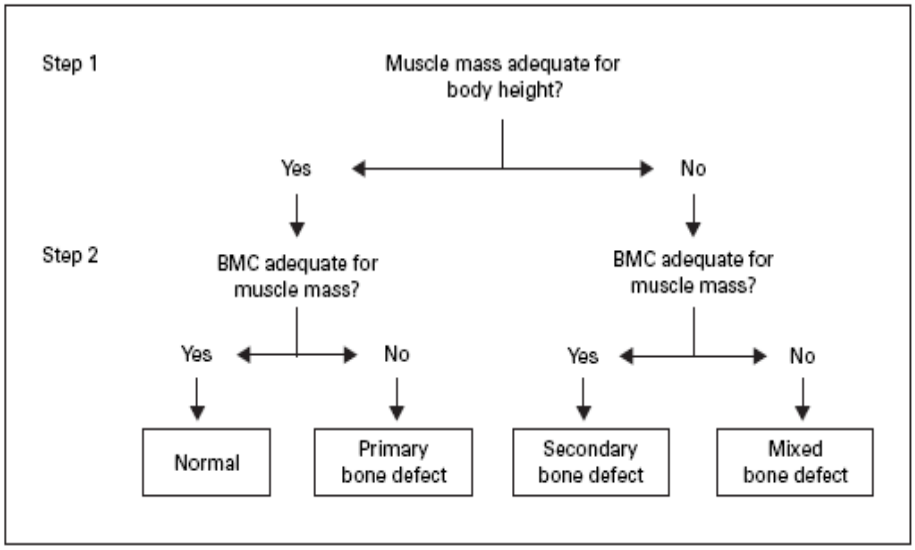
Although BMD plays a valuable role in fracture-risk assessment and clinical management in adults, it is advocated that its use in epidemiological research be discontinued (57).

RADIATION WITH DEXA

Contrary to popular belief, the amount of radiation exposure during a DEXA scan is minimal. The radiation dose is approximately 1/10th that of a standard chest X-ray (60).

DEXA AND INTERPRETATION OF BONE HEALTH

BMD (by DEXA) criteria for the diagnosis of osteoporosis in children do not currently exist. However, DEXA-based parameters (BMC) can be useful to understand the patient's bone health status (61). By applying an algorithm that is based on Frost's mechanostat theory, a primary, secondary, or mixed bone defect can be determined (62-64).



Algorithm for assessment of pediatric osteoporosis in the context of chronic illness (proposed by Schoenau et al. [65] for pQCT, and adapted to DEXA by Crabtree et al

FRACTURE RISK ESTIMATION IN CHILDREN

Oral corticosteroids are known to increase the risk of fracture in adults, but their effects in children remain uncertain.

The largest study to evaluate the incidence of fractures among pediatric glucocorticoid users was conducted in the UK by Van Staa et al (9). It was a case-control study involving over 37,000 children treated with steroids. Results showed that the risk of fracture was increased in children who received four or more courses of oral corticosteroids for a mean duration of 6.4 days. Fracture risk was also increased among children using 30 mg prednisolone or more each day.

Jones et al. (65), showed in healthy girls that a 1 SD reduction in areal BMD compared to the age-matched mean was associated with an almost 2-fold increased risk of forearm fractures.

SKELETAL MINERAL ACQUISITION

The fact that in the prepubertal age group, the rate of skeletal mineral acquisition remains fairly equal in both genders has been demonstrated.

In a study by Rio et al (66), on 471 healthy white Mediterranean children and adolescents to determine Bone Mineral Density of the Lumbar Spine showed that BMC and BMD values increased progressively from infancy to adulthood and values were similar in both sexes, with the only differences related to the earlier onset of puberty in girls. Faulkner, et al also found no significant differences in Total Body Bone Mineral Content at any age, between boys and girls 8 - 16 years of age (67).

CALCIUM AND VITAMIN D IN NEPHROTIC SYNDROME

Hypocalcaemia is a common finding in nephrotic syndrome, due primarily to hypoalbuminemia-induced reduction in calcium binding to albumin. A low serum total calcium concentration induced by hypoalbuminemia does not affect the physiologically important free (or ionized) calcium concentration. A small subset of patients with hypocalcaemia out of proportion to hypoalbuminemia has been reported, due to low serum calcitriol concentrations and perhaps increased fecal calcium losses. However, the frequency with which true hypocalcaemia and bone disease occurs in the nephrotic syndrome is unclear, as many investigators have found relatively normal calcium concentrations (68, 69).

Nephrotic syndrome is associated with urinary loss of vitamin D-binding protein (VDBP) (70). In serum, calcidiol (D2), the precursor of calcitriol (D3), is primarily bound to VDBP and is therefore also excreted in the urine (71,72). The net effect is a reduction in serum calcidiol concentrations, while those of calcitriol are normal or reduced (71, 73, 74). The physiologic consequences of these changes in vitamin D metabolism on calcium homeostasis are uncertain. Vitamin D replacement therapy is not routinely recommended in patients with the nephrotic syndrome.

CALCIUM, PHOSPHORUS, VITAMIN D & BONE METABOLISM

Calcium serves two major functions for bone. First, calcium is the bulk cation out of which bone mineral is constructed. It must be absorbed in sufficient quantity to build a skeleton during growth and to maintain skeletal mass in maturity. Second, calcium serves as an indirect regulator of skeletal remodeling.

Glucocorticoid administration is associated with diminished intestinal calcium absorption and increased renal tubular calcium excretion, resulting in a negative calcium balance (75).

Without vitamin D, only 10 to 15% of dietary calcium and about 60% of phosphorus is absorbed (76-78). The interaction of Vit D3 with the vitamin D receptor increases the efficiency of intestinal calcium absorption to 30 to 40% and phosphorus absorption to approximately 80% (76 - 79).

In one study, serum levels of 25-hydroxyvitamin D were directly related to BMD in white, black, and Mexican-American men and women, with a maximum density achieved when the 25-hydroxyvitamin D level reached 40 ng per milliliter or more (80).

Evaluation of the exclusive use of calcium or vitamin D_3 (RECORD trial) showed no antifracture efficacy for patients (81).

VITAMIN D: REQUIREMENTS AND TREATMENT STRATEGIES

Most experts agree that children and adults require approximately 800 to 1000 IU of Vitamin D3 per day (76, 77, 80, 82-86)

A cost-effective method of correcting vitamin D deficiency and maintaining adequate levels is to give patients 100,000 IU of vitamin D_3 once every 3 months (87). This has been shown to be effective in maintaining 25-hydroxyvitamin D levels at 20 ng per milliliter or higher and is also effective in reducing the risk of fracture. Alternatively, either 1000 IU of vitamin D_3 per day or 3000 IU of vitamin D_2 per day is effective (76, 84, 85).

RISK OF VITAMIN D TOXICITY

Doses of more than 50,000 IU per day raise levels of 25-hydroxyvitamin D to more than 150 ng per milliliter (374 nmol per liter) and are associated with hypercalcemia and hyperphosphatemia (76, 77). Doses of 10,000 IU of vitamin D_3 per day for up to 5 months, however, do not cause toxicity (88).

STUDIES ON STEROIDS, BONE HEALTH AND ROLE OF AND CA AND VIT D SUPPLEMENTATION

There are studies to suggest that patients with nephrotic syndrome on steroids are indeed at risk of low bone density.

In a study done on 100 Indian children with Relapsing Idiopathic Nephrotic Syndrome on long term steroids using BMD measurements at lumbar spine by DEXA, Gulati et al (89), found that these children are at risk for low bone mass, especially those administered higher doses of steroids, those with longer duration of disease and those with late onset.

Similar results were found by Basiratnia et al (90), when they measured BMD and BMC using DEXA in 37 Iranian children with Steroid Dependent Nephrotic syndrome, 6 girls and 31 boys aged from four to 21 years, as patient group and 37 age and sex-matched healthy individuals as control group. The percentage of BMC and BMD of lumbar spine and femoral bones of the patients were significantly lower than control group. BMD at femoral and lumbar bones was inversely correlated with cumulative steroid dose. Bone loss was directly proportional to longer duration of the disease and higher cumulative dose of steroid.

A meta-analysis was done by T. P. van Staa et al (91), using information from 66 papers on bone density and 23 papers on fractures to examine the effects of oral corticosteroids on bone mineral density and risk of fracture. Strong correlations were found between cumulative dose and loss of bone mineral density and between daily dose and risk of fracture. The risk of fracture was found to increase rapidly after the start of oral corticosteroid therapy (within 3 to 6 months) and decrease after stopping therapy. The risk remained independent of underlying disease, age and gender. They concluded that oral corticosteroid treatment using more than 5 mg (of prednisolone or equivalent) daily leads to a reduction in BMD and a rapid increase in the risk of fracture during the treatment period**.**

In contrast, in a recent study done by Leonard et al (20), on the effect of long-term treatment with glucocorticoids on bone mineral content in 60 children and adolescents with relapsing steroid sensitive nephrotic syndrome and 195 control subjects, showed that

children receiving corticosteroids do not appear to have deficits in the bone mineral content of the spine.

The effect of prolonged glucocorticoid treatment or intermittent high dose therapy on bone health in children has been studied but most of this evidence to date is cross-sectional in nature.

There is no clear data available on the effect of short term steroids on bone health. 'A study on skeletal effects of short term steroids on children with steroid dependent nephrotic syndrome' done by Kenichi Kano et al (92), on 9 Japanese children with steroid-responsive nephrotic syndrome without relapse showed that BMD and biochemical parameters of mineral and skeletal homeostasis returned to normal values at 16 weeks after the cessation of prednisolone therapy, thus leading the authors to conclude that the skeletal effects of short-term prednisolone therapy were transient. The change in BMD of normal healthy children during the period of study (using controls) would have helped establish whether their conclusions are indeed true. Further long term follow up of these children is needed to see if short term therapeutic doses of corticosteroids lead to acquisitional osteopenia.

In another study , Gulati et al (93), prospectively studied the role of Calcium (500 mg/day) and Vitamin D (200 IU/day) supplementation on bone health in 88 children with relapsing Nephrotic syndrome on steroids by performing DEXA scans at the lumbar spine before and six months after supplementation. They found that compared to baseline values, BMD values were significantly better on follow up. However, the basic assumption in this study was that if there was an increment in the BMD, it was because of supplemental Calcium and Vitamin D. The fact, that children will have an increase in BMD by virtue of growth was not accounted for.

Bak et al (94), conducted a randomized prospective study in Turkey on 40 children (mean age of 4.6 +/- 1.8 years) with new onset or relapsing Nephrotic Syndrome to determine the effects and prophylactic role of calcium (1 g daily) plus vitamin D (400 IU) treatment on bone and mineral metabolism in children receiving prednisolone treatment. Bone mineral density was significantly decreased in both the treatment and non-treatment group but the percentage of bone mineral density decrease was found to be

significantly lower in the treatment group (-2.1%) than in the non-treatment group (- 4%). This led them to conclude that steroid treatment decreases bone mineral density in children with nephrotic syndrome. Vitamin D plus calcium therapy in the above mentioned doses reduces but does not completely prevent bone loss, with no additional adverse effects.

A sizable proportion of pediatric population receives long term treatment with steroids for Nephrotic Syndrome. However, there are no clear-cut guidelines as to when bone protective strategies must be instituted. This study will help determine short term steroid induced bone damage and guide preventive therapy.

METHODOLOGY

STUDY DESIGN AND DURATION

This open randomised controlled interventional prospective study was conducted in the Paediatric Nephrology and Endocrine Departments of Christian Medical College Hospital, Vellore. The study was conducted for a duration of 3 months from May 2007 to July 2008.

SELECTION OF SUBJECTS

Children with new onset nephrotic syndrome were recruited into the study.

INCLUSION CRITERIA

- Patients in the age group of 1 to 13 years.
- Children with first presentation of Nephrotic syndrome.
- (Proteinuria more than 40 mg / m2 /hr or Urine spot protein/creatinine ratio of >2).
- No history of prior steroid use.
- No clinical or biochemical evidence of metabolic bone disease.

EXCLUSION CRITERIA

- Patients with a history of previously known kidney or bone disease
- Patients with a history, clinical or biochemical evidence of metabolic bone disease (e.g. chronic renal failure, liver disease)
- Children not fulfilling the criteria for Nephrotic syndrome (with gross hematuria, persistent hypertension or evidence of renal disease other than nephrotic syndrome)
- Patients with a serum creatinine > 1.5 mg/dl.
- Patients who were on or had received glucocorticoid therapy.
- Children with onset of puberty - Tanner stage >1
- Patients on steroid sparing immunosuppression (Azathioprine, Mycophenolate Mofetil , Cyclophosphamide, Cyclosporine)
- Patients with known or suspected history of hypersensitivity to Prednisolone

STUDY PLAN, PROCEDURE AND FOLLOW UP

All patients with new onset nephrotic syndrome were screened for inclusion in the study

The following tests were done to confirm the diagnosis of nephrotic syndrome:

- Urine Protein Creatinine Ratio
- Urine Routine examination / Urine Multistix
- Serum Protein
- Serum Albumin
- Serum Cholesterol

Once diagnosis was established, all those who fulfilled the inclusion criteria and who had none of the exclusion criteria were recruited.

Informed Consent: Written informed consent was taken from patients' parents / guardians prior to enrolment in the study. (See Annexure for Informed consent form)

Baseline tests were done to rule out metabolic bone disease. These included:

- Serum Calcium
- Serum Phosphorus
- Serum Alkaline Phosphatase
- Serum Creatinine

Randomization: The children were then randomized into Intervention (Group I) and Non Intervention (Group II) groups using block randomisation technique.

Baseline measurements of weight, height and BMI were recorded for all children. Baseline Bone Mineral Content (BMC) and Bone Mineral Density (BMD) measurements at Lumbar spine were carried out for both groups using DEXA scan. The model of the DEXA machine used was DELPHI W – Hologic QDR- 4500 with fan beam.

Both groups received oral Prednisolone in the dose of 60 mg per square metre per day (as single daily morning dose) in the first six weeks followed by 40 mg per square metre on alternate days (as a single morning dose) in the next six weeks as per the APN Regime. The cumulative dose of Prednisolone received by each patient was 3360 mg/m2.

Group I (Intervention), in addition, received the following supplements:

- Oral Vitamin D3(Calcirol granules) 90,000 IU as a single stat dose at the start of treatment
- Elemental Calcium 500 mg (as calcium carbonate) as a single morning dose for 12 weeks

The patients were followed up in Child Health OPD with a minimum of 4- 5 visits for each patient

Visit 1: 0 weeks - On admission to the study

Visit 2: 2 weeks - During therapy visit (to look for remission)

Visit 3: 4 weeks - If not in remission at the end of 2 weeks of treatment

Visit 4: 6 weeks- During therapy visit (steroid dose reduction)

Visit 5: 12 weeks - End of therapy visit

In addition, patients were also seen as and when required

At each visit a Urine Multi-stix was done to assess for response to steroids. The children were also examined for presence of hypertension, infection, adverse effects and compliance with medication.

At the end of 12 weeks both groups underwent DEXA scan for repeat measurements of BMD and BMC and Serum Calcium, Phosphorus and Alkaline Phosphatase levels were estimated.

Concomitant medication: The patients were given concomitant medications whenever it was imperative for the benefit of the patient.

Compliance: The compliance to therapy was evaluated on the basis of actual number of doses taken compared to the prescribed doses. This was done by asking the patient to bring the medicine along during the follow up visit and cross checking the same with the theoretical quantity.

Subject dropout: Those patients who did not complete the study were considered drop out cases.

Documentation: All relevant subject information was maintained in the in the proforma (Annexure) and outpatient case record

CALCULATION OF SAMPLE SIZE

In a randomised, controlled study on the protective efficacy of Calcium and

Vitamin D in children on Prednisolone for Nephrotic syndrome by Bak et al (94) , there was a decrease of BMD in lumbar spine by 13+/- 4% in control subjects whereas children who received Calcium and Vitamin D showed a decrease of only 4.6 +/- 2.1%. The treatment attributable difference was about 8% and the pooled variance was 10%. Using these figures in TRUE EPISTAT, it was calculated that there should be a total of 14 patients (7 in each arm) to be able to make out an 8% difference in BMD between the 2 groups with 99% confidence and with a power of 90%.

However, since this study had included children with relapsed nephrotic syndrome and since 1) we were studying only new patients diagnosed with nephrotic syndrome 2) the age range would also be different in our study, and 3) we would be using BMC as a primary diagnostic tool, we felt that it would be prudent to study a larger number of children.

INTERPRETATION OF RESULTS

There are several ways in which changes in BMD and BMC can be compared in studies. Z scores are individual values (of BMD) expressed as standard deviation from age sex matched normals. Such normative data are not currently available for Indian children.

When we are studying children of different ages, the baseline BMC and BMD values would vary widely so that absolute changes over short periods of time will be difficult to compare statistically. If we assume that the baseline BMD & BMC to be 100% for that individual and express changes over time , the percentage changes over the same period of time are comparable. This approach , also used by Bak et al (94) , is particularly suitable when small numbers are studied.

STATISTICAL ANALYSIS OF DATA

Data entry and statistical analysis was done using Microsoft Excel and SPSS for Windows Version 16.0. Percentage change in BMC and BMD over basal was determined for each subject. The means of this percentage change were calculated in both groups and compared using Paired‘t’ test and Mann Whitney U tests. Inferences on the protective effect of Calcium and Vitamin D supplementation on bone health were drawn using the results of these statistical tests.

RESULTS AND ANALYSIS

CATEGORIES

1. PATIENT DISTRIBUTION

Table 1 : PATIENT DISTRIBUTION		
CATEGORY	No of children (n=34)	Percentage
Intervention	18	52.94%
Non Intervention	16	47.06 %
Total	34	100%

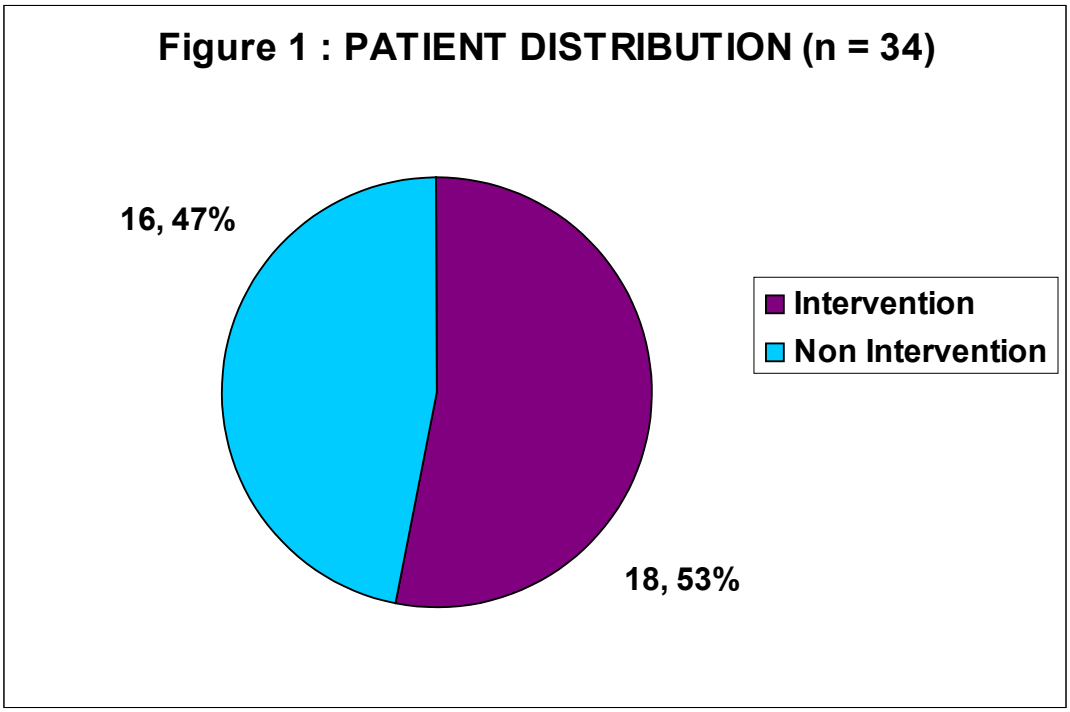


Table 1 and Figure 1 show patient distribution between the two groups.

34 children were randomized into Group I and II

52.94% (18/34) belonged to Group I

47.06% (16/34) children formed Group II

DEMOGRAPHIC PROFILE

2. AGE DISTRIBUTION

Table 2.1: AGE DISTRIBUTION		
AGE GROUPS	**No of children (n =34)**	**Percentage**
1 – 2.99 years	**16**	**47.1 %**
3 – 5.99 years	**11**	**32.4 %**
6 – 9.99 years	**2**	**5.9 %**
10 – 13 years	**5**	**14.7%**
Total	**34**	**100%**

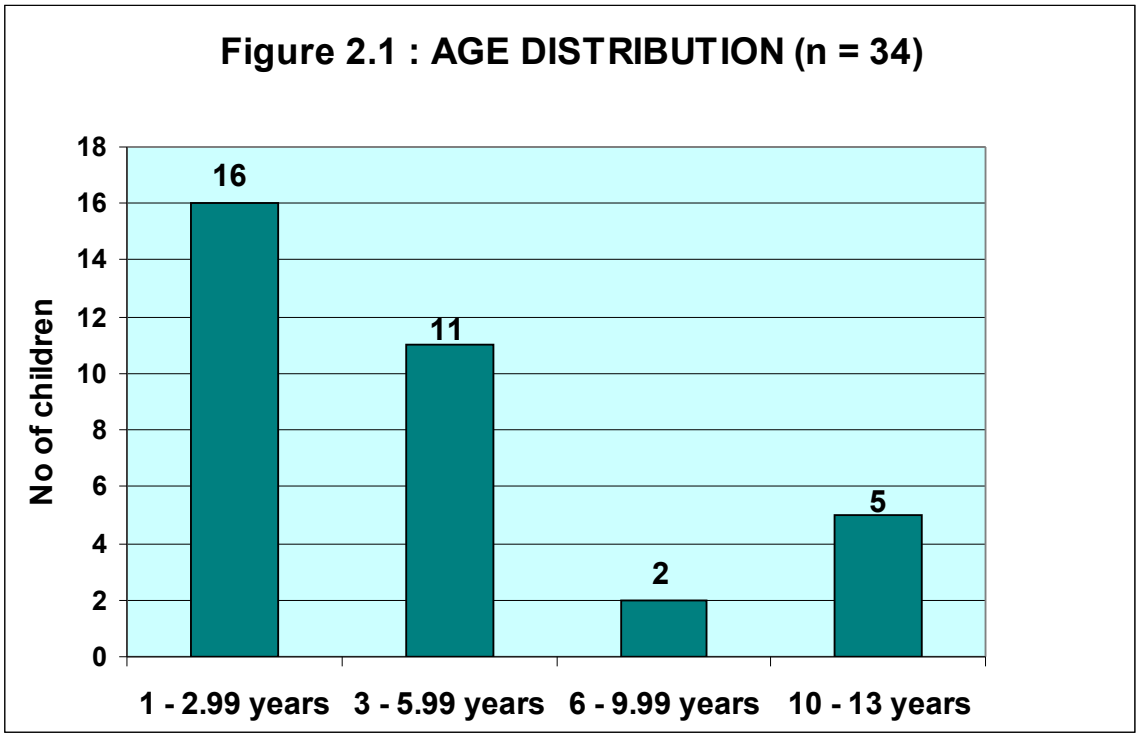


Table 2.1 and Figure 2.1 show the overall age distribution of the children included in the study

The mean age was 4 .13 years (range 1 year - 12. 4 years)

1- 3 year olds formed the largest group with 47% (16/34) children, followed by 32.4%

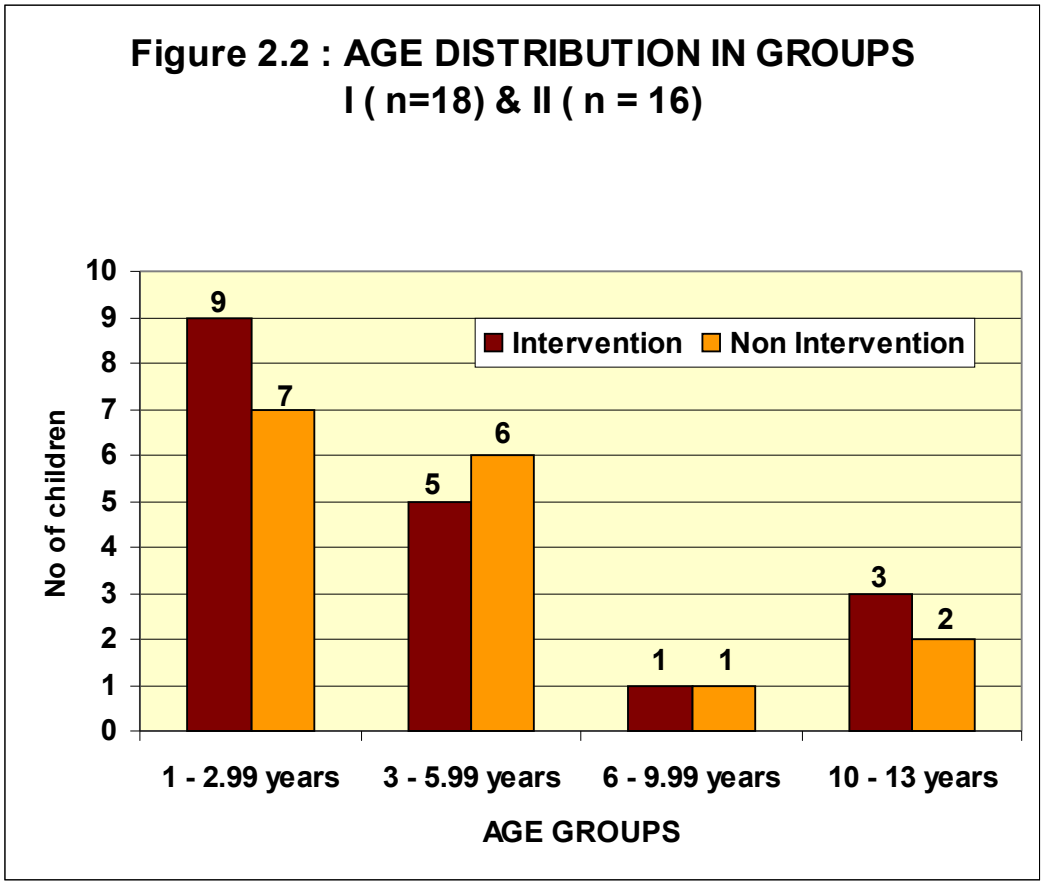
(11/34) in the 3-6 year age group

2 (5.9 %) children were between 6 – 10 years

5 (14.7%) children in the 10 -13 age group

Table 2.2 : AGE DISTRIBUTION BETWEEN GROUPS				
AGE GROUPS	GROUP I		GROUP II	
	n = 18	Percentage	n = 16	Percentage
1 - 2.99 years	9	50%	7	43.8%
3 – 5.99 years	5	27.2%	6	37.5%
6 – 9.99 years	1	5.6%	1	6.2%
10 – 13 years	3	16.7%	2	12.5%
Total	18	100.00	16	100.00

Table 2.3 : AGE CHARACTERISTICS		
	GROUP I	GROUP II
Minimum age	1 year	12 years 5 months
Maximum age	1 year 3 months	10 years 7 months
Mean age	4. 28 years	3. 97 years



Both the groups were comparable in age distribution.

The mean age in Group I was 4. 28 years and in Group II was 3.97 years.

3. SEX DISTRIBUTION

Figure 3.1: SEX DISTRIBUTION

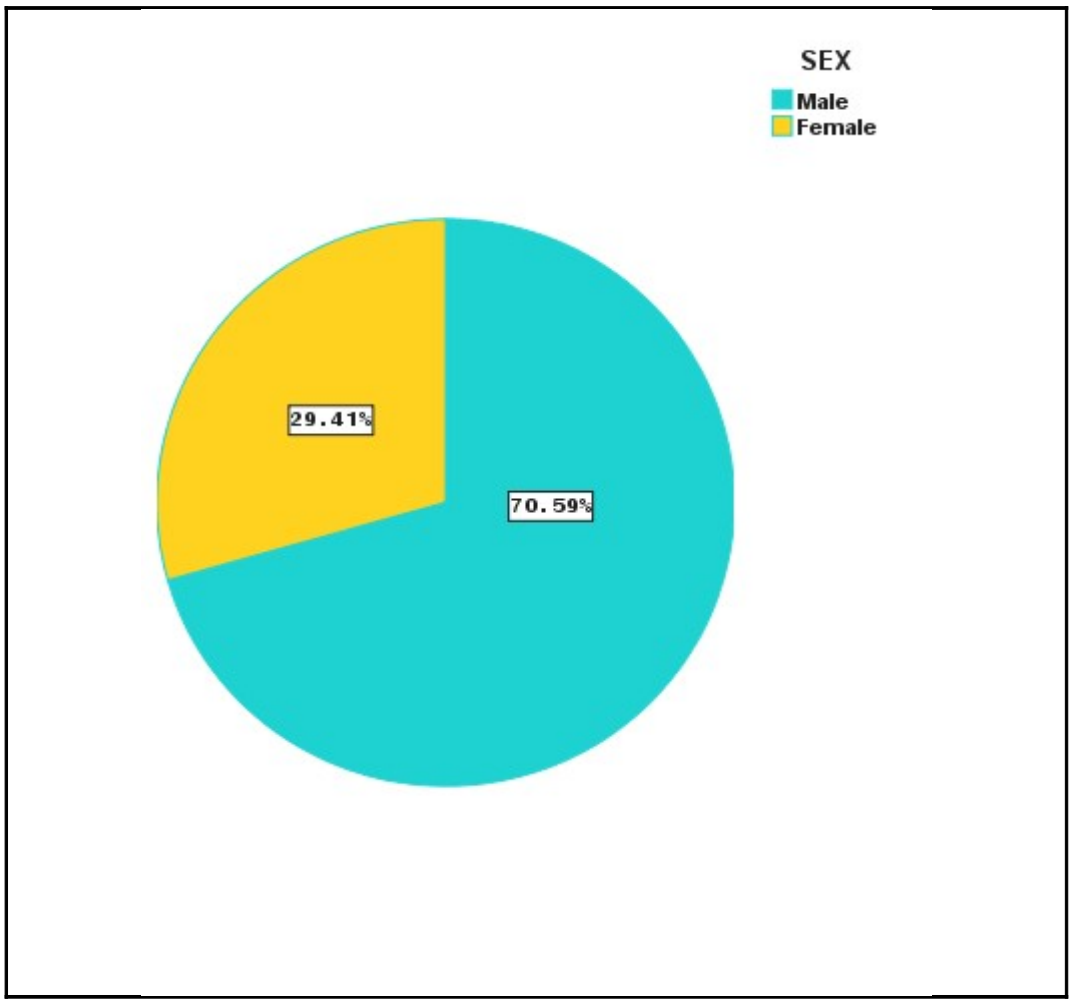


Table 3.1 and Figure 3.1 show the overall sex distribution of the Nephrotic children recruited in the study

Male preponderance was noted with a M: F ratio of 2.4:1.

Table 3.2 : SEX DISTRIBUTION BETWEEN GROUPS				
GENDER	GROUP I		GROUP II	
	Frequency	Percentage	Frequency	Percentage
Male	11	61.1%	13	81.2%
Female	7	38.9%	3	18.8%
Total	18	100%	16	100%

Figure 3.2: SEX DISTRIBUTION between the 2 groups

Table 3.2 and Figure 3.2 show the gender distribution between the two groups

The male: female ratio in Group I was 1.6:1, while in Group II it was 4.3:1

4. ETHNIC DISTRIBUTION

Table 4 : ETHNIC DISTRIBUTION		
STATE	No of children (n=34)	Percentage
Tamil Nadu	24	70.6%
West Bengal	5	14.7%
Jharkhand	2	5.9%
Tripura	2	5.9%
AndhraPradesh	1	2.9%
Total	34	100%

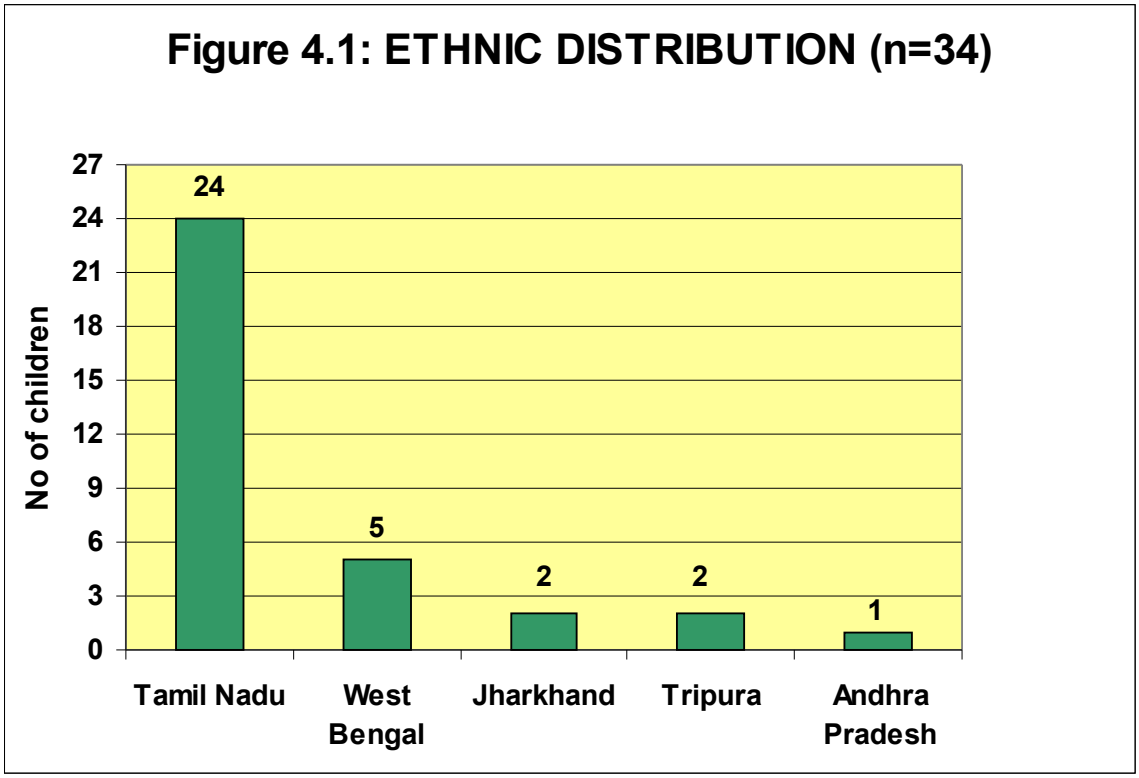


Table 4 and Figures 4.1 and 4.2 (below) represent the Ethnic distribution of the subjects included in the study

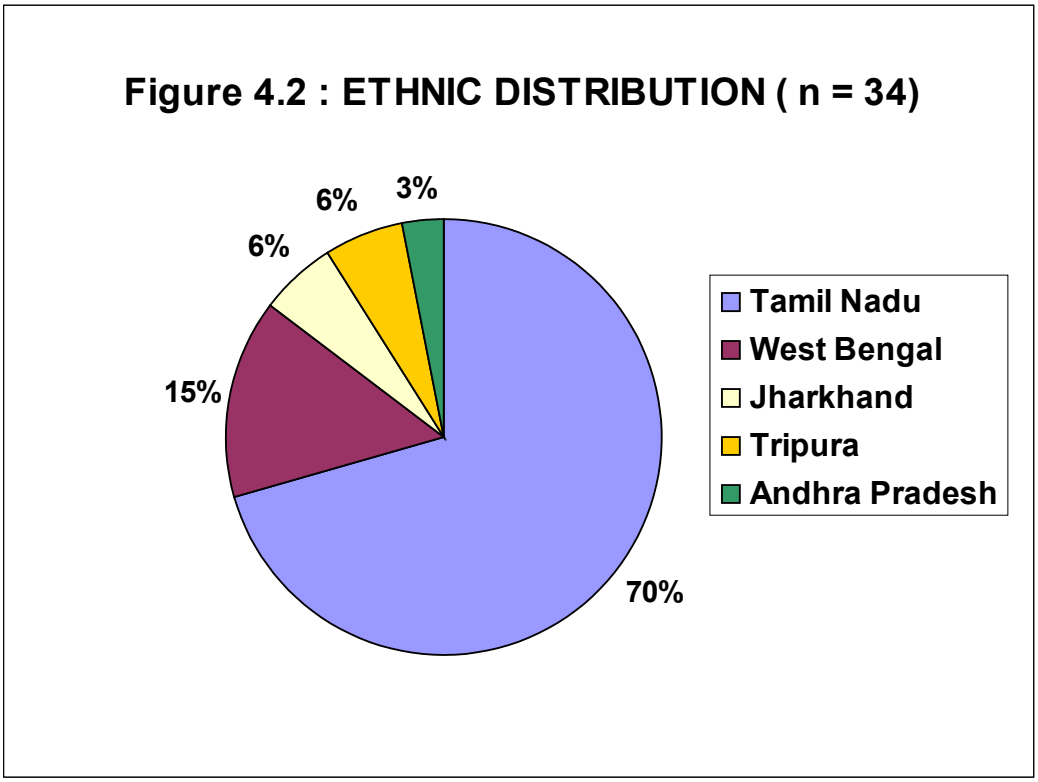


Table 4 and Figures 4.1 and 4.2 represent the Ethnic distribution of the subjects included in the study

The children recruited came from varied ethnic backgrounds

Majority of the subjects – 70.6% (27/34) belonged to Tamil Nadu.

5 (14.7%) children were natives of West Bengal

2 (5.9%) each came from Jharkhand and Tripura

1 (2.9%) were from Andhra Pradesh.

DISEASE CHARACTERISTICS

5. INFECTION AT ONSET

Table 5.1 : INFECTION AT ONSET		
	No of children(n=34)	Percentage
Infection	12	35.3 %
No Infection	22	64.7 %
Total	34	100 %

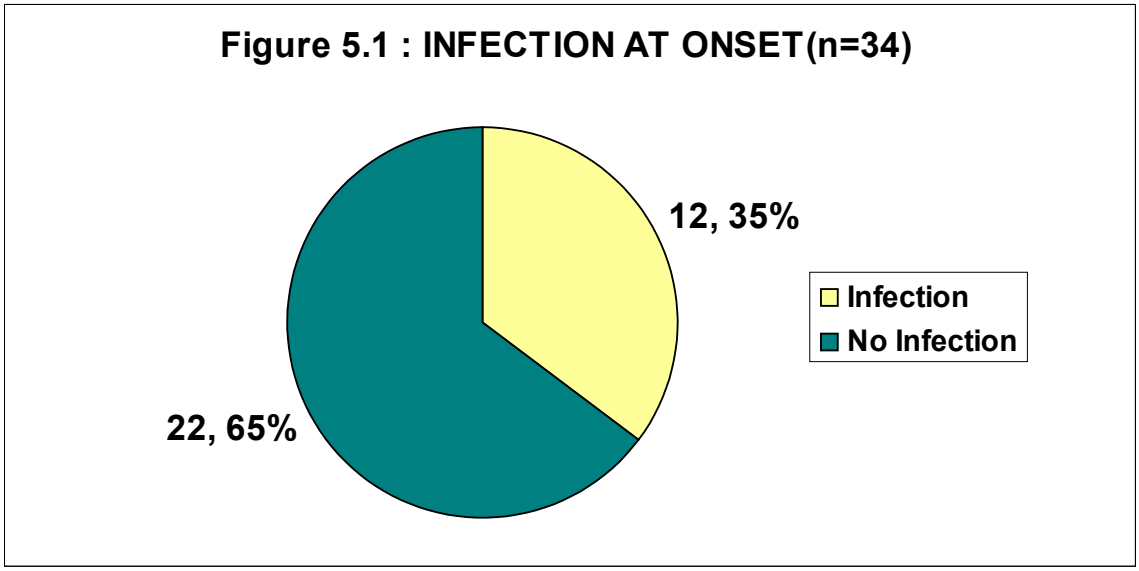


Table 5.1 and Figures 5.1 show the proportion of children who had infection at presentation

35.3% (12/34) children had infections heralding the onset of Nephrotic syndrome

Table 5.2 : TYPE OF INFECTION		
Type of Infection	**No of children (n=34)**	**Percentage**
LRI	**6**	**17.6 %**
URI	**4**	**11.7 %**
AGE	**1**	**2.9 %**
Hepatitis A	**1**	**2.9 %**
UTI	**1**	**2.9 %**

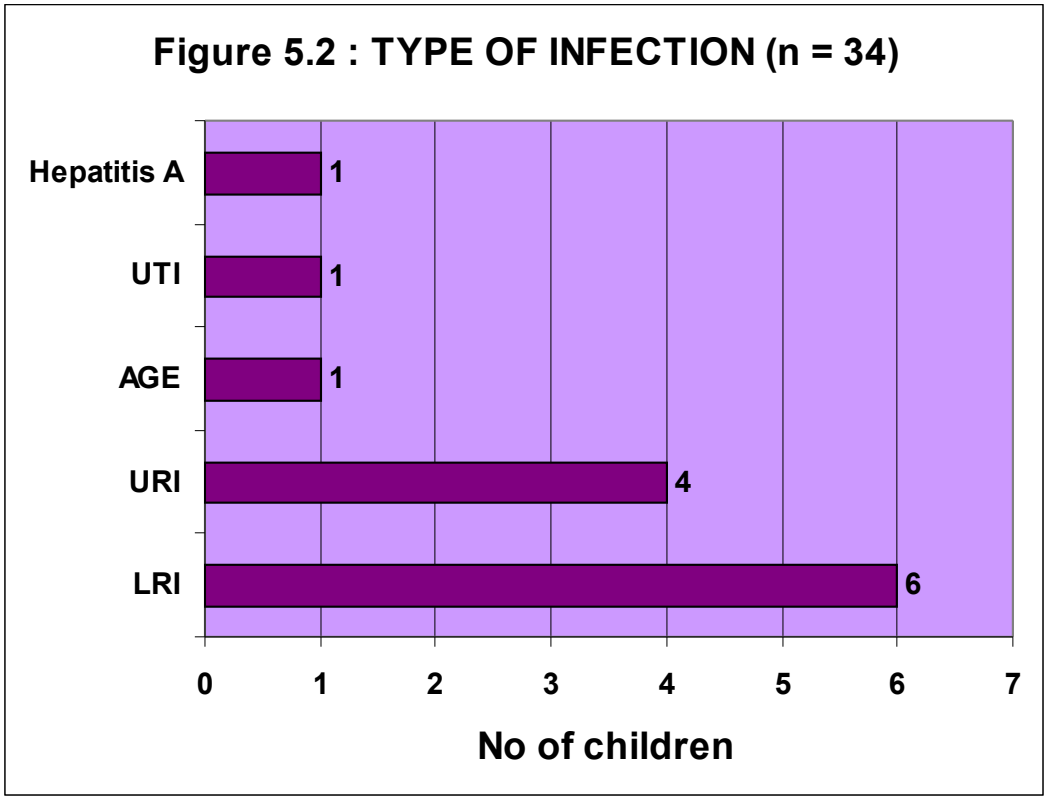


Table 5.2 and Figure 5.2 show the types of infections at onset

The most common was Lower respiratory tract infection in 50 %(6/12) followed by Upper Respiratory Tract Infections in 11.7% (4/12).

Acute Gastroenteritis, Hepatitis A, and Urinary tract Infections affected 1 child each

6. HYPERTENSION AT ONSET

Table 6 : HYPERTENSION AT ONSET		
	No of children (n=34)	Percentage
Hypertension	7	20.6%
No Hypertension	27	79.4%
Total (n = 34)	34	100 %

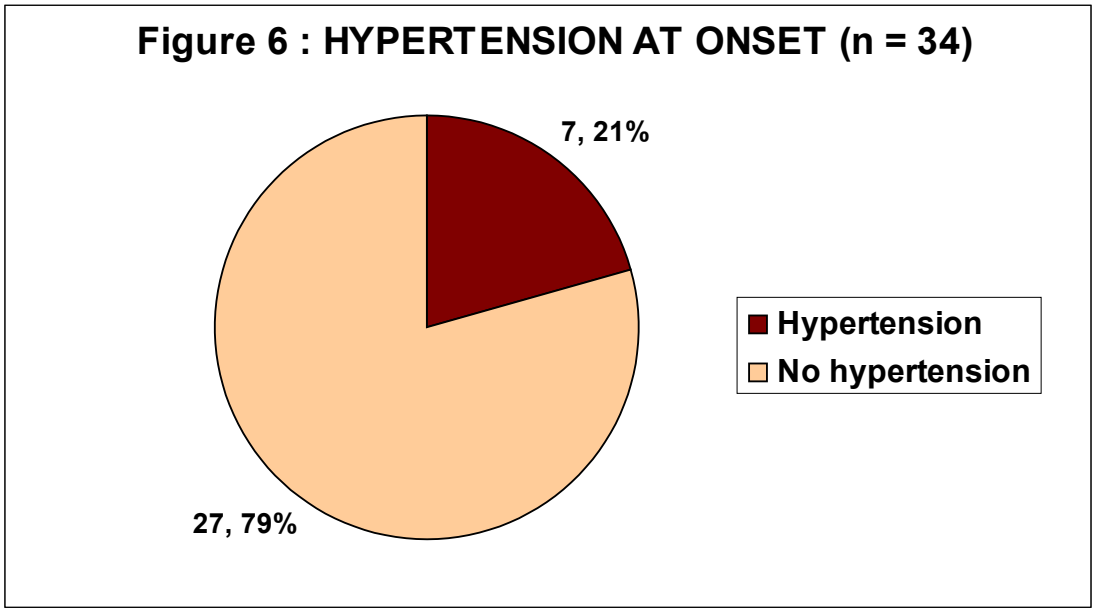


Table 6 and Figure 6 represent the incidence of hypertension at disease onset in children with Nephrotic Syndrome

21% (7/34) patients were hypertensive at presentation

7. REMISSION

Urine analysis was done to look for proteinuria. This was done at every visit to evaluate response to steroid therapy. Remission was concluded based on the clinical features of resolution of edema and Urine Multistix being normal. The remission rates of the subjects were assessed at 2, 4, 6 & 12 weeks.

Table 7 : REMISSION RATE				
REMISSION	**2 weeks**	**4 weeks**	**6 weeks**	**12 weeks**
Proteinuria -	**28 (82.4 %)**	**30 (88.2%)**	**33 (97.1%)**	**31 (91.2%)**
Proteinuria +	**6 (17.6 %)**	**4 (11.8%)**	**1 (2.9%)**	**3 (8.8%)**
Total (n = 34)	**34**	**34**	**34**	**34**

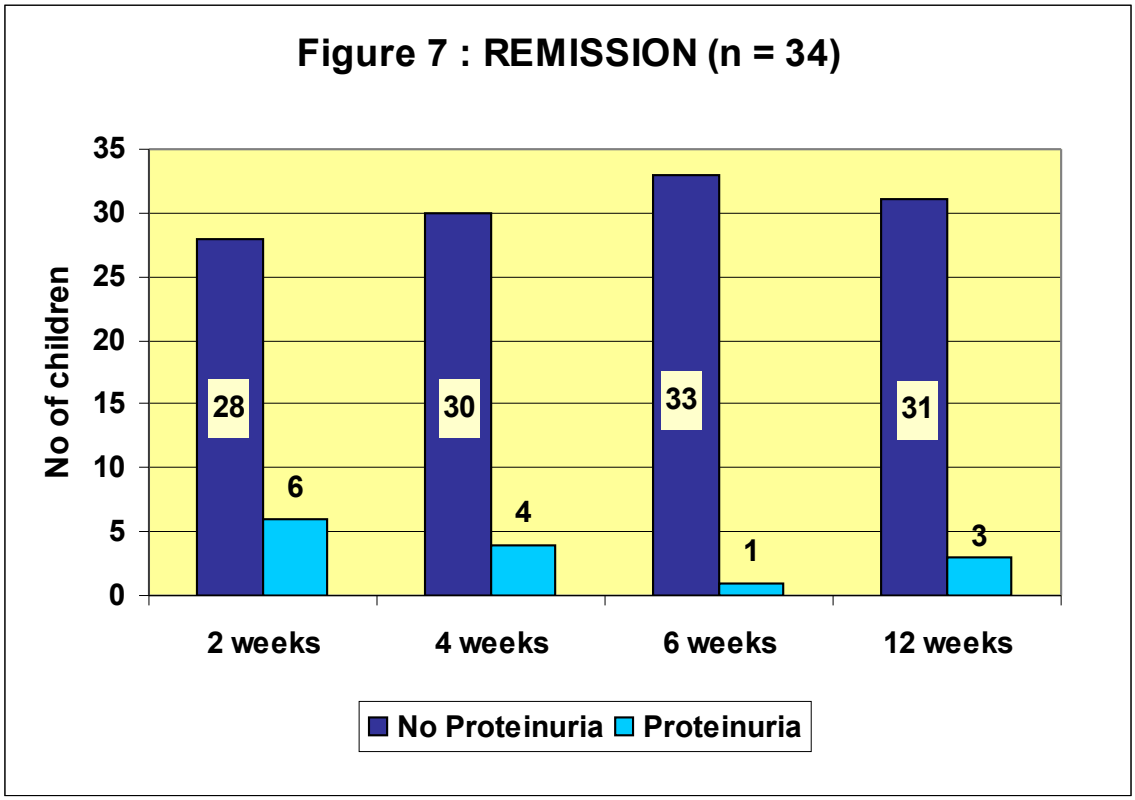


Table 7 and Figure 7 demonstrate the remission characteristics of all the children included in this study

82.4% (28/34) children went into remission by 2 weeks,

88.2% (30/34) by 4 weeks and

97.1% (33/34) by 6 weeks.

91.2 %(31/34) children remained in remission at the end of 12 weeks

2 children who were in remission at 6 weeks, relapsed on tapering steroid dose.

1 went into remission on restarting full dose steroids; the second remained non responsive (Renal biopsy showed MesPGN**)**

8. RELAPSE

Table 8.1 : RELAPSE		
	No of children (n=34)	**Percentage**
Relapse	**13**	**38.6 %**
No relapse	**21**	**61.8 %**
Total (n = 34)	**34**	**100 %**

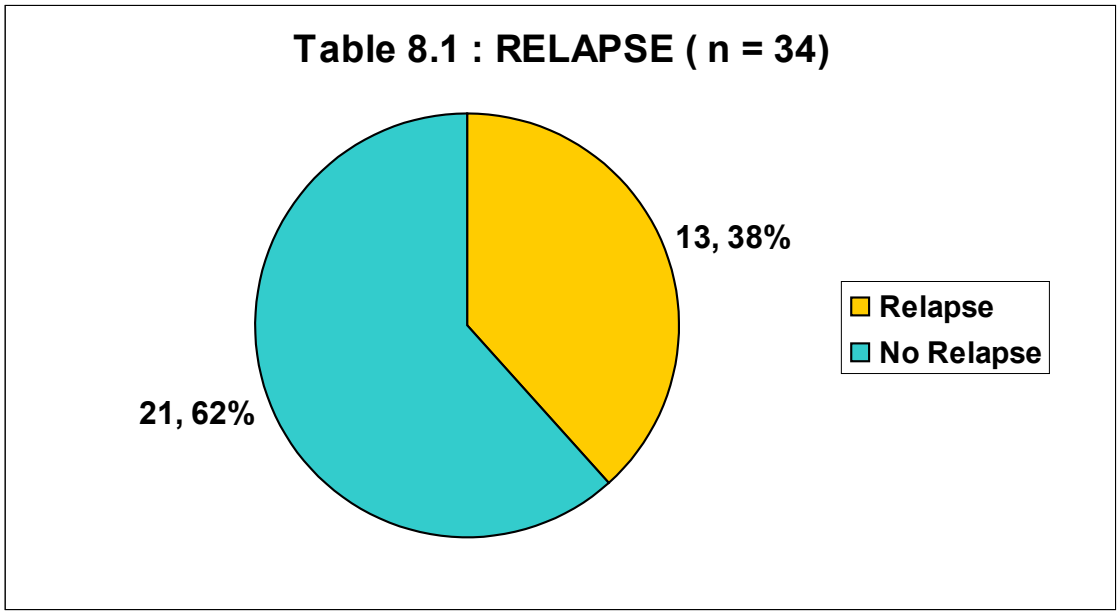


Table 8.1 and Figure 8.1 show the incidence of relapse

Of the total number of children recruited in the study 38.6% (13/ 34) relapsed

Table 8.2 : RELAPSE ON/ OFF TREATMENT		
	No of children (n=13)	Percentage
Relapse on steroids	2	15.4 %
Relapse off steroids	11	84.6 %
Total	13	100 %

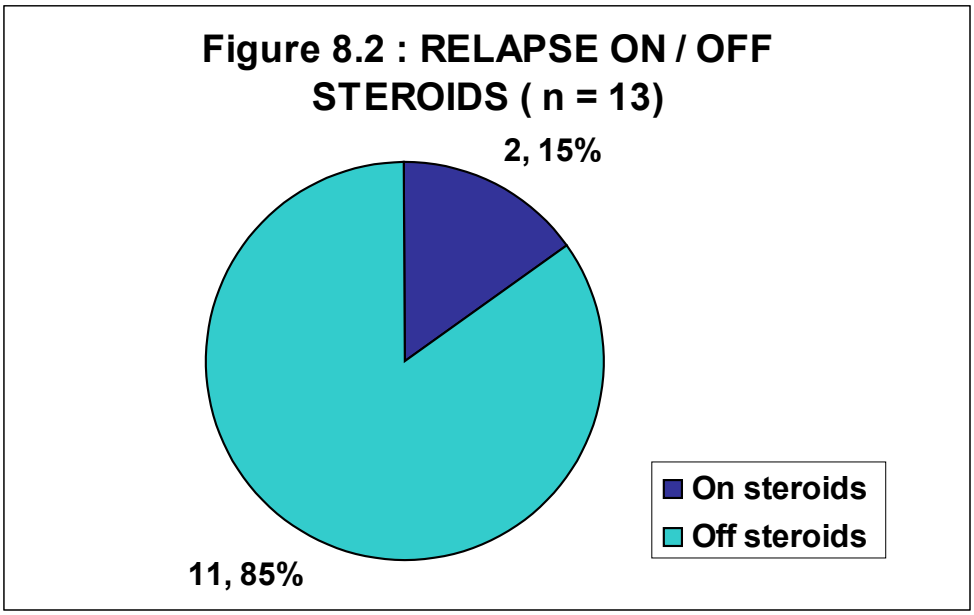


Table 8.2 Figure 8.2 show proportion of relapse while on steroids

15.4% (2/13) children relapsed while on treatment with steroids.

Majority (85%-11/13) relapsed after stopping steroids

Mean time to relapse was 11.5 weeks (range 7 - 22 weeks)

Table 8.3 : CAUSE OF RELAPSE		
Cause of relapse	**No of Patients**	**Percentage of Patients**
Spontaneous	**7**	**53.8 %**
Due to Infection	**6**	**46.2 %**
Total (n = 13)	**13**	**100 %**

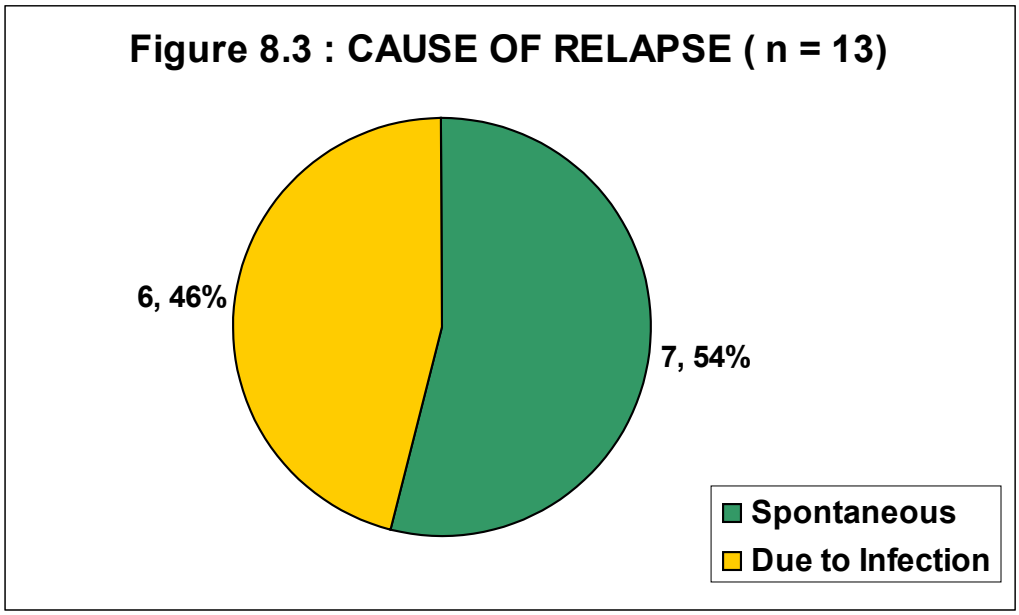


Table 8.3 and Figure 8.3 show causes of relapse

46.2% (6/13) children had a relapse following an infection

Viral fever and URI were the most common infections precipitating relapse

9. SIDE EFFECTS OF STEROIDS

Table 9 : SIDE EFFECTS OF STEROIDS				
SIDE EFFECT	At 6 weeks		At 12 weeks	
	Frequency	Percentage	Frequency	Percentage
Cushingoid	28	82.4%	34	100%
Hypertrichosis	5	14.7%	21	61.8 %
Gastritis	27	79.4%	25	73.5 %
Striae	0	0	2	5.9%
Infection	7	20.6%	3	8.8%
Behaviour change	2	5.9%	3	8.8%
Hypertension	0	0	0	0
Acne	0	0	0	0
Purpura	0	0	0	0
Cataract	0	0	0	0
Glucosuria	0	0	0	0

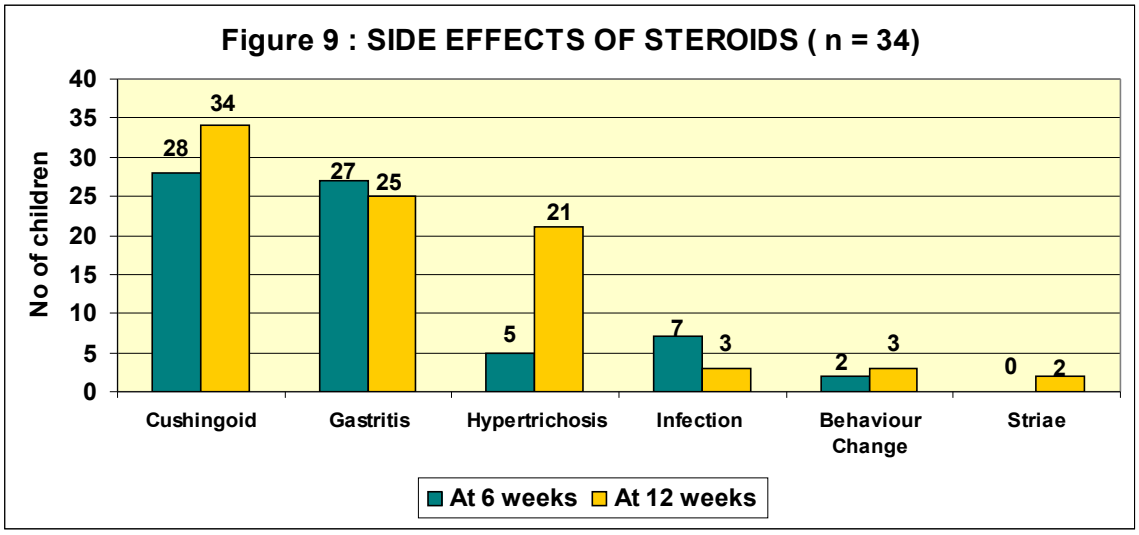


Table 15 and Figure 15 illustrate the side effects of steroids experienced by the subjects participating in the study

Side effects of steroids experienced by the children were recorded at 6 and 12 weeks.

Cushingoid habitus (100%), gastritis (79.4%), hypertrichosis (67.8%) and infection (20.6%) were the most commonly noted side effects.

8.8 %(3/34) children had behavior changes and 5.9% (2/34) had striae.

A decrease in the incidence of gastritis was noted from 79.4% (27/34) at 6 weeks to 73.5% (25/34) at 12 weeks.

Marked increase in hypertrichosis seen at 12 weeks (67.8%) compared to 6 weeks (14.7%)

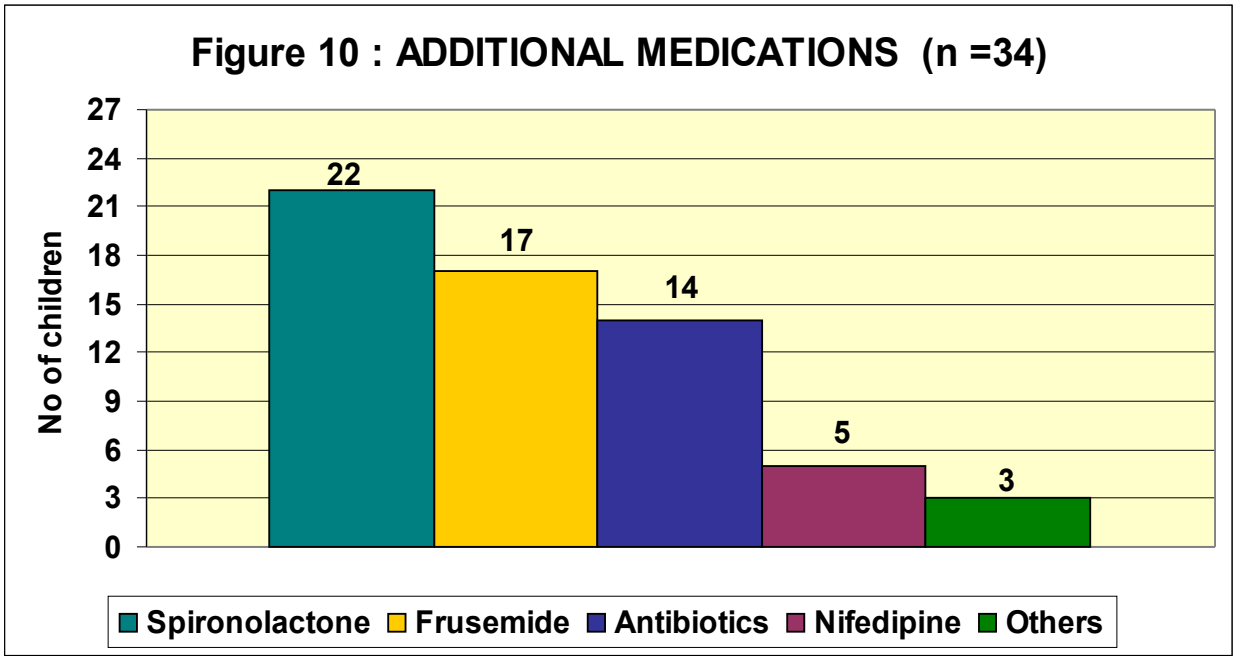
20.6% (7/34) children had infections at 6 weeks and

8.8% (3/34) at 12 weeks.

10. ADDITIONAL MEDICATIONS

Table 10.1 : ADDITIONAL MEDICATIONS		
Additional medications used	No of children (n=34)	Percentage
Yes	26	76.4%
No	8	23.6%
Total	34	100%

Table 10.2 : MEDICATIONS		
MEDICATION	No of children (n = 34)	Percentage
Spironolactone	22	64.7 %
Frusemide	17	50 %
Antibiotics	14	41.2 %
Nifedipine	5	14.7%
Others (Atenolol, Metalozone, ATT)	3	8.8 %



Tables 10.1 & 10.2 and Figure 10 represent the additional medications used during

the duration of the study

76.4% (26/34) children required additional medications

The commonest were diuretics for control of edema

64.7% (22/34) were given Spironolactone

50% (17/34) required Frusemide

1 child received Metalozone

41.2% (14/34) children received antibiotics to treat infections

Blood Pressure control was achieved with Nifedipine in 5 (14.7%) children and Atenolol in 1 (2.9%) child

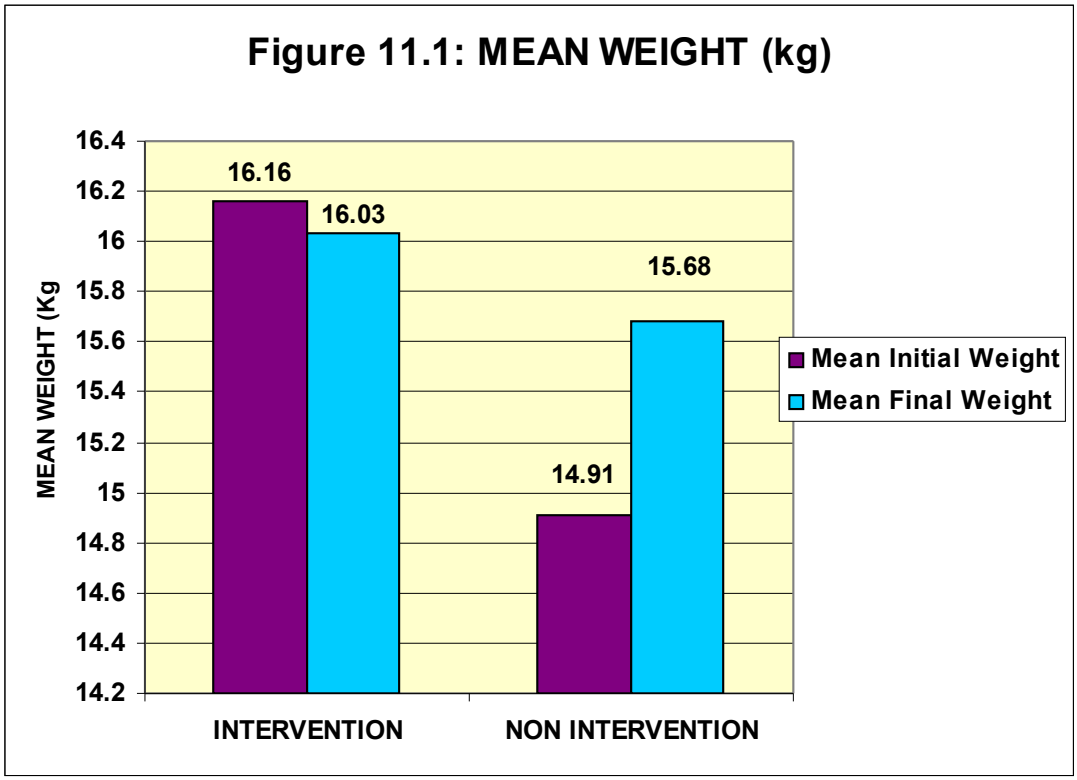
1 child was given Anti Tuberculous Therapy (ATT) because of asymptomatic Mantoux positivity.

BODY CHARACTERISTICS

11. WEIGHT

Table 11.1: WEIGHT CHARACTERISTICS - GROUP I			
	Mean Weight (Kg)	Minimum Weight (Kg)	Maximum Weight (Kg)
Baseline	16.16	7.3	41.7
At 12 weeks	16.03	8.0	37.6

Table 11.2:WEIGHT CHARACTERISTICS - GROUP II			
	Mean Weight (Kg)	Minimum Weight (Kg)	Maximum Weight (Kg)
Baseline	14.91	8.2	32.7
At 12 weeks	15.68	9.8	27.4



Tables 11.1 &11.2 and Figure 11.1 shows the weight characteristics in Groups I & II

Table 11.3 : MEAN WEIGHT CHANGE		
PARAMETERS	**GROUP I**	**GROUP II**
Mean Weight Change (%) = $\frac{\sum(\text{Final Wt} - \text{Initial Wt})}{\text{(Initial Weight)}} \times 100$	**+ 1.2477%**	**+ 7.7362%**

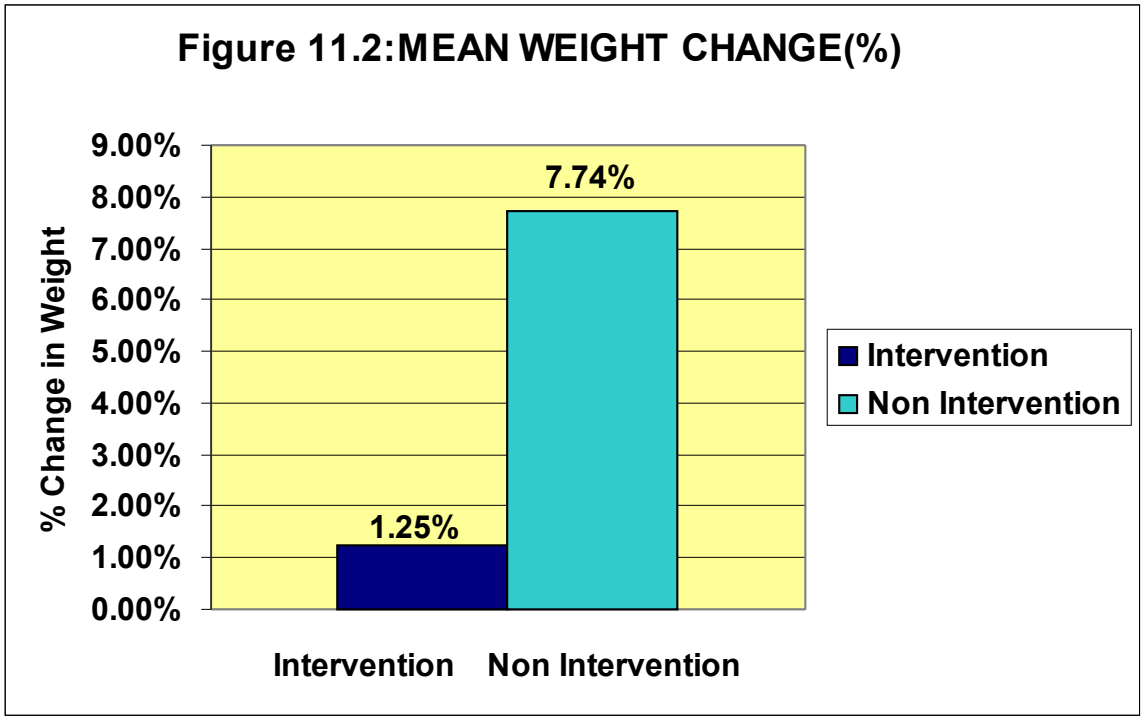


Table 11.3 and Figure 11.2 illustrate the mean % weight change in the 2 groups

There was a net weight gain in both groups.

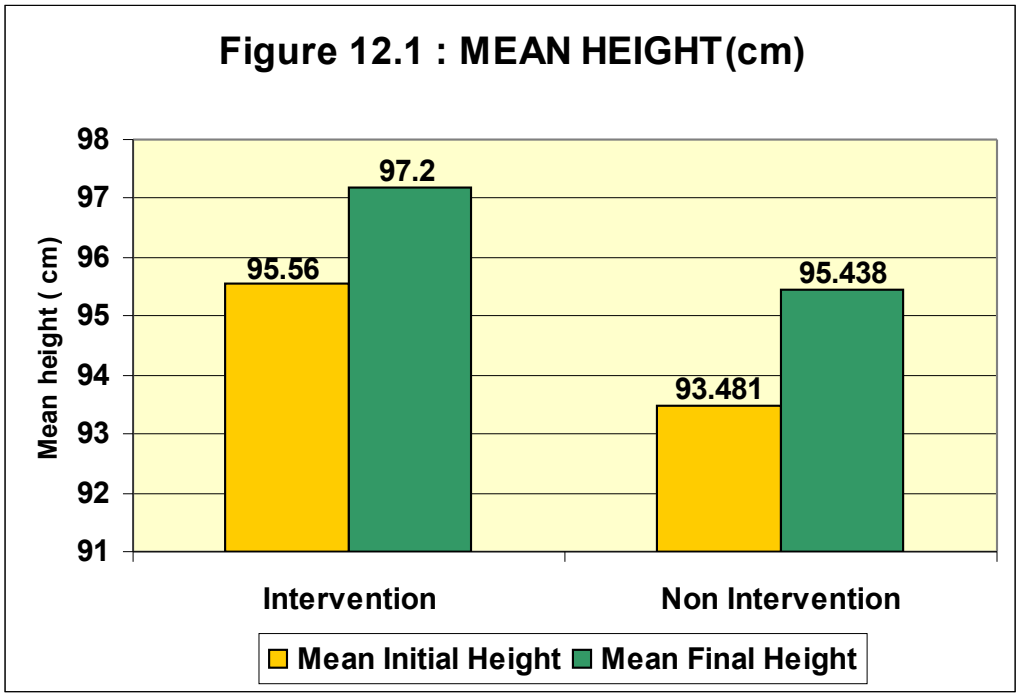
An average 1.25 % increase in weight in Group I and 7.7 % weight gain in Group II over a 12 week period.

The difference in the mean (%) change in weight between the 2 groups was not statistically significant (p value = 0. 222, 95% CI = - 17.09 to +4.12 on Paired 't' test).

12. HEIGHT

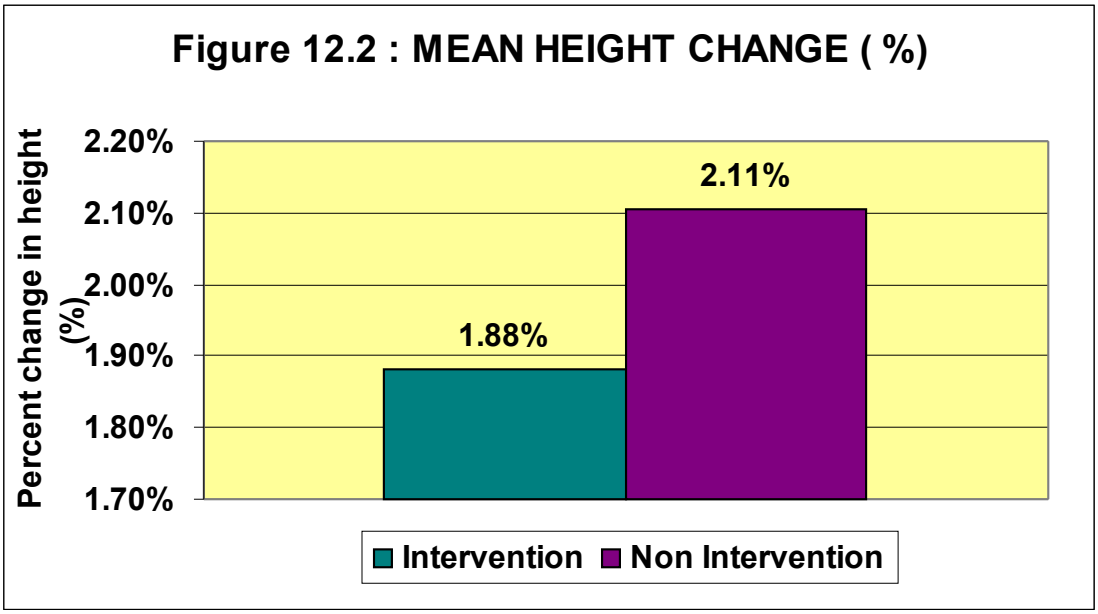
Table 12.1 : HEIGHT CHARACTERISTICS – GROUP I			
	Mean Height (cm)	Minimum Height (cm)	Maximum Height (cm)
Baseline	95.561	70	148
At 12 weeks	97.200	70	149

Table 12.2 : HEIGHT CHARACTERISTICS – GROUP II			
	Mean Height (cm)	Minimum Height (cm)	Maximum Height (cm)
Baseline	93.481	74	127.5
At 12 weeks	95.438	75	129



Tables 12.1 & 12.2 and Figure 12.1 shows the height characteristics of Groups I &II

Table 12. 3 : HEIGHT CHANGE	
GROUP	Mean Height Change (%) = $\Sigma \frac{\text{(Final Height - Initial Height)}}{\text{(Initial Height)}} \times 100$
Intervention	1.8820 %
Non Intervention	2.1050 %



Tables 12.3 and Figure12.2 represent the mean % height change in the 2 groups

At 12 weeks, children in both the groups stood taller.

1.88 % gain in height in Group 1 and 2.11 % in Group II.

No statistically significant difference was found in the mean % change in height in the 2 groups (z = - 0.518, p = 0.605 on Mann Whitney U test)

13. BMI

TABLE 13 : BMI CHARACTERISTICS				
PARAMETERS	**GROUP I**		**GROUP II**	
	Initial	**Final**	**Initial**	**Final**
Minimum BMI (kg/m2)	**14.5**	**13.6**	**13.8**	**12.9**
Maximum BMI (kg/m2)	**20.2**	**19.5**	**21.0**	**26.9**
Mean BMI (kg/m2)	**16.567**	**16.178**	**16.569**	**16.988**
Mean BMI change (%) =				

$\sum$ (Final BMI – Initial BMI) / (Initial BMI)	- 1.783%	+ 3.826%

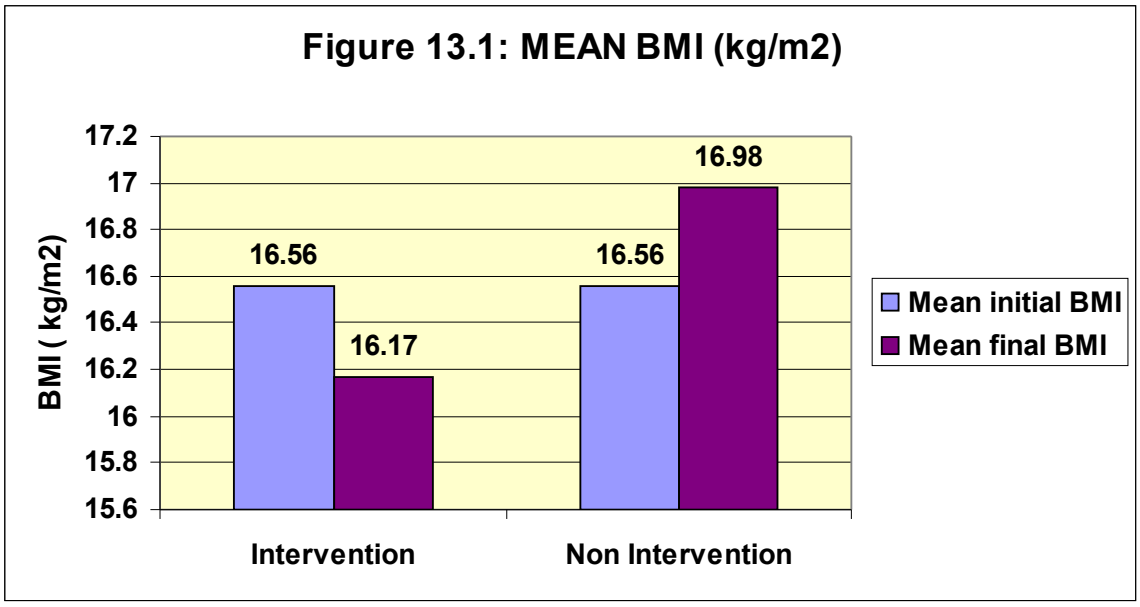


Table 13 and Figure 13.1 represent the BMI characteristics in Groups I & II

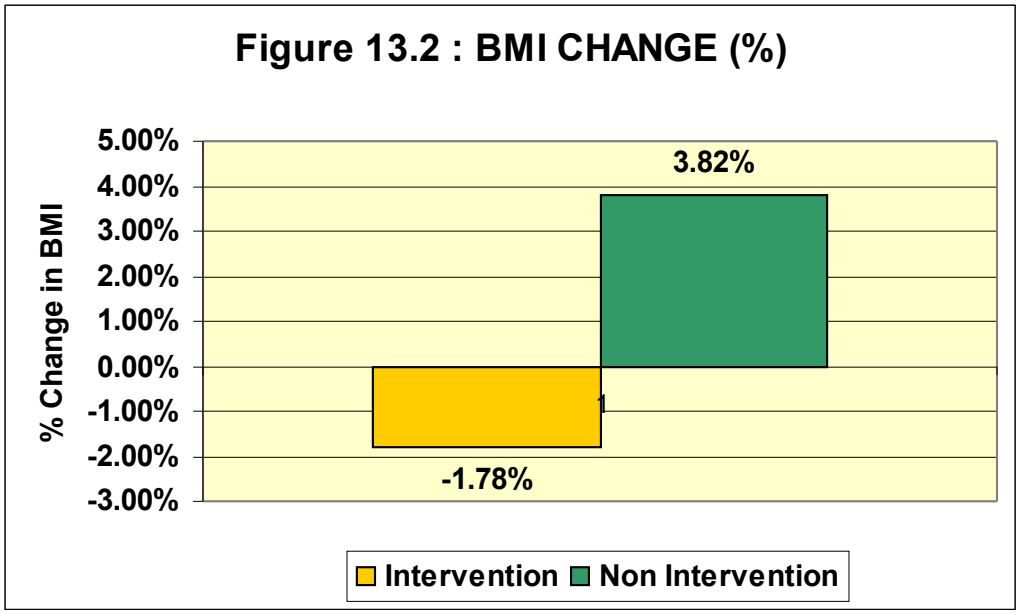


Table 13 and Figure 13.2 represent the mean % BMI change in Groups I & II

Mean 1.783 % decrease in BMI in Group I over 12 weeks.

In contrast, 3.826% increase in BMI in Group II.

No statistically significant difference in the 2 Groups

(z = -1. 242, p = 0.214 on Mann Whitney U test).

14. SERUM CALCIUM

Table 14 : CHANGE IN CALCIUM				
PARAMETERS	INTERVENTION		NON INTERVENTION	
	Initial	Final	Initial	Final
Minimum Ca (mg/dL)	8.8	8.5	8.8	8.6
Maximum Ca (mg/dL)	10.6	10.0	10.5	10.8
Mean Ca (mg/dL)	9.550	9.422	9.653	9.520
Mean %Ca change = $\sum \frac{\text{(Final Ca – Initial Ca)}}{\text{(Initial Ca)}}$	- 1.1595 %		- 0.6928%	

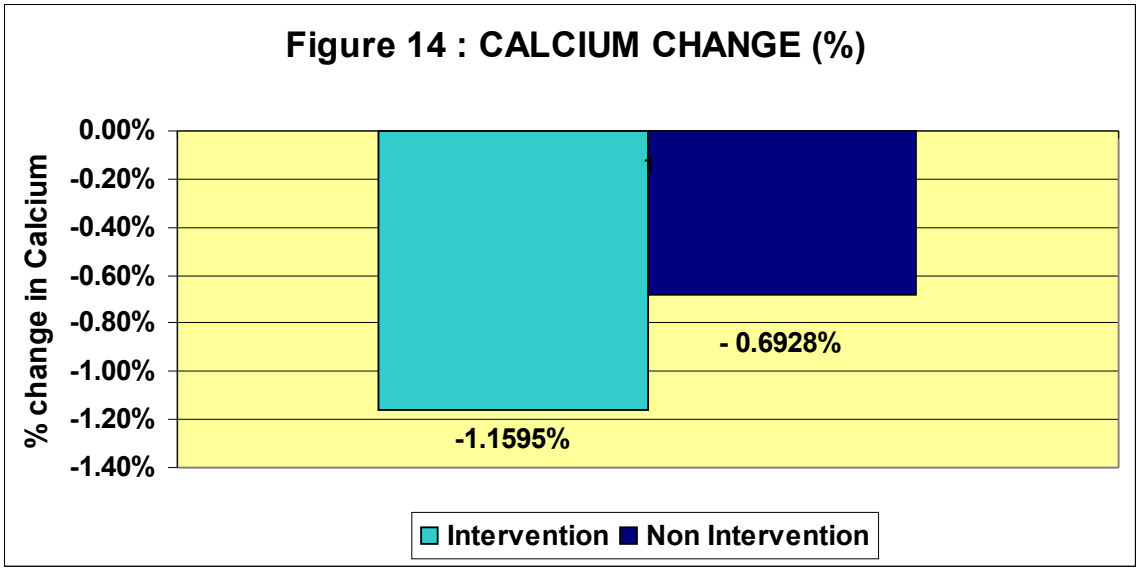


Table 14 and Figure 14 show the % change in Serum Calcium levels in Groups I & II

Serum Calcium (corrected for the corresponding Serum albumin) was maintained in the normal physiological range in all children in both groups both at baseline and at 12 weeks.

Drop in Serum Calcium in both Groups when calculated as % change over baseline: 1.16% decrease in Group I (received Calcium & Vitamin D supplements), 0.7% decrease in Group II. No statistically significant difference between the 2 groups (z = -0.057, p = 0.955 on Mann Whitney test)

DEXA

In order to evaluate the changes occurring in bone with short term steroid use and the prophylactic role of Calcium and Vitamin D in preventing the deleterious bone changes, serial DEXA scans were performed and both Bone Mineral Content (BMC) and Bone Mineral Density (BMD) were estimated. A baseline DEXA Scan was done prior to starting therapy with steroids, followed by repeat testing at end of treatment at 12 weeks.

The 12 week estimations were compared to the baseline and percentage change over baseline was calculated. Thus, each patient was his/ her own control .The mean percentage change in BMC and BMD was computed for the both the groups. Paired T – test and Mann Whitney tests were used for determining statistically significant difference between the two groups.

1

5. BONE MINERAL DENSITY (BMD in g/cm2)

Table 15.1: BMD DATA IN GROUP I

Table 15.2: BMD DATA IN GROUP II

		NON INTERVENTION GROUP	
Baseline BMD (gm/cm2)	BMD at 12 weeks (gm/cm2)	Change in BMD (gm/cm2)	% change in BMD over baseline
0.464	0.469	0.005	1.08
0.306	0.31	0.004	1.31
0.395	0.396	0.001	0.25
0.438	0.426	-0.012	-2.74
0.302	0.334	0.032	10.60
0.472	0.499	0.027	5.72
0.432	0.469	0.037	8.56
0.285	0.289	0.004	1.40
0.497	0.496	-0.001	-0.20
0.459	0.436	-0.023	-5.01
0.457	0.451	-0.006	-1.31
0.302	0.331	0.029	9.60
0.421	0.448	0.027	6.41
0.355	0.344	-0.011	-3.10
0.4	0.393	-0.007	-1.75
0.427	0.407	-0.02	-4.68
			Mean = 1.6338

Tables 15.1 and 15.2 represent the BMD data for each of the subjects in the Intervention and Non Intervention groups

Figure 15.1: Distribution of BMD variables in Intervention group

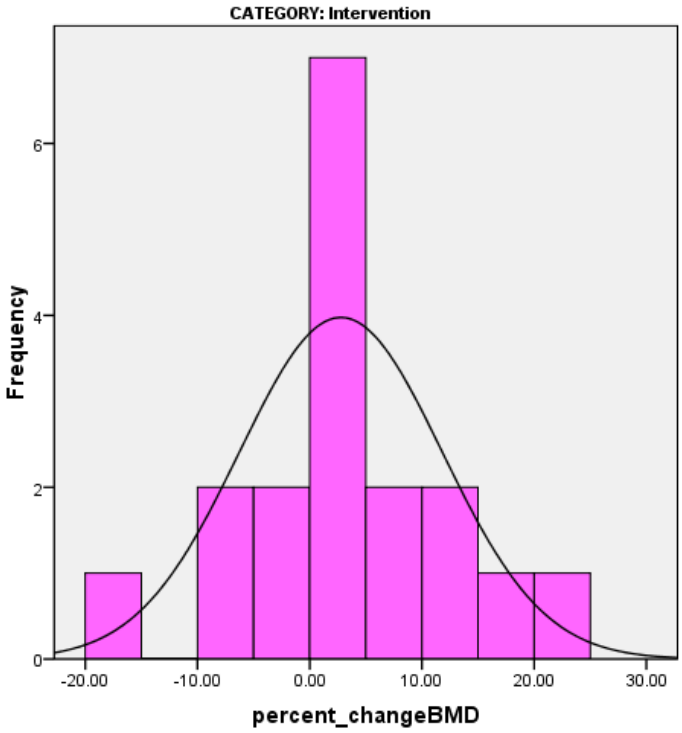


Figure 15.2: Distribution of BMD variables in the Non Intervention group

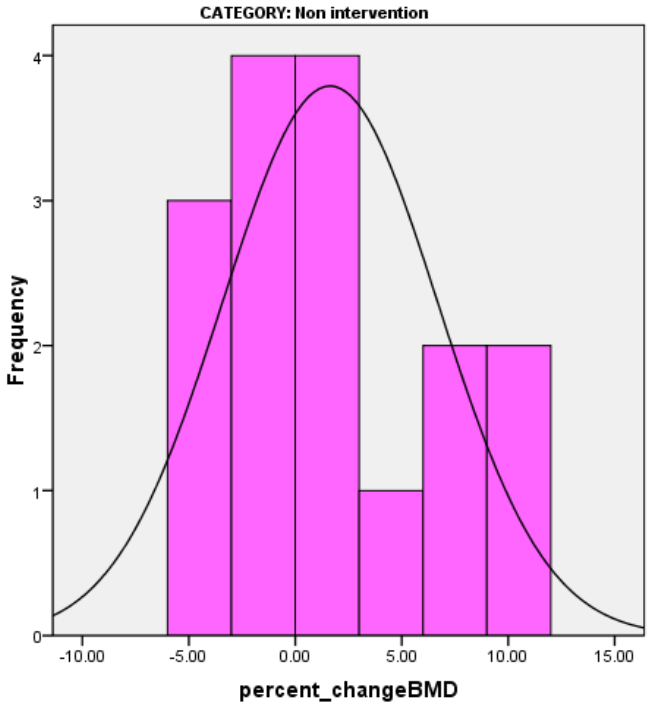


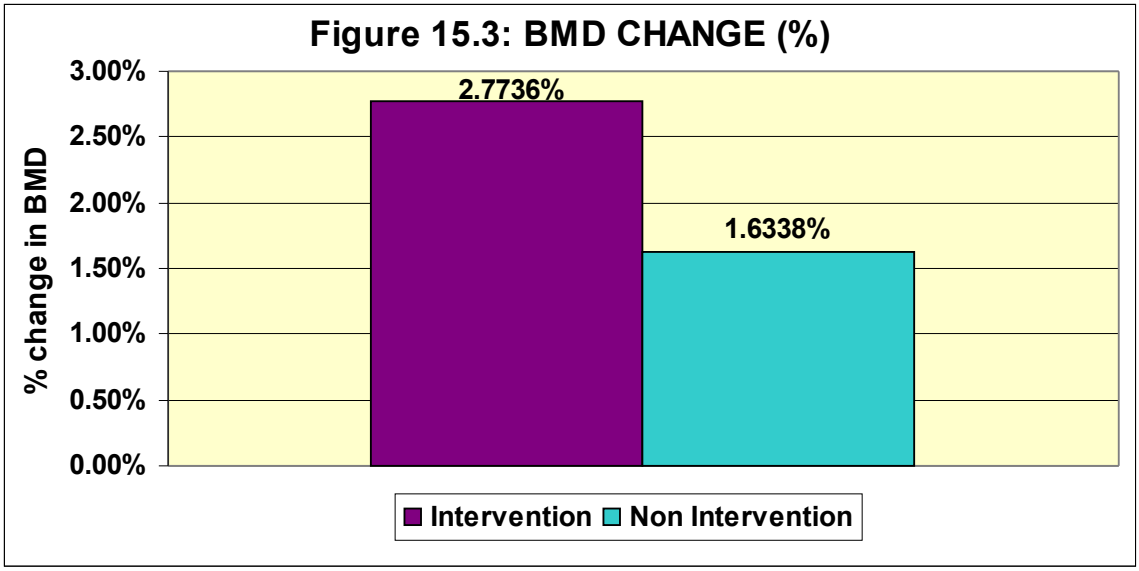
Table 15.3 : BMD CHANGE

PARAMETERS	INTERVENTION (I)		NON INTERVENTION(NI)	
	Initial	Final	Initial	Final
Minimum BMD (g/cm2)	0.285	0.276	0.285	0.289
Maximum BMD (g/cm2)	0.702	0.671	0.497	0.499
Mean BMD (g/cm2)	0.410	0.418	0.400	0.406
Mean % BMD change = $\sum \frac{\text{(Final BMD – Initial BMD)}}{\text{(Initial BMD)}} \times 100$	+ 2.7736 %		+ 1.6338 %	

MANN WHITNEY U TEST: MEAN (%) BMD CHANGE IN GROUPS I & II

Ranks				
	CATEGORY	N	Mean Rank	Sum of Ranks
Mean (%) change in BMD	Intervention	18	18.56	334.00
	Non intervention	16	16.31	261.00
	Total	34		

Test Statistics[b]	
Mann-Whitney U	125.000
Wilcoxon W	261.000
Z	- 0.656
Asymp. Sig. (2-tailed)	0.512
Exact Sig. [2*(1-tailed Sig.)]	0.528[a]
a – not corrected for ties	



Tables 15.3 and Figure 15.3 show the mean % change in BMD over baseline in Groups I & II over 12 weeks.

There was an increase in BMD in both groups

In Group I (Intervention group) the BMD increased by 2.77%

In Group II, the rise was by 1.63%

The percent change in BMD was not normally distributed in the two groups (Figure 15.1 & 15.2). Therefore Mann -Whitney U test (a non parametric test) was used for comparing the 2 groups. This showed no difference between the 2 groups in this parameter ($z = -0.656$, $p = 0.512$)

16. BONE MINERAL CONTENT (BMC in g)

Table 16.1: BMC DATA IN GROUP I

		INTERVENTION GROUP	
Baseline BMC in gms	BMC at 12 weeks in gms	Change in BMC in gms	% change in BMC over baseline
12.57	12.21	-0.36	-2.86
11.64	10.87	-0.77	-6.62
25.53	24.62	-0.91	-3.56
6.46	6.93	0.47	7.28
4.22	5.14	0.92	21.80
4.58	7.73	3.15	68.78
9.96	10.38	0.42	4.22
6.43	7.52	1.09	16.95
7.39	7.21	-0.18	-2.44
8.37	10.01	1.64	19.59
6.18	7.27	1.09	17.64
5.52	6	0.48	8.70
5.71	7.19	1.48	25.92
12.61	13.12	0.51	4.04
5.56	5.08	-0.48	-8.63
8.2	9.36	1.16	14.15
21.42	23.51	2.09	9.76
14.03	15.14	1.11	7.91
			Mean = 11.2565

Table 16.2: BMC DATA IN GROUP II

		NON INTERVENTION GROUP	
Baseline BMC in gms	BMC at 12 weeks in gms	Change in BMC in gms	% change in BMC over baseline
12.95	13.05	0.1	0.77
7.41	6.5	-0.91	-12.28
11.73	9.07	-2.66	-22.68
10.03	7.66	-2.37	-23.63
6.73	5.83	-0.9	-13.37
10.82	9.39	-1.43	-13.22
16.63	13.97	-2.66	-16.00
5.55	5.4	-0.15	-2.70
12.46	10.46	-2	-16.05
9.6	7.62	-1.98	-20.62
9.72	10.08	0.36	3.70
5.63	5.46	-0.17	-3.02
12.05	10.66	-1.39	-11.54
6.02	6.1	0.08	1.33
7.97	7.34	-0.63	-7.90
10.1	9.06	-1.04	-10.30
			Mean = -10.4689

Tables 16.1 and 16.2 represent the BMC data for each of the subjects in the Intervention and Non Intervention groups.

Figure 16.1: Distribution of BMD variables in Intervention group

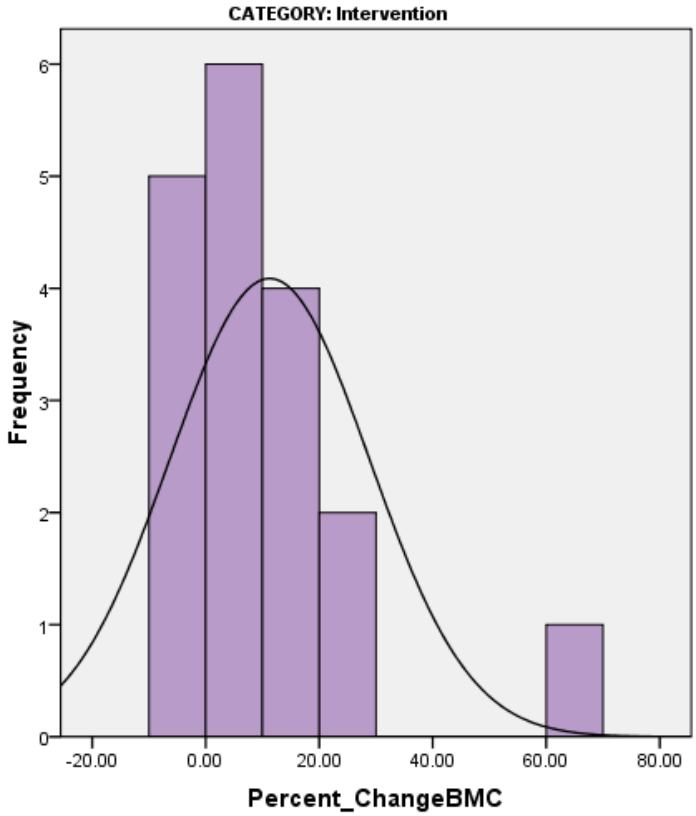


Figure 16.2: Distribution of BMC variables in the NI group

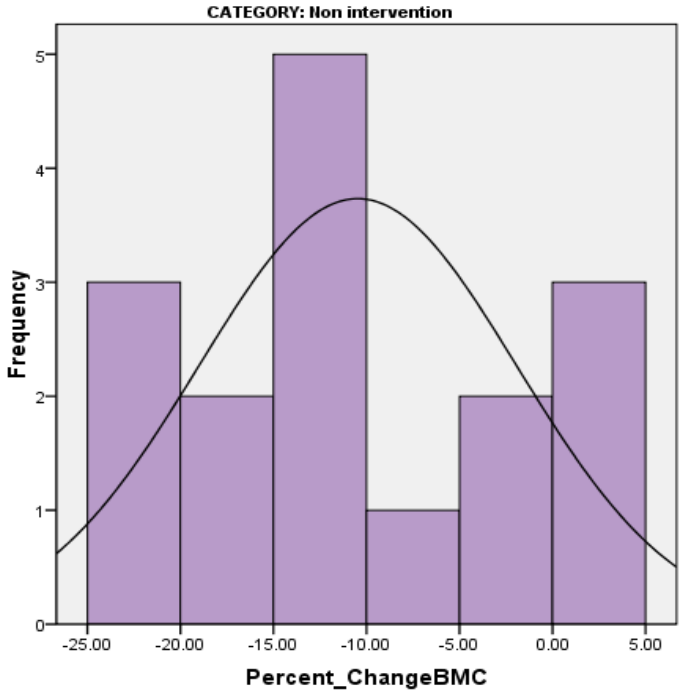


Table 16.3 : BMC CHARACTERISTICS IN I & NI GROUPS				
PARAMETERS	INTERVENTION		NON INTERVENTION	
	Initial	Final	Initial	Final
Minimum BMC (g)	4.22	5.08	5.55	5.40
Maximum BMC (g)	25.53	24.72	16.63	13.97
Mean BMC (g)	9.798	10.516	9.712	8.603
Mean % BMD change = $\sum \frac{\text{(Final BMC – Initial BMC) x 100}}{\text{(Initial BMC)}}$	+ 11.2565 %		- 10.4689%	

MANN WHITNEY U TEST ON MEAN (%) BMC CHANGE IN GROUPS I& II

Ranks	CATEGORY	N	Mean Rank	Sum of Ranks
Mean Change in BMC (%)	Intervention	18	24.22	436.00
	Non intervention	16	9.94	159.00
	Total	34		

Test Statistics[b]	
	Mean Change in BMC (%)
Mann-Whitney U	23.000
Wilcoxon W	159.000
Z	-4.175
Asymp. Sig. (2-tailed)	0.000
Exact Sig. [2*(1-tailed Sig.)]	0.000[a]

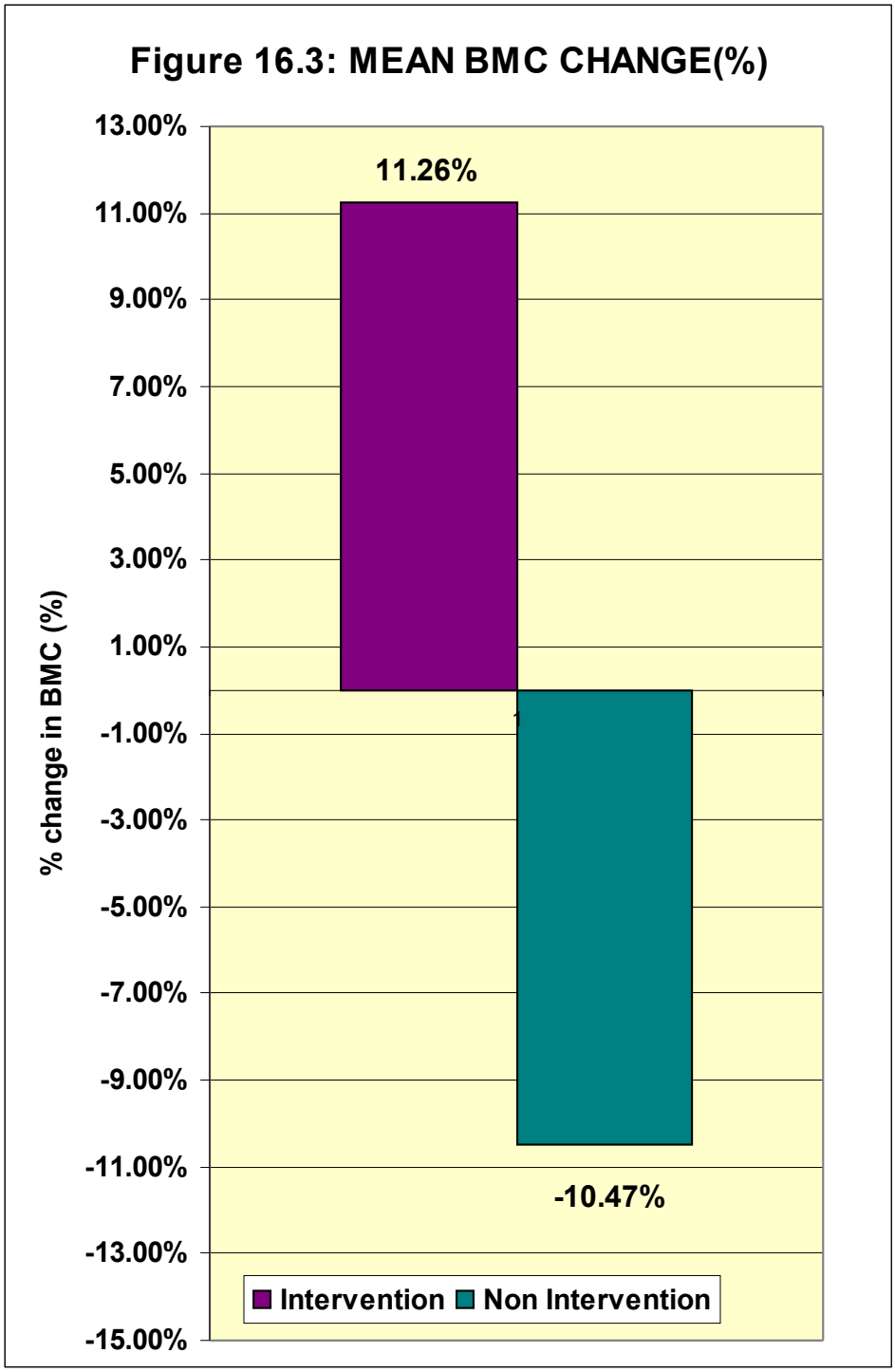


Table 16.3 and Figure 16.3 show the BMC characteristics and mean % change in BMC over baseline in Groups I & II and the distribution of values

11.3% increase in the BMC of subjects in Group I (Intervention group) over a 12

week period

As opposed to that, in Group II, over the same period, the BMC decreased by 10.4689 %.

It is apparent that the values for percentage change over basal are not normally distributed in the two groups (Figures 16.1 & 16.2). Therefore a Mann Whitney U test was performed and this showed a statistically significant percentage increase in BMC in children who received Calcium and Vitamin D compared to children who did not receive this intervention ($z = -4.175$, $p < 0.001$).

The net intervention attributable difference in Bone Mineral Content in the 2 groups was 21.6%.

DISCUSSION

This open randomized controlled interventional prospective study to evaluate the role of prophylactic Calcium and Vitamin D in preventing short term steroid induced bone loss in children with Nephrotic syndrome was conducted in the Paediatric Nephrology subunit of the Child Health Department and the Endocrinology Department of the Christian Medical College Hospital, Vellore.

Of the 46 children recruited, 4 children dropped out during the course of treatment and did not complete the study. 34 children had completed their 3 month follow up and were considered for the final analysis. The remaining 8 patients were still on treatment and have thus not been included in the analysis.

Of the 34 children analyzed, 18 (53%) were randomized into Group I (Intervention group) and 16 (47%) into Group II (Non Intervention group) (Table 1, Figure 1).

The age of the children recruited ranged from 1 year to 12 year 5 months. The mean age was 4.13 years (Table 2.1 and Figure 2.1). According to literature, children develop Nephrotic Syndrome while younger than 18 years. Approximately 75% are under the age of 6 years with peak incidence between 2-3 years (95).The age distribution of the children in our study was also predominantly 1-6 years. The largest group, 16/34 (47%), was formed by 1- 3 year olds, followed by 11 (32.4%) in the 3-6 year age group. 2 (14.7%) children were between 6 – 10 years and 5 (14.7%) children in the 10 -13 age group). The mean age in Group I and II was 4.28 years and 3.97 years respectively. Both the groups were comparable with respect to age distribution. (Tables 2.2 & 2.3, Figure 2.2)

Of the 34 children, 70.6% (24/34) were boys and 29.4% (10/34) were girls (Table

3.1, Figure 3.1).The male: female ratio was 2.4:1. In the Cochrane Database review done by Hodson et al (17) on children with Nephrotic syndrome, the male to female ratio was 1.2:0.9. An unpublished study done on Nephrotic children in the department of Child Health in CMC, Vellore in 2006 reported a male: female ratio of 1.5:1.In our study also a male preponderance was observed.

The children recruited came from different ethnic backgrounds (Table 4, Figures 4.1 & 4.2). Majority of the subjects 70.6% (27/34) belonged to the state of Tamil Nadu. 14.7% (5/34) were natives of West Bengal, 5.9% (2/34) each hailed from Jharkhand and Tripura and 2.9% (1/34) were from Andhra Pradesh.

Minor infections are known to precipitate Nephrotic syndrome in children (1). In our study, we found that 35.3% (12/34) children had infections heralding the onset of Nephrotic syndrome (Table 5.1, Figure 5.1). Of these, the most common were Lower respiratory tract infections (17.6%), followed by Upper Respiratory Tract Infections (11.7%). Acute Gastroenteritis, Hepatitis A, and Urinary tract Infections affected 1 child each (2.9%) (Table 5.2, Figure 5.2). None of the infections were life threatening and most could be treated on an outpatient basis. 26% (9/34) required hospitalization and antibiotic therapy.

ISKDC studies (12) demonstrate that approximately 30% of patients with Minimal Change Nephrotic Syndrome have both systolic and diastolic pressures above the 90th percentile for age. According to them, when values above the 98th percentile were used to denote an abnormality, then approximately 20% had systolic pressures that were elevated and about 13% of the diastolic pressures were aberrant. Our study showed similar results. 20.6% (7/34) patients had hypertension at onset of the Nephrotic syndrome (Table 6 & Figure 6). However, hypertension was transient and antihypertensive medications could

be withdrawn by 2 weeks.

Urine analysis (using Multistix) was done to evaluate response to steroid therapy. Remission was concluded based on clinical features of resolution of edema and proteinuria (i.e. urine multistix showing nil or trace proteinuria). The Remission rate was assessed at 2, 4, 6 and 12 weeks in our study (Table 7 & Figure 7).82.4% (28/34) children went into remission by 2 weeks, 88.2% (30/34) by 4 weeks and 97.1% (33/34) by 6 weeks. At 12 weeks, 31 (91.2%) patients remained in remission.

These figures were consistent with earlier studies. Most of the literature suggests that 80 to 90% of children will respond to therapy by 2 weeks (1). In a report from the International Society of Kidney Disease in Children (ISKDC), it was found that approximately 90 percent of patients who will respond to steroids do so within four weeks after starting steroids, with the remaining 10 percent going into remission after two to four more weeks of a daily steroid therapy (12). This implies that it is probably worthwhile waiting for 6 weeks to achieve remission in children with nephrotic syndrome, thereby avoiding renal biopsy which is invasive and can have complications.

In our study, 2 children underwent renal biopsy because of late onset of nephrotic syndrome and were found to have Mesangioproliferative Glomerulonephritis. Of the two, 1 was steroid responsive and the other required slow tapering of steroids.

At the time of analysis, 38.6% (13/34) of the children relapsed during or after treatment (Table 8.1 & Figure 8.1). 2 (15.4%) children who relapsed had achieved remission by 6 weeks on full dose of steroids, but had proteinuria on lowering the steroid dose (Table & Figure 8.2). The time to relapse after stopping steroids ranged between 7 and 22 weeks, average being 11.5 weeks. In 46.2% (6/13) children, the relapse was precipitated by an infection (Table 8.3 & Figure 8.3). Viral fever and URI were the most

common infections precipitating relapse. The duration of the study was not designed for long term follow up, and therefore, the number of children who relapsed does not represent the true incidence.

In his report on the prognostic significance of the early course of minimal changes nephrotic syndrome, Tarshish et al (15) stated that 30 percent of treated patients will not have a relapse and therefore will be cured after the initial course of therapy. Ten to 20 percent will relapse several months after steroid treatment is discontinued, but will have less than four steroid-responsive episodes before permanent remission occurs. A relapse rate of 38.6% was found in our study.

During the course of the study, children were assessed for the presence of side effects of steroids. Adverse effects of steroids are represented in Table 9 & Figure 9. Cushingoid habitus (100%), gastritis (79.4%), hypertrichosis (67.8%) and infection (20.6%) were the most commonly noted side effects. 8.8% children each had behavior changes and 5.9% striae. Elevated blood pressures, acne, purpura, cataract and glucosuria were not found in any of the subjects during the 12 weeks of steroid treatment.

The higher incidence of gastritis and infections at 6 weeks compared to 12 weeks may reflect their dose dependent nature. Marked increase in hypertrichosis seen at 12 weeks compared to 6 weeks implies it appears after prolonged steroid use.

Steroid therapy mainly had minor side effects in our study. Infection was the most serious side effect observed. 20.6% (7/34) children had infections at 6 weeks of treatment, and 8.8% (3/34) at 12 weeks. It is known that children with Nephrotic syndrome have lowered ability to fight infections and that steroids suppress the immune system. Higher doses cause greater suppression. This indicates the need for an active search of any focus

of infection and prompt treatment of the same including hospitalization (if required) in these children.

76.4% (26/34) children required additional medications (Tables 10.1 & 10.2, Figure 10).The commonest were diuretics for control of edema - 64.7% (22/34) were given Spironolactone and 50% (17/34) required Frusemide. 41.2% (14/34) children received antibiotics to treat infections. Blood Pressure control was achieved with Nifedipine in 5 (14.7%) children and Atenolol in 1 (2.9%) child. 1 child was given Anti Tuberculous Therapy (ATT) because of asymptomatic Mantoux positivity.

At each outpatient visit the weight was recorded. The percentage change in the weight over 12 weeks duration compared to the initial weight was calculated for each child. The mean of this percentage change in weight in Group I and II were computed. Both groups showed weight gain, 1.25% in Group I and 7.7% in Group II (Table 11.3&Figure 11.2). The difference in weight gain was not found to be statistically significant. The exact significance of this is not known as both groups had received the same dose of steroids.

Growth suppression is a known adverse effect of Glucocorticoid therapy and occurs in children on long term therapy. Emma et al (96) found that children with steroid-responsive Nephrotic syndrome are at risk of permanent growth retardation secondary to prolonged courses of steroid treatment. Whether Calcium and Vitamin D co-administration with steroids can prevent this stunting is therefore an important question.

The height of all children was thus recorded at each visit and the change analyzed. The percentage change in height in 12 weeks (over baseline height) was computed for each subject and the mean was calculated for both the groups. Children in both groups

stood taller at the end of 12 weeks. There was an average height gain of 1.88% in Group I and 2.11% in Group II (Table 12.3&Figure 12.2). No statistically significant difference was found between the 2 groups. The increase in height was probably a reflection of the normal physiological growth of children. It is also pertinent to mention here that a 12 week period is too short to demonstrate stunting or the beneficial effect of Calcium and Vitamin D on the same in children on steroids.

Percentage change in BMI over baseline was calculated in a fashion similar to the weight and height change (Table 13, Figure 13.2). Group I patients showed a fall of 1.78% in 12 weeks. In contrast, in Group II patients BMI increased by 3.82%. When subjected to analysis, no statistically significant difference in the % change in BMI was found in the two groups

Hypocalcaemia is a common finding in nephrotic syndrome, due primarily to hypoalbuminemia-induced reduction in calcium binding to albumin. A low serum total calcium concentration induced by hypoalbuminemia does not affect the physiologically important free (or ionized) calcium concentration. A small subset of patients with hypocalcaemia out of proportion to hypoalbuminemia has been reported, due to low serum calcitriol concentrations and perhaps increased fecal calcium losses. However, the frequency with which true hypocalcaemia and bone disease occurs in the nephrotic syndrome is unclear, as many investigators have found relatively normal calcium concentrations (68, 69).

A published study from Switzerland conducted by Lippuner et al (97) on renal transplant children who received steroids demonstrated a less than normal level of Calcium among his subjects. In our study, Serum Calcium measurements were performed

at baseline and after 12 weeks. Serum Calcium (corrected for the corresponding Serum albumin) was maintained in the normal physiological range in all 34 (100%) children during both measurements. The percentage change in serum calcium levels over baseline values was determined for each subject and the mean in Group I (which received supplemental Calcium & Vitamin D) and Group II were compared. Both groups showed a drop in Calcium levels (1.1% in the Group I and 0.7% in Group II (Table 14, Figure 14), however the difference was not statistically significant. Serum Calcium estimation may be reserved for patients with symptoms of hypocalcaemia or a low corrected serum calcium concentration.

There is increasing awareness that children are not exempt from developing osteoporosis. Threats to bone health that are operative during the pediatric years may be particularly costly long-term, since growth and development of the skeletal system play a critical role in determining bone strength and stability in later years (10).

Glucocorticoids are used in myriad pediatric diseases including nephrotic syndrome, asthma, juvenile rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, and organ transplantation. It is estimated that 10% of children may require some form of glucocorticoids at some point in their childhood (3). Prolonged steroid use is known to cause osteoporosis. Osteopenia in children receiving a prednisolone dose of less than 0.16 mg/kg/day has been reported (7, 8).

Childhood Steroid sensitive nephrotic syndrome provides a clinical model of chronic glucocorticoids therapy in the absence of significant underlying disease activity. The course of SSNS is characterized by relapses which result in protracted, repeated courses of glucocorticoids**.** The standard prednisone dose for new onset disease and relapses is 2 mg/kg per day (18) which far exceeds the 5 mg/day that is considered a risk

factor for glucocorticoid induced osteoporosis in adults (3).

The largest study to evaluate the incidence of fractures among pediatric glucocorticoid users was conducted in the UK by Van Staa et al (9). It was a case-control study involving over 37,000 children treated with steroids. Results showed that the risk of fracture was increased in children who received four or more courses of oral corticosteroids for a mean duration of 6.4 days. Fracture risk was also increased among children using 30 mg prednisolone or more each day.

The deleterious effects of steroids on bone are maximum during the first 6 months of treatment. Studies have shown that the greatest reduction in bone mineral content (BMC) and BMD among children with leukemia occurred during the first 6–8 months of chemotherapy (23-26). Hence, new onset nephrotic syndrome was chosen for determining the effect of steroids on bone over a 3 month period.

Glucocorticoid (GC) toxicity appears to have a predilection for trabecular bone (29). This is supported by the propensity of GCs to affect the spine. Hence, spine would be the target area for assessing steroid induced bone changes.

Dual energy x-ray absorptiometry (DEXA) is a cheap, easily accessible method with high precision and accuracy for the measurement of mineral content that employs low levels of radiation. DEXA determines the mineral quantity in grams (Bone Mineral Content- BMC) contained in a given projection of bone (BA). Dividing this mineral content by the bone area of the location obtains Bone Mineral Density (BMD). Hence, BMC and BMD measurements at lumbar spine using the DEXA scan can be used for the diagnosis and follow-up of steroid induced bone disease. In children acquisition of bone mass is due to a) increase in length and width of bone and b) an increase in bone mineral density. If one uses only bone mineral density, it may not truly reflect changes in bone

mass.

Nephrotic syndrome is associated with urinary loss of vitamin D-binding protein (VDBP) (70). In serum, calcidiol (25- hydroxy Vitamin D), the precursor of calcitriol (1, 25- dihydroxy Vitamin D), is primarily bound to VDBP and is therefore also excreted in the urine (71, 72). The net effect is a reduction in serum calcidiol concentrations, while those of calcitriol are normal or reduced (71, 73, and 74). The physiologic consequences of these changes in vitamin D metabolism on calcium homeostasis are uncertain and Vitamin D replacement therapy is not routinely recommended in patients with nephrotic syndrome.

There is data to suggest that Vitamin D plus Calcium is superior to no therapy or Calcium alone in the management of corticosteroid-induced osteoporosis (80, 81). In our study, we used Vitamin D to counter steroid induced bone changes. The dose used (1000 IU/day) was much higher than the dose used for routine supplementation (200 - 400 IU /day) but was in the dose range used for preventing steroid induced bone disease. The safety and efficacy of administering such high dose Vitamin D has been proved (88).

Although the detrimental effect of steroid treatment on children's bones has been well known for years, no recommendations have been suggested for the prevention of diminished BMD and BMC in children with nephrotic syndrome. There are no clear cut guidelines as to when bone protective strategies must be instituted. This prospective randomized study was thus undertaken to determine the need of prophylactic calcium and Vitamin D supplementation in children on short term steroids. Using Bone Mineral Density (BMD) and Bone Mineral Content (BMC) as tools, those receiving supplementation were compared with those not receiving it.

BMD interpretation is difficult in children.

Comparing the BMD of children to the reference data of adults (T-score) will lead to an over diagnosis of osteopenia for children. BMD scores must therefore be compared to reference data for the same age (Z-score). There are very few patterns of normative (reference) data available for BMD in children.

BMD is obtained based on area and not volume and because the area does not increase in the same proportion as the volume during growth, large bones are overestimated and small bones are underestimated in terms of BMD. The confounding effect of differences in bone size is due to the missing depth value in the calculation of BMD. It is assumed that BMC and BA are directly proportional to one another, such that a 1% change in BA is matched by a 1% change in BMC, but this is not true.

BMD is therefore is not the preferred measurement during growth, because it factors out most of the component of bone accumulation that is associated with change in bone size (57, 59). What is important in assessing skeletal mineral acquisition is bone mineral content (BMC).

Except for a study done by Leonard et al (20), there are no other studies using BMC as a tool to assess bone loss. He studied the effect of long-term glucocorticoids on BMC in 60 children and adolescents with relapsing steroid sensitive nephrotic syndrome and 195 normal control subjects. He showed that children receiving corticosteroids do not appear to have deficits in the BMC of the spine. It was not possible to include normal controls in our study due to ethical considerations of subjecting healthy children to DEXA scans.

In a study done on 100 Indian children with Relapsing Idiopathic Nephrotic Syndrome on long term steroids using BMD measurements at lumbar spine by DEXA, Gulati et al (89) found that these children are at risk for low bone mass, especially those

administered higher doses of steroids, those with longer duration of disease and those with late onset.

Similar results were found by Basiratnia et al (90) when they measured BMD and BMC using DEXA in 37 Iranian children with Steroid Dependent Nephrotic syndrome. In their study, 6 girls and 31 boys with ages ranging from four to 21 years formed the patient group and 37 age and sex-matched healthy individuals were taken as control group. The percentage of BMC and BMD of lumbar spine and femoral bones of the patients were significantly lower than control group. BMD at femoral and lumbar bones was inversely correlated with cumulative steroid dose. Bone loss was directly proportional to longer duration of the disease and higher cumulative dose of steroid.

The effect of prolonged glucocorticoid treatment or intermittent high dose therapy on bone health in children has been studied but most of this evidence to date is cross-sectional in nature.

There is little data available on the effect of short term steroids on bone health. 'A study on skeletal effects of short term steroids on children with steroid dependent nephrotic syndrome' done by Kenichi Kano et al (92) on 9 Japanese children with steroid-responsive nephrotic syndrome without relapse showed that BMD and biochemical parameters of mineral and skeletal homeostasis returned to normal values at 16 weeks after the cessation of prednisolone therapy, thus leading the authors to conclude that the skeletal effects of short-term prednisolone therapy were transient. The change in BMD of normal healthy children during the period of study (using controls) would have helped establish whether their conclusions are indeed true. Their sample size was probably too small to make valid conclusions. Further long term follow up of these children is needed to see if short term therapeutic doses of corticosteroids lead to acquisitional osteopenia.

In another study , Gulati et al (93) prospectively studied the role of Calcium (500 mg/day) and Vitamin D (200 IU/day) supplementation on bone health in 88 children with relapsing Nephrotic syndrome on steroids by performing DEXA scans at the lumbar spine before and six months after supplementation. They found that compared to baseline values, BMD values were significantly better on follow up. However, the basic assumption in this study was that if there was an increment in the BMD, it was because of supplemental Calcium and Vitamin D. The fact, that children will have an increase in BMD by virtue of growth was not accounted for. This problem could have been avoided by the use of age matched controls, whose BMD change over the same period could have been assessed and used as a comparison.

Bak et al (94) conducted a randomized prospective study in Turkey on 40 children (mean age of 4.6 ± 1.8 years) with new onset or relapsing Nephrotic Syndrome to determine the effects and prophylactic role of calcium (1 g daily) plus vitamin D (400 IU) treatment on bone and mineral metabolism in children receiving prednisolone treatment. BMD was significantly decreased in both the treatment and non-treatment group but the percentage of BMD decrease was found to be significantly lower in the treatment group (- 4.6 %) than in the non-treatment group (-13%) , showing a net treatment attributable difference of 8.4 % in the BMD. Here, it would be pertinent to point out that > 50% subjects included were children with relapsing nephrotic syndrome who would have been previously treated with steroids and therefore may have had pre existing bone mineral deficits. This may have minimized the steroid induced changes as in relapsing nephrotic syndrome children may have started off with lower BMD and BMC values to begin with.

Measurement of changes in skeletal mineral acquisition during childhood should take into consideration the following facts

a) Bones increase in length

b) Bones increase in girth

c) There is increased mineral deposition in unit volume of bone.

During steroid therapy, all three components of skeletal mineral acquisition are affected due to

a) Inhibition of growth hormone secretion and action

b) Increased resorptive osteoclastic activity

c) Reduced osteoblastic activity

Therefore it has been suggested that height, skeletal X ray and DEXA measurements should be used in conjunction to derive normative values.

If one were to use DEXA measurements, BMC is better than BMD because at the lumbar spine level BMC would take into account girth of the bone and the amount of mineral deposited in unit area.

There is a further problem in assessing changes with time in children with nephrotic syndrome. This is because children of different ages will be studied and the rate of mineral acquisition varies depending on age. We therefore studied only pre-pubertal patients in the age 1 to 12.4 years as the rate of mineral acquisition is linear in during this period.

In order to overcome the effects of inclusion of children of different ages, some workers use age and sex matched control values and express individual values as standard deviation scores called ‘Z’ scores. However, these have to be derived by study of large number of children in each age group belonging to the same ethnic group. Such normative values are not available for Indian children.

Some others use percentage change over basal values so that the change in BMD or BMC over time reflects the effect of disease or intervention. If one chooses children between 1-12 years of age when skeletal mineral acquisition is linear, this approach is quite useful. However, this cannot be used in pubertal children where the rate of bone growth and mineral acquisition differs between the two sexes and the changes are non linear.

In our study, it was noted that BMD increased only marginally, both in absolute value and in percentage change calculated over baseline in both groups. (Table 15.3, Figure 15). In Group I (Intervention group) the BMD increased by 2.77%. In Group II, the rise was by 1.63%. The difference in % change in BMD in the 2 groups was not statistically significant

Our analysis showed that percentage change in BMC was starkly different between the 2 groups (Table 16.3, Figure 16). There was a 11.3% increase in the BMC (over baseline) of subjects in Group I (Intervention group) over a 12 week period. As opposed to that, in Group II, over the same period, the BMC decreased by 10.4689 %. The difference in the average (%) change in BMC between the Group I and Group II was found to be highly significant on a Mann Whitney U test ($z = -4.175$, $p < 0.001$).

In our study, bone mineral density expressed as percent change over basal did not show a significant difference between nephrotic children who received Calcium and Vitamin D and those who did not in contrast to observations by Bak et al and Gulati et al. However, BMC increment in the treated group was significantly higher than in the control group indicating a positive 21.6% treatment effect in those treated.

This occurred in the absence of any significant differences in height increment. This implies that the observed change in BMC in the treatment group is attributable to

increases in vertebral girth rather than to vertebral height or bone mineral density changes.

The fact that Bone Mineral Content of growing children decreased after 12 weeks of steroid therapy in the control group in our study just reaffirms the detrimental effects of steroids on the bone. BMD was not a sensitive indicator of steroid induced bone changes in our study. This confirms the superiority of BMC measurements over BMD in determining changes in bone health in growing children.

Studies by Gulati et al, Kano et al and Bak et al all used BMD as a tool for bone health evaluation. The pitfalls of using BMD as an evaluation tool in growing children have been pointed out. This may be a major drawback in their studies. The use of BMC could have validated the observations made in their studies.

In our study, children receiving Calcium and Vitamin D supplements showed a marked increase in BMC (11.3%) in contrast to controls that showed a 10.4 % fall in the same. This proves the beneficial effect of Calcium & Vitamin D supplementation on bone mass in children on steroid therapy. The exact quantitation of this beneficial effect would have been possible by comparison with healthy age, sex matched controls.

The net treatment attributable difference in Bone Mineral Content in the 2 groups was 21.6%. Hence, it would be logical to conclude that prophylactic Calcium (500 mg elemental calcium per day) and Vitamin D (1000 IU / day) supplementation in children with 1st episode of nephrotic syndrome helps rectify defects in bone mineral acquisition caused by steroids.

SUMMARY

- 46 children were recruited into the study and followed up over 12 weeks. 34 children had completed the study at the time of analysis, 4 were dropouts and 8 are still undergoing treatment.
- The children were randomized into 2 groups:
    - Group 1: 18 children received steroids and Calcium and Vitamin D
    - Group 2: 16 children received steroids only
- Children in the age group of 1 year to 12.42 years were recruited into the study over a period of 15 months. The mean age was 4.13 years. Group 1 and Group 2 had similar age distribution.
- There were 24 boys and 10 girls. The male: female ratio was 2.4: 1.
- Majority of the children belonged to Tamil Nadu (24), followed by West Bengal (5), Jharkhand (2) , Tripura (2) and Andhra Pradesh (1).
- In 35% (12/34) children, infections triggered onset, majority being LRI (6/12), followed by URI (4/12). 1 each had Acute Gastroenteritis, Hepatitis A and Urinary Tract Infection.
- 20.6% (7/34) children had hypertension at onset.
- By 2 weeks, 82.4% (28/34) children were in remission, 88.2% (30/34) by 4 weeks and 97% (33/34) by 6 weeks.
- By 12weeks, 91.2% (31/34) remained in remission.
- 38.6% (13/34) patients relapsed, 85% after stopping steroids and 15% while tapering steroids. In 46% (6/13), relapse was triggered by an infection. Viral fever and URI were the most common infections precipitating relapse.
- Cushingoid features (100%), gastritis (79.4%), hypertrichosis (67.8%) and infections (20.6%) were the most commonly observed side effects of steroids. 8.8% had

behavior changes and 5.9% had striae.

- Higher incidence of gastritis and infections at 6 weeks compared to 12 weeks may reflect dose dependent nature of these side effects.
- 76.4% (26/34) received additional medications in the form of diuretics – spironolactone (64.7%) and frusemide (50%), antibiotics (41.2%), antihypertensives – nifedipine (14.7%), atenolol (2.9%) and ATT (2.9%).
- Change in Weight , Height and BMI and Serum Calcium over 12 weeks calculated over baseline showed no statistically significant difference between the 2 groups
- A net weight gain of 1.24 % in Group I and 7.7% in Group II was observed.
- Group I & II showed 1.88 % and 2.11 % increase in height respectively.
- BMI decreased by 1.78 % in Group I; in Group II it increased by 3.826%
- Serum Calcium (corrected for the corresponding Serum albumin) was maintained in the normal physiological range in all children.
- Serum Calcium dropped by 1.16% in Group I and 0.69 % in Group II. Despite the drop, Serum calcium values remained within the normal range at 12 weeks.
- There was a small gain in BMD in both groups 2.77% in Group I and 1.63% in Group II. The difference between the 2 Groups was not significant.
- Children receiving Calcium and Vitamin D supplements showed a marked increase in BMC (11.3%) in contrast to controls who showed a 10.4 % fall in the same. The difference in the 2 groups was highly significant ($z = - 4.175$, $p < 0.001$)
- The net intervention (Ca & Vitamin D administration) attributable difference in Bone Mineral Content in the 2 groups was 21.6%.

CONCLUSIONS

1. Bone Mineral Content of growing children decreased by 10% after 12 weeks of steroid therapy in the control group confirming the detrimental effects of high dose short term steroids on the bone.
2. BMD increased only marginally both in absolute value as well as a percentage change over baseline in both treatment and control groups. BMD measurements failed to detect steroid induced bone changes in our study. This confirms the superiority of BMC rather than BMD in determining changes in bone health in growing children.
3. Children receiving Calcium and Vitamin D supplements showed a significant improvement (11.3%) in the BMC in contrast to controls who showed a 10% decrease in the same.
4. Prophylactic Calcium and Vitamin D supplementation is useful in preventing steroid induced bone changes as demonstrated by a net treatment attributable change in BMC of 21.6%.
5. Short term steroid therapy had minor adverse effects - Cushingoid features , Gastritis and Hypertrichosis being the most common. Infections were the only serious adverse effect noted.

RECOMMENDATIONS

1. Supplementation with Calcium (500 mg /day of elemental Calcium) and
2. Vitamin D (1000 IU /day) during steroid therapy in children with new onset nephrotic syndrome.
3. Use of Bone Mineral Content (BMC) as a diagnostic tool in growth studies assessing bone health
4. Further long term follow up of these children with nephrotic syndrome is needed to determine if short term therapeutic doses of corticosteroids lead to acquisitional osteopenia in later years. These studies will assess the need to continue Calcium and Vitamin D supplementation after stopping steroids.
5. Studies of bone mineral acquisition in normal healthy children so that normative data can be obtained . This will be useful for deriving 'Z' scores for interpreting DEXA studies in children.

LIMITATIONS

1. BMC and BMD measurements could not be performed on age, sex and body surface area matched healthy children due to ethical reasons. If performed, they could have helped us determine the extent of steroid induced bone loss and the degree of protection provided by supplementation with Calcium and Vitamin D.

2. The study could not be double blinded as it was not possible to obtain a suitable placebo.

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ANNEXURE - I

DATA COLLECTION PROFORMA

GENERAL INFORMATION

- **Name :**
- **Hospital No:**
- **Date of birth :**
- **Sex : M / F**
- **Category : Intervention / Non Intervention**
- **Address:**

- **Phone no :**

ANTHROPOMETRY

	Baseline	12 weeks
Weight		
Height		
BMI *		
BSA**		

*** BMI = Body Mass Index**

**** BSA = Body Surface Area**

MONITORING OF NEPHROTIC STATUS

	Baseline	2 weeks	4 weeks	6 weeks	12 weeks
Urine Protein / Creatinine Ratio					
Serum Cholesterol					
Total Protein					
Serum Albumin					
Edema					
Urine Multistix					
Proteinuria					

INVESTIGATIONS

		Baseline	12 weeks
Serum Calcium			
Serum Phosphate			
Serum Alkaline Phosphatase			
Serum Creatinine			----
DEXA			
Lumbar spine	BMC		
	BMD		

Additional Medications used

Hospital admissions

OTHER COMPLICATIONS OF STEROIDS

Complications	Baseline	6 weeks	12 weeks
Hypertension			
Hirsutism			
Acne			
Striae			
Purpura			
Cushingoid			
Behavioural change			
Cataract / Glaucoma			
Infection			
Type of infection			
Glucosuria			
Gastritis			

TREATMENT DETAILS

- **Date of starting treatment:**
- **Date of completing treatment:**
- **Duration of treatment > 12 weeks: Yes / No**
- **Total duration of treatment :**
- **Cumulative dose of steroids :**
- **Relapse : Yes / No**
  - **Time of relapse :**
  - **On treatment: Yes / No**
  - **If No, duration since stopping treatment ….....weeks**

- **Cause of relapse : spontaneous / infection**

  Type of infection :

ANNEXURE - II

INFORMED CONSENT DOCUMENT

The Child Health Department of Christian Medical College Hospital, Vellore would like you to read this informed consent document (If you cannot read it, it would be read out to you). It involves your child's illness – nephrotic syndrome, the investigations involved, its treatment and follow up.

Corticosteroids like Prednisolone are the recommended first line treatment for nephrotic syndrome. The usual duration of treatment is 12 weeks. The drug used for treatment does cause thinning of bones. There are no standard recommendations for preventing such bone loss.

In a previous study on similar children, Calcium and Vitamin D were shown to have a protective effect when steroids had to be used for several months. Therefore, it would be important to know if supplements of Calcium and Vitamin D would have a protective effect on bones when a short course of steroids is used for this disorder.

The way to assess changes in bone mineral density is by doing a DEXA scan. This will be done two times during the study. The radiation exposure when this scan is done is about 1/10th of the radiation exposure when a Chest X ray is performed. Serum Calcium, Phosphorus and Alkaline Phosphatase will also be measured 2 times during the study. We

will undertake to investigate your child free of cost to you. You are requested to agree to the tests recommended by the doctors. You are free to refuse. Should you refuse, it will in no way affect the medical care provided for your child here.

This is a randomised clinical trial. Therefore, 50% of children in the study will not get Calcium or Vitamin D. There are no known adverse effects to these doses of Calcium and Vitamin D. This study will help us to determine whether routine Calcium and Vitamin D supplementation is needed in children with this disorder.

Should you have any further questions, you can contact
Dr Surabhi Choudhary, Department of Child Health, Christian Medical College Hospital, Vellore – 632004, Phone No : 09443288151
A copy of this information paper is for you to keep. If you are willing please sign the attached consent form.

Patient's name :

Hospital No:

CONSENT FORM

Title of the Project: Short term steroids and BMD

I confirm that I have read and understand the information sheet for the above study and have had the opportunity to ask questions ☐

1. I understand that my child's participation is voluntary and that I am free to withdraw him / her at any time , without giving any reason , without his/her medical care or legal rights being affected. ☐

2. I understand that sections of any of the medical notes (pertaining to my child taking part in this research) may be looked at by responsible individuals. I give permission for these individuals to have access to my child's records. ☐

3. I agree to have my child take part in the above study ☐

Name of the parent / legal guardian	Signature	Date
Name of the Witness	Signature	Date
Name of the Researcher	Signature	Date

सूचना पत्र

क्रिश्चियन मेडिकल कॉलेज वेल्लोर का बाल विभाग आपसे इस सूचना (जो आपके बच्चे की बीमारी नेफ्रोटिक सिंड्रोम की जांच, चिकित्सा और पुनः जांच के बारे में है) को पढ़ने का अनुरोध करता है.अगर आप पढ़ नहीं सकते तो सूचना आपको पढ़ कर सुनायी जाएगी.

नेफ्रोटिक सिंड्रोम की चिकित्सा में प्रमुख रूप से प्रेडनिसोलोन जैसे स्टेरोइड्स का प्रयोग किया जाता है.चिकित्सा की सामान्य अवधि 12 हफ्ते होती है. इस दवाई के प्रयोग से हड्डियाँ पतली हो जाती हैं. हड्डियों की इस क्षति को रोकने के लिए कोई मानक अनुशंसा नहीं है.

पूर्व में इस तरह के बच्चों पर किये गए एक अध्ययन में पाया गया है कि कई महीनों तक स्टेरोइड्स का सेवन करनेवाले बच्चों को कैल्शियम और विटामिन डी देने से हड्डी पर स्टेरोइड्स के कुप्रभावों से उनकी रक्षा होती है. इसलिए ये जानना महत्वपूर्ण होगा कि इस रोग से ग्रस्त बच्चों को अल्प अवधि के स्टेरोइड्स के साथ यदि कैल्शियम और विटामिन डी को पूरक के रूप में दिया जाए तो क्या इसका उनकी हड्डियों पर रक्षात्मक प्रभाव होगा ?

हड्डी में इससे होनेवाले परिवर्तनों के मूल्यांकन के लिए डेक्सा स्कैन किया जायेगा. इस परीक्षा में होनेवाला रेडिएशन सीने के एक्स रे में होनेवाले रेडिएशन का दशांश है. अध्ययन के दौरान डेक्सा दो बार होगा. अध्ययन की अवधि में खून में कैल्शियम, फोस्फोरस और अल्कलाइन फोसफेटेस की जांच भी दो बार की जायेगी. ये सारी जांच मुफ्त में की जायेगी.

हमें क्रिश्चियन मेडिकल कॉलेज से ये जांच करने की अनुमति दी गयी है. आपसे आग्रह है कि आप जांच करने के लिए अपनी सहमति दे दें.आप सहमति देने से मना करने के लिए स्वतंत्र हैं. अगर

आप सहमति नहीं भी देते हैं तो भी आपके बच्चे का सही इलाज होगा.

ये अध्ययन एक रैनडमआइसड क्लीनिकल ट्रायल है. इसलिए इस अध्ययन में शामिल 50 % बच्चों को कैल्शियम और विटामिन डी नहीं दिया जायेगा. कैल्शियम और विटामिन डी की इन खुराकों के कोई ज्ञात कुप्रभाव नहीं हैं .इस अध्ययन से हमें ये निशिचित करने में मदद होगी कि इस रोग से ग्रस्त बच्चों को सामान्य अनुपूरक के रूप में कैल्शियम और विटामिन डी की आवश्यकता है या नहीं .

अगर आपके इस बारे में कुछ और सवाल हैं तो आप निन्मलिखित से सम्पर्क करें -
डॉ सुरभि चौधरी , बाल विभाग , सी एम् सी एच वेल्लोर , फ़ोन न : 09443288151

इस सूचना पत्र की एक प्रति आपके पास रहेगी. अगर आप स्वेच्छा से अपने बच्चे को इस अध्ययन में शामिल करने की सहमति देते हैं तो सहमति पत्र पर अपने हस्ताक्षर कर दें .

बच्चे का नाम :
हॉस्पिटल नंबर :

सहमति पत्र

शोध का शीर्षक : अल्प अवधि स्टेरोइड्स बी म डी शोध

1. मैं इसकी पुष्टि करता हूँ कि मैंने उपरोक्त अध्ययन से संबंधित सूचना पत्र को पढा और समझा है तथा मुझे उससे जुडे प्रश्न पूछने का मौका भी मिला है . ☐

2. मैं समझता हूँ कि इस अध्ययन में मेरे बच्चे / बच्ची की सहभागिता ऐच्छिक है तथा यह कि मैं किसी भी समय बिना कोई कारण बताये उसे वापस लेने के लिए स्वतंत्र हूँ , जिसका उसके स्वास्थ्य की देखभाल एवं कानूनी अधिकारों पर कोई प्रभाव नहीं पड़ेगा . ☐

3. मैं समझता हूँ कि मेरे बच्चे/बच्ची के इलाज सम्बन्धी नोट्स का कोई अंश (जो इस शोध कार्य से प्रासंगिक है) जिम्मेवार व्यक्तियों द्वारा देखा जा सकता है . मैं उन व्यक्तियों के लिए अपने बच्चे के रेकॉर्ड्स को देखने की अनुमति देता हूँ . ☐

4. मैं अपने बच्चे के उपरोक्त अध्ययन में शामिल होने से सहमत हूँ . ☐

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माता /पिता/अभिभावक का नाम हस्ताक्षर

दिनांक

---------- ---------- ----------

साक्षी का नाम हस्ताक्षर

दिनांक

---------- ---------- ----------

शोधकर्ता का नाम हस्ताक्षर

दिनांक

ஒப்புதல் படிவத் தகவல்

கிறிஸ்தவ மருத்துவக் கல்லூரி மருத்துவமனையின் குழந்தைகள் நலப்பிரிவு இந்த ஒப்புதல் படிவ விளக்கத்தை வாசிக்கும்படி தங்களைக் கேட்டுக் கொள்கிறது. (தங்களால் வாசிக்க இயலாவிட்டால் வாசித்து காண்பிக்கப்படும்) இது தங்கள் குழந்தையின் நோயான நெப்ரோடிக் சிண்ட்ரோம், அதற்குரிய மருத்துவ ஆய்வுகள், சிகிச்சை முறை மற்றும் .ாலோ அப் பற்றியது.

பிரெட்னிசிலோன் போன்ற கார்டிகோ ஸ்டீராய்ட் வகை மருந்துகளே நெப்ரோடிக் சின்ட்ரோம் நோய்க்கு முதல் தரமான மருந்தாகும். வழக்கமாக 12 வாரங்களுக்கு இந்த மருந்தை தொடர்ந்து எடுக்க வேண்டும். இந்த மருந்தை தொடர்ந்து எடுப்பதினால், எலும்புகள் பாதிக்கப்பட்டு மெலிவடையும்.

முன்பு செய்யப்பட்ட மற்றொரு ஆய்வில் இதே மாதிரியான குழந்தைகளுக்கு ஸ்டீராய்டை அதிக மாதங்கள் கொடுக்கும் நேரத்தில் கால்சியம் மற்றும் விட்டமின் 'டி' எலும்புகள் மெலிவடைவதைத் தடுப்பது கண்டறியப்பட்டுள்ளது. எனவே இந்த குறைந்த கால சிகிச்சை முறையிலும், குழந்தைகள் எலும்புகள் மெலிவடைவதை கால்சியம் மற்றும் விட்டமின் 'டி' தடுக்கிறதா என்பதை கண்டறிவது அவசியமாகிறது.

டெக்சா ஸ்கேன் என்ற ஒருவகை ஸ்கேன் மூலம் எலும்புகள் மெலிவடையும் அளவைத் துல்லியமாகக் கண்டறியலாம்.இந்த ஸ்கேன் மூலம் ஏற்படும் எக்ஸ்ரே கதிர் பாதிப்பு, நெஞ்சில் எடுக்கப்படும் எக்ஸ்ரே அளவில் பத்தில் ஒரு பங்கு மட்டுமே ஆகும்.இந்த ஆய்வில் இரத்தத்தின் கால்சியம், பாஸ்பரஸ் மற்றும் ஆல்கலைன் பாஸ்படேஸ் அளவுகள் இரண்டு முறை அளவிடப்படும்.இந்த ஆய்வில் தங்கள் குழந்தைக்கான ஸ்கேன் மற்றும் இரத்தப் பரிசோதனைகள் இலவசமாகச் செய்யப்படும்.மருத்துவர் பரிந்துரை செய்யும் ஸகேன் மற்றும் இரத்தப் பரிசோதனைகளை ஒப்புக் கொள்ளுமாறு கேட்டுக் கொள்ளப்படுகிறீர்கள்.எனினும் மேற்கண்ட ஆய்வினை மறுப்பதற்கு தங்களுக்கு முழுச் சுதந்திரம் உண்டு.தாங்கள் மறுப்பதினால்,அது தங்கள் குழந்தைக்கு கொடுக்கப்படும் மருத்துவ சிகிச்சையை எவ்விதத்திலும் பாதிக்காது.

இது ஒரு ரண்டமைஸ்ட் க்ளினிகல் ட்ரயல்.அதாவது 50% குழந்தைகளுக்கு கால்சியம் மற்றும் விட்டமின்-'டி' கொடுக்கப்படும்.கால்சியம் மற்றும் விட்டமின்-'டி' எடுப்பதினால் எந்த ஒரு தெரிந்த பக்கவிளைவுகளும் ஏற்படாது.இந்த ஆய்வு நெப்ரோடிக் சிண்ட்ரோம் உள்ள குழந்தைகளுக்கு சிகிச்சையின் போது கால்சியம் மற்றும் விட்டமின்-'டி' கொடுப்பது எலும்புகளுக்கு நல்லதா என்பதைத் தீர்மானிக்க உதவும்.

ஏதேனும் சந்தேகங்கள் இருந்தால் டாக்டர்.சுரபி சௌத்ரி, குழந்தைகள் நலப்பிரிவு, கிறிஸ்தவ மருத்துவக் கல்லூரி மருத்துவமனை, வேலூர்-632004. தொலைபேசி எண்:09443288151 என்ற முகவரியில் தொடர்பு கொள்ளலாம்.

இந்த தகவல் படிவத்தின் ஒரு நகல் தங்களிடம் கொடுக்கப்படும்.தாங்கள் ஒப்புக் கொண்டால் கீழ்க்கண்ட ஒப்புதல் படிவத்தில் கையெழுத்து இடவும்.

நோயாளியின் பெயர் : _____

மருத்துவமனை எண் : _____

கட்டத்தில் குறியிடவும் ✓

ஒப்புதல் படிவம்

ஆய்வின் தலைப்பு : குறைந்த கால ஸ்டீராய்ட் தெரப்பி மற்றும் போன் மினரல் டென்சிடி.

1. இந்தப்படிவத்தில் கொடுக்கப்பட்ட தகவல்களை அறிந்து கொண்டு எனது சந்தேகங்களை தீர்த்துக் கொண்டேன் என்பதை உறுதி செய்கிறேன். ☐

2. எனத குழந்தை இந்த ஆய்வில் ஈடுபடுவது எனது சொந்த விருப்பம். எந்நேரத்திலும் எவ்வித காரணமும் இன்றி அவன்/அவளை இந்த ஆய்விலிருந்து விலக்கிக் கொள்ள முடியும் மற்றும் அவ்வாறு செய்வது அவனது/அவளது சிகிச்சையைப் பாதிக்காது என்பதை உணர்ந்து கொண்டேன். ☐

3. எனது குழந்தையின் மருத்துவ ஏடுகளை (இந்த ஆய்வு சம்பந்தமான ஏடுகள் மட்டும்) தேவைப்படின் மற்ற பொறுப்பான நபர்கள் பார்வையிடுவார்கள் என்பதை உணர்ந்து கொள்கிறேன். மேலும் அவர்கள் அதைப் பார்ப்பதற்கு அனுமதி அளிக்கிறேன். ☐

4. எனது குழந்தை இந்த ஆய்வில் ஈடுபட ஒப்புக் கொள்கிறேன். ☐

_____	_____	_____
பெற்றோர்/காப்பாளர் பெயர்	கையொப்பம்	தேதி
_____	_____	_____
சாட்சியின் பெயர்	கையொப்பம்	தேதி
_____	_____	_____
ஆய்வாளர் பெயர்	கையொப்பம்	தேதி

ইনফর্মড কনসেন্ট পত্র

শিশু চিকিৎসা বিভাগের তরফ থেকে, এই পত্র পড়তে আপনাকে অনুরোধ করা হচ্ছে। আপনি না পড়তে পারলে আপনাকে এ পত্র পড়ে শোনানো হবে। এটা আপনার বাচ্চার ব্যাধী সম্পর্কে - নেফ্রটিক সিনড্রোম।

স্টিরয়েড অসুধ (প্রেডনিসোলন) এই ব্যাধীর চিকিৎসার জন্য ব্যবহার করা হয়- ১২ হপ্তা ধরে এর চিকিৎসা। এই-অসুধ হাড় কমজোরী করে। এই ক্ষতি কমানোর জন্য কোন সঠিক তথ্য নেই।

আগে একটি রিসার্চে দেখানো হয়েছে যে ক্যালসিয়াম এবং ভিটামিন ডি এই ক্ষতি কম করে, যদি স্টিরয়েড বহু দিন ধরে ব্যবহার করা হয়। ঠিক সেই রকম, এই ক্ষেত্রে এ উপকারী হবে কি না সেটা দেখার বিষয়।

হাড়ে কমজোরী পরীক্ষা করার জন্য ২ বার ডেক্সা নামক এক স্ক্যান করতে হবে। এই স্ক্যান এর রেডিয়েশন, বুকের এক্স-রে'র তুলনায় ১/১০ অংশ। রক্তের ক্যালসিয়াম, ফসফোরাস আলকালাইন ফসফেটেজ পরীক্ষা করা হবে দুবার। এর জন্য আপনার পয়সা লাগবে না। এই পরীক্ষা গুলি করাতে আপনার অনুমতি চাই। তবে এই বিষয়ে আপনি অনুমতি না ও দিতে পারেন। তাতে আপনার বাচ্চার চিকিৎসার কোন ফারাক বা ক্ষতি হবে না।

এই রিসার্চে (যার নাম র‍্যান্ডোমাইজড কনট্রোল ট্রায়াল) সব বাচ্চার অর্ধেক ৫০% কে ক্যালসিয়াম ও ভিটামিন ডি দেওয়া হবে - বাকীকে নয়। এই অসুধের কোন ক্ষতি নেই। এ থেকে আমাদের বুঝতে সুবিধা হবে যে এই অসুধ এই ব্যাধিতে উপকারী হচ্ছে কি না।

আপনার আরও কিছু জিজ্ঞাস্য থাকলে এই ঠিকানায়ে লিখতে / যোগাযোগ করতে পারেন:

ডাঃ সুরভী চৌধুরী
চাইল্ড হেল্থ ডিপার্টমেন্ট
বি এম সি, ডেলোর - ৬৬২০০৪
ফোন: ০৯৪৪৬২৮৯৫৩

এই ফর্মের একটি কপি আপনার কাছে থাকবে। আপনার ইচ্ছা হলে আপনি সেখানে সই করতে পারেন।

পোকেমন এর নাম:
রেজিস্ট্রেশন নাম্বার:

কনসেন্ট ফর্ম

রিসার্চ এর নাম: ডিহাইড্রেড এবং হাড়ের ঘনত্বজোরীয়তা

১. আমি এই ফর্ম পড়েছি - আমি বুঝেছি এতে কি লেখা আছে - আমি প্রশ্ন করার সুযোগ পেয়েছি। ☐

২. আমার বাচ্চা আমার স্বইচ্ছায় এই রিসার্চে অংশ নিচ্ছে। যে কোন সময়ে কোন কারন না দেখিয়ে আমি তাকে রিসার্চ থেকে সরিয়ে নিতে পারি - তাতে তার চিকিৎসার কোন ক্ষতি হবে না। ☐

৩. আমি বুঝি যে আমার বাচ্চার চিকিৎসার কাজগুলি দ্বায়িত্বরত মানুষের দ্বারা ব্যবহারিত হবে - তাতে আমি স্বইচ্ছায় রাজি দি। ☐

৪. আমি আমার বাচ্চাকে এই রিসার্চে অংশ নিতে স্বইচ্ছায় অনুমতি দি। ☐

পিতার নাম	স্বাক্ষর	তারিখ
উইটনেস এর নাম	স্বাক্ষর	তারিখ
রিসার্চারের নাম	স্বাক্ষর	তারিখ

వివరించబడిన సమ్మతిపత్రం

సి.యం.సి ఆసుపత్రిలో ఉన్న చిన్నపిల్లల విభాగము వారు చదువవలెనని లేదా వినిపించవలెనని (చదువురాని వారికి) ఆశిస్తున్నారు. ఇది మూత్రపిండాల వ్యాధి గురించి, దానికి కావలసిన పరీక్షలు, చికిత్స విధానము మరియు దాని అనుసరణ పద్ధతి గురించి తెలియపరుస్తుంది.

మూత్రపిండాల వ్యాధి నివారణ కొరకు ప్రెడ్నిసోలోన్ (మందు) అనే స్టెరాయిడ్ ను ప్రప్రథమ పద్ధతిగా ఉపయోగిస్తారు. ఈ మందును 12 వారాలు వాడుతారు. ఈ మందు వలన ఎముకలలోని సత్తువ తగ్గుతుంది. దీనికి ఏ విధమైన నియమితమైన మందులు లేవు.

ఇంతకు ముందు జరుపబడిన ప్రయోగ ఫలితాలలో, చాలా నెలలు స్టెరాయిడ్ ను ఉపయోగించిన వారికి ఎముకలలో కాల్షియం మరియు విటమిన్ 'డి' తగ్గుతుందని తెలిసింది. ఈ స్టెరాయిడ్ వలన నష్టాన్ని, కాల్షియం మరియు విటమిన్ 'డి' ఇవ్వడం ద్వారా పూరించవచ్చు.

"డెక్సా" అనే స్కాన్ ద్వారా ఎముకల యొక్క సాంద్రత మరియు దాని మార్పులు తెలుసుకొనవచ్చును. ఈ స్టడీ సమయంలో కాల్షియం, విటమిన్ 'డి' పరీక్ష రెండు సార్లు చేయవలెను. ఛాతీ ఎక్స్‌రే తీసినప్పుడు ఉండే రేడియేషన్ లో 1/10 వంతు మాత్రమే "డెక్సా" పరీక్షలో ఉంటుంది. సీరం కాల్షియం, ఫాస్ఫరస్ మరియు ఆల్కలైన్ ఫాస్ఫటేజ్ పరీక్షలు రెండుసార్లు చేసి తెలుసుకొనవలసి ఉంటుంది. ఈ పరీక్షలన్నీ మీ బిడ్డకు ఉచితంగా జరుపబడుతుంది. మీకు ఇష్టమైతే పాల్గొనవచ్చు లేదా తిరస్కరించవచ్చు. దీని ద్వారా మీ బిడ్డకు ఇచ్చే చికిత్స విధానంలో ఏ విధమైన మార్పు ఉండదు.

ఇది ఊహాత్మకమైన ప్రయోగం. ఇందులో సగం మంది పిల్లలకు కాల్షియం మరియు విటమిన్ 'డి' ఇవ్వబడదు. దీని వలన పిల్లలకు అనారోగ్యమైన మార్పు రాదు. కాని ఎంతవరకు కాల్షియం మరియు విటమిన్ 'డి' అవసరం ఉండవచ్చు అని తెలుసుకోవచ్చు.

మీకు ఏ విధమైన సందేహాలున్నా, మీరు పిల్లల విభాగములో పని చేసే డా॥ సురభి చౌదరిని అడిగి తెలుసుకొనవచ్చును. వారి ఫోన్ నెంబరు : 09443288151.

మీకు పూర్తి విషయము తెలిపిన ఈ పత్రమును మీకిస్తున్నాము. మీకు ఇష్టమైతే ఈ పత్రంలో సంతకము చేసి ఇవ్వవలెను.

రోగి పేరు :
ఆసుపత్రి నెంబరు :

సమ్మతి పత్రము

ప్రయోగం పేరు :- కొద్దికాలము ప్రిరాయిప్స్ మరియు బి.యమ్.ఐ.

1. నేను పూర్తిగా చదివి, వివరముగా పై ప్రయోగమును గురించి తెలుసుకొనబడినాను మరియు నేను ప్రశ్నలు అడుగుటకు అవకాశమును కల్పించారు. ☐
2. నా బిడ్డ ఈ ప్రయోగములో పాలుపంచుకొనుట మరియు విరమించుట నా ఇష్టము అని గ్రహించాను. నా బిడ్డకు న్యాయబద్ధంగా కలిగే చికిత్సావిధానములో ఎటువంటి మార్పు ఉండదని తెలుసుకున్నాను. ☐
3. నా బిడ్డకు సంబంధించిన మెడికల్ రికార్డును, ఈ ప్రయోగానికి సంబంధించిన వారు ఎవరైనా చూచుటకు సమ్మతిని తెలియపరుస్తున్నాను. ☐
4. నా బిడ్డ ఈ ప్రయోగములో పాలు పంచుకొనుటకు నా సమ్మతిని తెలియపరుస్తున్నాను. ☐

తల్లి/తండ్రి పేరు/ సంరక్షకుడు	సంతకము	తేది
సాక్షి సంతకము	సంతకము	తేది
ప్రయోగం చేయువారి పేరు	సంతకము	తేది