Effects of 3 to 6 months of systemic glucocorticoids on bone mineral density in children

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Abstract

Introduction: Studies on the effects of systemic steroids on bone mineral density (BMD) in children have shown conflicting results.

Objectives: To measure the effect of 3-6 months of systemic glucocorticoids on BMD in children.

Method: Thirty cases (20 nephrotic syndrome, 7 systemic lupus erythematosus and 3 juvenile dermatomyositis) and 30 age and sex matched controls were recruited. Dual energy x-ray absorptiometry of whole body (WB), lumbar spine (LS) and non-dominant distal radius (DR) were done at baseline and at the end of steroid therapy for cases and controls. Total body less head (TBLH) values were derived from WB values. For analysis, age and sex adjusted values of bone densitometric parameters were used. Student t-test or Mann-Whitney U-test was used to compare baseline data and paired t-test or Wilcoxon signed-rank test to compare patient data. Correlations were determined by Pearson and Spearman correlation coefficients. $p < 0.05$ was taken as significant.

Results: Mean cumulative dose and duration of steroids were 217.99mg/kg and 124.23 days respectively. After steroid therapy, bone mineral content (BMC) of WB, TBLH, LS and DR decreased by 8.9%, 6.3%, 6% and 8.4% respectively whereas BMD decreased by 18%, 9.8%, 12% and 3.3% respectively. The decrease was statistically significant for BMD WB ($p=0.005$), DR ($p=0.004$) and LS ($p=0.001$) as well as Z scores WB ($p=0.008$) and LS ($p=0.014$). Negative correlation of Z score LS with duration of treatment and BMD WB, DR, Z score LS and BMC TBLH with cumulative dose of steroids were seen.

***Conclusions*:** The present study revealed that 3-6 months of steroid use adversely affects both the cortical and trabecular bone.

(Key words: Bone mineral density, Dual energy x-ray absorptiometry, Glucocorticoids)

Introduction

Corticosteroid use is associated with decreased bone formation and increased bone resorption which together with muscle mechanics affect bone mineral density (BMD)[1-3]. Dual Energy X-ray Absorptiometry (DEXA) is currently the preferred modality for determining BMD in children[4,5]. A few studies in children have reported on the effect of systemic steroids on BMD, some reporting decreased BMD[6-18], some no effect[17] and occasionally mixed effects[18,19]. A few studies have reported association of cumulative dose of steroids with BMD[6-10] and some revealed no association[16-17]. Few longitudinal studies have assessed the effect of steroids on bone health and most of these have been done on patients receiving steroids for three months or less[20-23] or more than 6 months[19,24-27]. No study has been reported in the literature assessing the effect of steroids of 3 to 6 months duration on BMD.

Objectives

To measure the effect of 3-6 months of systemic glucocorticoids on BMD in children

Method

A longitudinal study was carried out at the Departments of Paediatrics and Radio-diagnosis in a tertiary care hospital at New Delhi, India.

Sample size was calculated taking the study by Trapani S, *et al*[24] as reference. They evaluated BMD at lumbar spine of twenty children with systemic lupus erythematosus (SLE) at baseline and after steroid therapy. They reported a mean BMD of 0.978 ± 0.165 g/sq. cm at baseline and 0.947 ± 0.184 g/sq. cm a year later. The difference

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in mean BMD at two point intervals was 0.031. The mean difference of standard deviation (SD) between the two values was not provided. Hence to detect a mean difference of 0.031 with an assumed mean difference of SD of 0.05 for the paired data, with an alpha error of 0.05, beta error of 2, a sample size of 21 patients was calculated.

Inclusion criteria: Thirty patients in the paediatric age group who were to receive systemic glucocorticoids for 3-6 months or more were included in the study. Thirty age and sex matched healthy children of hospital staff were enrolled as controls.

***Exclusion criteria*:** Children with malnutrition, rickets, chronic kidney disease, chronic liver disease, endocrine disorder and chronic malabsorption were excluded from the study. Patients receiving drugs like cyclophosphamide, anti-epileptics, long term furosemide or who received vitamin D or calcium supplementation in the last 6 months, or who were receiving glucocorticoids as replacement therapy were also excluded.

Data collection: Following data were obtained from all patients and controls at enrollment: name, age, sex, weight, height, body mass index (BMI) and sexual maturity rating (SMR). Daily calcium and vitamin D intake, frequency of weight bearing physical activity (WBPA) per week and daily sunlight exposure prior to illness were calculated for cases and controls as per previously described method[6]. In addition, diagnosis, date of starting steroids, dose of steroids, date of stoppage of steroids, total duration of steroids and cumulative dose of steroids were obtained from patients. For patients receiving methylprednisolone, equivalent dose of prednisolone was calculated. Weight was measured on a clinical balance to nearest 0.1kg and height was measured using a stadiometer to nearest 0.1cm. BMI was calculated in kg/m^2 from height and weight values. SMR was determined by physical examination using Tanner criteria. Fully ambulatory patients were advised sunlight exposure and WBPA as far as possible. Adequacy of sunlight exposure and frequency of WBPA per week were assessed every two weeks by direct questioning of caregiver. All patients were supplemented with oral calcium (800-1000mg/day) and vitamin D (600 IU/day). Cases and controls with deficient serum vitamin D levels were additionally given 600,000 IU of vitamin D2 once intramuscularly.

Serum calcium, phosphorus, alkaline phosphatase, vitamin D and parathormone levels were done at baseline and at the end of steroid therapy for both cases and controls. Serum calcium, phosphorus and alkaline phosphatase were estimated by an automated analyser - Vitros Chemistry 350. Serum 25(OH) vitamin D and parathormone level were measured by an automated machine (Evolis Twin Plus) by ELISA chemiluminescence technique. A Hologic (Discovery QDR series S/N 84571, Hologic, USA) bone densitometer was used to do DEXA scan on patients and controls and APEX System Software Version 3.1 was used for data acquisition and derivation of areal BMD (aBMD). DEXA scans were performed at three sites on all patients and controls: whole body (WB), lumbar spine (LS) and non-dominant distal radius (DR). Densitometric measurement of total body less head (TBLH) was also derived as per International Society of Clinical Densitometric Official Position statement[4]. Subject positioning was carried out according to manufacturer guidelines. Bone Mineral Content (BMC) and aBMD values were obtained as a machine generated printed report for each skeletal site. Unit for expressing BMC was g and for aBMD was g/cm^2.

Z score of BMD value at each site was calculated for patients and controls using the formula:
Z score of BMD (at specific skeletal site) = (Measured BMD – mean BMD of control population)/SD of BMD of control population.
In patients, DEXA scans were performed twice – at start of study (base line) and at end of steroid therapy.

Ethical issues: Study was approved by the Institutional Ethics Committee of Atal Bihari Vajpayee Institute of Medical Sciences, Dr. Ram Manohar Lohia Hospital, New Delhi, India (No. RMLH/ 7808/16 dated 05th October 2016). Written informed consent was given by parents/ caretaker/guardian of patients and controls and assent was taken wherever necessary.

Statistical analysis: Mean ± SD was used for continuous data and frequency with percentages for categorical data. Normality of continuous variables was tested by Kolmogorov-Smirnov and Shapiro-Wilk test. Student t-test or Mann-Whitney U-test was used for continuous variables between cases and controls. Within group comparison was done using paired t-test for normal data and Wilcoxon signed-rank test for non-normal data. Since different physiological factors are related to bone densitometric measurements, a multiple linear regression analysis using multivariate analysis of covariants (ANCOVA) was done at baseline for assessing the effect of age, sex, weight, height and BMI on BMD and thereafter adjusted values were derived and used for further analysis and comparison of laboratory and BMD parameters between cases and controls at baseline and in cases between baseline and end of steroid therapy. Pearson and Spearman correlation coefficients

were applied to correlate between bone densitometric data and cumulative dose and duration of steroid. $p<0.05$ was considered significant. Statistical software IBM PASW (version 22.0) was used for entire analysis.

Results

Thirty cases and 30 age and sex matched controls were enrolled. Among cases and controls 73.3% and 66.7% were males respectively. Table 1 compares anthropometric profile, dietary calcium, vitamin D intake, sunlight exposure, physical activity and biochemical parameters among cases and controls at baseline. Ages and sex were comparable. Mean height and weight of cases were significantly lower than that of controls. However, BMI of cases and controls were comparable. Average daily dietary intake of calcium and vitamin D, sunlight exposure and WBPA were also comparable. Serum phosphorus and vitamin D levels were comparable. Vitamin D levels were in deficient range (<20 IU/ml) in 16 (53%) cases and 9 (30%) controls. Serum calcium level was significantly lower in cases than controls and serum alkaline phosphatase level was significantly higher in cases. Even though serum calcium levels were lower in cases, they were in the normal range. After end of therapy, Vitamin D levels among cases were within normal range.

Table 1: ***Comparison of anthropometric profile, dietary calcium, vitamin D intake, sunlight exposure, physical activity and biochemical parameters among cases and controls at baseline (n=60)***

Characteristics and biochemical parameters	Cases (n=30)	Controls (n=30)	p-value
	Mean ± SD	Mean ± SD	
Age (years)	7.37± 3.43	8.80± 3.25	0.102
Weight (kg)	22.53± 9.06	28.97± 9.93	0.011
Height (cm)	113.00± 21.28	130.20± 17.83	0.001
Body mass index (kg/m^2)	17.25± 2.96	16.70± 3.05	0.481
Calcium intake (mg/day)	857.67± 194.84	773.33± 274.09	0.175
Vitamin D intake (IU/day)	377.07± 75.25	354.87± 80.48	0.274
Sunlight exposure (mins x m^2/day)	51.00± 17.77	60.03± 19.52	0.066
Frequency of physical activity (times per week)	5.37± 0.62	5.33± 0.76	0.852
Serum calcium (mg/dl)	9.09± 0.47	9.557± 0.49	<0.001
Serum phosphorus (mg/dl)	5.417± 0.38	5.22± 0.41	0.060
Serum alkaline phosphatase (U/L)	358.33± 106.77	285.3± 113.29	0.013
Serum vitamin D3 (nmol/l)	22.38± 2.35	25.48± 2.18	0.381

Among cases 70%, 23.3% and 3.7% belonged to Tanner stages I, II and IV respectively, whereas 63.3%, 20%, 13.3% and 3.4% of controls belonged to stages I, II, III, and IV respectively. Of the 30 patients 20 were nephrotic syndrome (NS), 7 were SLE and 3 were juvenile dermatomyositis (JDM). NS patients were first episode patients who defaulted after taking 4-6 weeks of steroids and were restarted on steroids shortly thereafter or first episode relapsers who relapsed within 2-3 weeks of stopping steroid on follow up and were again put on steroids. These patients were treated as per standard protocol[28]. In all enrolled patients total duration of steroid and cumulative dose were calculated from the time when steroid was first started.

Table 2 shows the baseline comparison of bone densitometry measurements between cases and controls. It was found that the bone mineral content (BMC) of DR ($p<0.001$), LS ($p=0.003$), TBLH ($p=0.002$), WB ($p=0.043$) were significantly lower in cases than the controls at the baseline. (Table 2)

Table 2: ***Baseline comparison of bone densitometry measurements between cases and controls***

Site	Bone densitometry value	Cases Mean ± SD	Controls Mean ± SD	p value
Whole body (WB)	Bone mineral content (g)	694.35 ± 269.62	830.72 ± 240.69	0.043
	Bone mineral density (g/sq.cm)	0.67 ± 0.11	0.68 ± 0.09	0.522
	Z score (BMD)	-0.23 ± 1.19	-0.02 ± 0.75	0.424
Total body less the head (TBLH)	Bone mineral content (g)	419.71 ± 197.25	580.87 ± 195.21	0.002
	Bone mineral density (g/sq.cm)	0.53 ± 0.24	0.57 ± 0.1	0.482
	Z score (BMD)	-0.35 ± 2.52	-0.07 ± 0.85	0.566
Lumbar spine (LS)	Bone mineral content (g)	13.58 ± 6.64	18.9 ± 6.79	0.003
	Bone mineral density (g/sq.cm)	0.45 ± 0.09	0.52 ± 0.11	0.007
	Z score (BMD)	-0.63 ± 0.84	0.04 ± 0.9	0.004
Non-dominant distal radius (DR)	Bone mineral content (g)	1.31 ± 2.9	3.95 ± 1.8	<0.001
	Bone mineral density (g/sq.cm)	0.35 ± 0.15	0.32 ± 0.05	0.333
	Z score (BMD)	0.59 ± 3.06	-0.03 ± 0.85	0.291

SD: standard deviation, BMD: bone mineral density

Changes after glucocorticoid exposure

The mean cumulative dose of steroid received was 217.99mg/kg (range 162-264mg/kg) and mean duration of steroid therapy was 124.23 days (range 99-168 days). The cases were followed up till the end of steroid therapy. Mean weight, height, BMI after glucocorticoid exposure were 23.9kg, 113cm and 18.48kg/m^2 which were not significantly altered compared to baseline. At the end of steroid therapy serum calcium, phosphorus and vitamin D level were normal. At end of steroid therapy, a statistically significant decrease was observed in BMD WB (p=0.005), DR (0.004) and LS (p<0.001) as well as Z score WB (p=0.008) and Z score LS (p=0.014). BMD was below -2SD in WB in 8/30 (26.7%) cases whereas in LS and TBLH 4/30 (13.3%) cases each at the end of steroid therapy. No value of BMD was below -2SD in DR. At end of therapy BMC also had significantly decreased at TBLH, WB and LS (Table 3).

Table 3: ***Comparison of BMD parameters within cases at baseline and at follow up***

Site	Bone densitometry value	Cases at baseline Adjusted mean (SD)	Cases after end of therapy Adjusted mean (SD)	Percentage change between baseline and follow up	p value
Whole body	BMC (g)	694.35 (269.62)	632.06 (240.86)	-8.88	0.003
	BMD (g/sq.cm)	0.67 (0.11)	0.54 (0.23)	-17.98	0.005
	Z score (BMD)	-0.23 (1.19)	-1.51 (2.60)		0.008
Total body less the head	BMC (g)	419.71 (197.25)	388.22 (169.61)	-6.43	<0.001
	BMD (g/sq.cm)	0.53 (0.24)	0.47 (0.21)	-9.78	0.169
	Z score (BMD)	-0.35 (2.52)	-0.92 (2.36)		0.156
Lumbar spine	BMC (g)	13.59 (6.64)	12.60 (5.97)	-6.0	<0.001
	BMD (g/sq.cm)	0.45 (0.09)	0.40 (0.10)	-11.9	<0.001
	Z score (BMD)	-0.63 (0.84)	-1.15 (0.93)		0.014
Distal radius (DR)	BMC (g)	1.31 (2.90)	0.79 (0.82)	-8.35	0.291
	BMD (g/sq.cm)	0.35 (0.15)	0.33 (0.15)	-3.34	0.004
	Z score (BMD)	0.59 (3.06)	0.05 (0.50)		0.491

*SD: standard deviation**;** BMC: Bone mineral content; BMD: Bone mineral density; WB: Whole body; TBLH: Total body less the head; LS: Lumbar Spine; DR: Distal radius*

It was also found that Z score LS (p=0.018) was negatively associated with duration of treatment (Table 4) whereas BMD WB (0.017), BMD DR (p=0.09), Z score LS (p=0) and BMC TBLH (p=0.008) were negatively associated with the cumulative dose (Table 5).

Table 4: ***Multiple regression analysis to determine correlation between bone densitometric parameters and duration of steroids***

Parameters	Beta coefficient	Standard error	t value	p value
BMC LS	5.188	2.727	1.902	0.072
Z score LS	-12.482	4.84	-2.579	0.018

BMC: Bone mineral content; BMD: Bone mineral density; LS: Lumbar Spine

Table 5: ***Multiple regression analysis to determine correlation between bone densitometric parameters and cumulative dose of steroids***

Parameters	Beta coefficient	Standard error	t value	p value
BMC WB	0.01	0	4.19	0.001
BMD WB	-427.55	155.25	-2.75	0.017
Z score WB	39.33	13.65	2.88	0.014
BMD DR	-270.89	151.33	-1.79	0.099
BMC LS	22.8	6.22	3.67	0.003
Z score LS	-57.09	11.97	-4.77	0.000
BMC TBLH	-0.39	0.12	-3.19	0.008

BMC: Bone mineral content; BMD: Bone mineral density; WB: Whole body; TBLH: Total body less the head; LS: Lumbar Spine; DR: Distal radius

The NS patients were albumin free after steroid use. Patients with SLE and JDM also improved clinically and exhibited decrease in erythrocyte sedimentation rate and C-reactive protein levels.

Discussion

Foundation for skeletal health is established early in life, so determination and identification of risk factors of low BMD in children is important for skeletal wellbeing in adulthood[2-4]. Long term use of glucocorticoids are associated with several risks, most important being the glucocorticoid induced osteoporosis[5,6]. Glucocorticoids adversely affect bone mass accrual by decreased osteoblast differentiation, increased osteocyte apoptosis, osteoclastogenesis induced bone resorption and

altered muscle mechanics[7-9]. Ours was a longitudinal observational study on 30 children who received steroids for 3-6 months showing the effect on BMD at four different sites representing both cortical and trabecular bones and correlation with duration and cumulative dose of steroids.

At time of enrolment it was found that BMC of all 4 sites and BMD of LS were significantly lower in cases than controls after adjustment for fixed characteristics. This could be due to effect of disease itself, significantly lower weight and height of cases, lower vitamin D levels in cases and more number of vitamin D deficient cases[7,10,11,14]. After steroid therapy for 3-6 months, BMC and BMD were reduced at all four sites .BMC of WB, TBLH, LS and DR decreased by 8.88%, 6.33%, 6% and 8.35% respectively whereas BMD decreased by 17.98%, 9.78%, 11.95% and 3.34% respectively. Decrease was statistically significant in BMD of WB, LS and DR and Z score WB and LS.

Absence of studies in the English literature on effect of 3-6 months of steroid use on BMD precluded any comparison of present study. However a few longitudinal studies of steroid use have reported similar or different results. Two months[20], three months[21-23] and one year[24] of steroid therapy has been shown to negatively affect BMD LS. In contrast BMC and BMD were increased after one year[19,21] or two years[27] of steroid use. The increase was attributed to increase in weight or greater muscle mass area or suppression of cortical bone modelling by glucocorticoids[10,21,27].

Cortical bone constitutes 80% and trabecular bone 20% of the skeletal mass. LS is mainly trabecular and DR is more cortical[1,29,30]. In adults, trabecular bone is more susceptible than cortical bone to effects of glucocorticoids[29,30]. In present study BMC and BMD were decreased at all four sites i.e. WB, TBLH, DR and LS, suggesting that both trabecular and cortical bones were affected adversely in children after 3-6 months of steroid use. Since we used adjusted values for comparison, neutralising effect of age, sex, weight, height, BMI, puberty staging, supplemented calcium and Vitamin D, decrease in BMC and BMD was probably due to steroid use. The effect of disease could be minimal since disease process improved after steroid use. In present study the cumulative steroid dose was negatively associated with BMD WB, BMD DR, Z score LS and BMC TBLH. This was similar to some previous studies[21,24] and dissimilar to others[19,27]. Duration of steroid treatment was also negatively associated with Z score LS.

There are certain strengths and limitations of study. This was the first study where four sites namely WB, DR, LS and TBLH were evaluated for BMC and BMD in patients on steroids for three to six months. We have tried to neutralize the effect of various confounding factors (sex, weight, height, BMI, sun exposure, SMR, calcium intake, vitamin D intake and exercise). Negative correlation was found between bone densitometric parameters and both dose and duration of steroid. Hence the findings of our study are truly reflective of the effects of 3-6 months of steroids on BMC and BMD. However, we did not study muscle mechanics which have a significant effect on bone mass accrual. More studies with larger sample size of each disease are needed with longer follow up to elucidate for how long the negative effect of longer duration of steroid use on bone densitometric parameters persists at each of the four sites. It would be advisable to monitor BMD of patients on steroids and take necessary action to prevent or treat decrease in BMC and BMD.

Conclusions

The present study revealed that 3-6 months of steroid use adversely affects both cortical and trabecular bone.

References

1. Canalis E, Mazziotti G, Giustina A, Bilezikian JP. Glucocorticoid-induced osteoporosis: Pathophysiology and therapy. *Osteoporosis International* 2007; **18**:1319-28. https://doi.org/10.1007/s00198-007-0394-0 PMid: 17566815

2. Gupta P, Bhatia B. Corticosteroid physiology and principles of therapy. *Indian Journal of Pediatrics* 2008; **75**(10): 1039-44. https://doi.org/10.1007/s12098-008-0208-1 PMid: 19023528

3. Cimaz R, Falcini F. Skeletal maturation and bone mineralisation. In: Cassidy JT, Petty RE, Laxer RM, Lindsley CB, editors. Textbook of Paediatric Rheumatology. 6th ed. Philadelphia: Elsevier Saunders; 2011.p.730-41. https://doi.org/10.1016/B978-1-4160-6581-4.10049-4

4. Bain S, Leonard MB, Bianchi M, Hans DB, Kalkwarf HJ, Langman CB. Official positions of the International Society for Clinical Densitometry and executive

summary of the 2007 ISCD Pediatric Position Development Conference. *Journal of Clinical Densitometry* 2008; **11**:6-21.
https://doi.org/10.1016/j.jocd.2007.12.002
PMid: 18442749

5. Gordon CM, Bachrach LK, Carpenter TO, Crabtree N, El-Hajj Fuleihan G, Kutilek S, *et al.* Dual energy x-ray absorptiometry interpretation and reporting in children and adolescents: the 2007 ISCD Pediatric Official Positions. *Journal of Clinical Densitometry* 2008; **11**:43-58.
https://doi.org/10.1016/j.jocd.2007.12.005
PMid: 18442752

6. Dey S, Jahan A, Yadav TP, Sachdev N, Bhawani DK. Measurement of bone mineral density in patients of Juvenile Idiopathic Arthritis by Dual energy X-Ray absorptiometry. *Indian Journal of Pediatrics* 2014; **81**: 126-32.
https://doi.org/10.1007/s12098-013-1037-4
PMid: 23645223

7. Alsufyani KA, Ortiz-Alvarez O, Cabral DA, Tucker LB, Petty RE, Nadel H, *et al*. Bone mineral density in children and adolescents with systematic lupus erythematosus, juvenile dermatomyositis, and systemic vasculitis: relationship to disease duration, cumulative corticosteroid dose, calcium intake, and exercise. *Journal of Rheumatology* 2005; **32**(4): 729-33.

8. Tantawy AAG, El Bostany EA, Matter RM, El Ghoroury EA, Ragab S, ElSherif NHK. Bone mass and biochemical markers of bone turnover in children and adolescents with chronic immune thrombocytopenia: Relation to corticosteroid therapy and Vitamin D receptor gene polymorphisms. *Platelets* 2013; **24**: 282-7.
https://doi.org/10.3109/09537104.2012.690544
PMid: 22671537

9. Hamalainen H, Arkela-Kautiainen M, Kautiainen H, Haapasaari J, Leirisalo_RM. Bone mineral content in young adults with active or inactive juvenile idiopathic arthritis and in controls. *Scandinavian Journal of Rheumatology* 2010: **39**: 219-22.
https://doi.org/10.3109/03009740903337885
PMid: 20059447

10. Compeyrot-Lacassagne S, Tyrell PN, Atenafu E, Doria AS, Stephens D, Gilday D, *et al*. Prevalence and etiology of low bone mineral density in juvenile systemic lupus erythematosus. *Arthritis and Rheumatism* 2007; **56**(6):1966-73.
https://doi.org/10.1002/art.22691
PMid: 17530722

11. Nurmalia LD, Tambunan T, Amir I. Comparisons of bone mineral density in steroid dependent, frequent relapse, and infrequent relapse nephrotic syndrome children. *Paediatrica Indonesiana* 2010; **50**(4): 193-208.
https://doi.org/10.14238/pi50.4.2010.193-8

12. Okumus O, Erguven M, Deveci M, Yilmaz O, Okumus M. Growth and bone mineralisation in patients with juvenile idiopathic arthritis. *Indian Journal of Pediatrics* 2008; **75**(3): 239-43.
https://doi.org/10.1007/s12098-008-0052-3
PMid: 18376091

13. Pereira RMR, Corrente JE, Chahade WH, Yoshinari NH. Evaluation by dual x-ray absorptiometry of bone mineral density in children with juvenile chronic arthritis. *Clinical and Experimental Rheumatology* 1998; **16**: 495-501.

14. Kashef S, Saki F, Karamizadeh Z, Kashef MA. Bone mineral density in children with systemic lupus erythematosus and juvenile rheumatoid arthritis. *Annals of Saudi Medicine* 2007; **27**(6): 427-31.
https://doi.org/10.5144/02564947.2007.427
PMid: 18059123 PMCid: PMC6074168

15. Riberio D, Zawadynski S, Pillet LF, Chevalley T, Girardin E, Parvex P. Effect of glucocorticoids on growth and bone mineral density in children with nephrotic syndrome. *European Journal of Pediatrics* 2014; **27**:123-5.

16. Castro T, Terreri M, Szejnfeld V, Castro C, Fisberg M, Gabay M, *et al.* Bone mineral density in juvenile systemic lupus erythematosus. *Brazilian Journal of*

Medical and Biological Research 2002, **35**; 1159-63.
https://doi.org/10.1590/S0100879X2002001000008
PMid: 12424488

17. Mishra OP, Meena SK, Singh SK, Prasad R, Mishra RN. Bone mineral density in children with steroid sensitive nephrotic syndrome. *Indian Journal of Pediatrics* 2009; **76**(12): 1237-9.
https://doi.org/10.1007/s12098-009-0256-1
PMid: 19936659

18. Leonard MB, Feldman HI, Shults J, Zemel BS, Foster BJ, Stallings VA. Long-term, high-dose glucocorticoids and bone mineral content in childhood glucocorticoid-sensitive nephrotic syndrome. *New England Journal Medicine* 2004; **351**: 868-75.
https://doi.org/10.1007/s12098-009-0256-1
PMid: 19936659

19. Tsampalieros A, Gupta P, Denburg RM, Shults J, Zemel SB, Mostoufi-Moab S, *et al*. Glucocorticoid effects on changes in bone mineral density and cortical structure in childhood nephrotic syndrome. *Journal of Bone and Mineral Research* 2013; **28**(3); 480-8.
https://doi.org/10.1002/jbmr.1785
PMid: 23044926 PMCid: PMC3578070

20. Bak M, Serdaroglu E, Guclu R. Prophylactic calcium and vitamin D treatments in steroid-treated children with nephrotic syndrome. *Pediatric Nephrology* 2006; **21**(3):350-4.
https://doi.org/10.1007/s00467-005-2118-z
PMid: 16382319

21. Kosan C, Ayar G, Orbak Z. Effects of steroid treatment on bone mineral metabolism in children with glucocorticoid sensitive nephrotic syndrome. *West Indian Medical Journal* 2012; **61**:627-30.

22. Kim SD, Cho BS. Pamidronate therapy for preventing steroid-induced osteoporosis in children with nephropathy. *Nephron Clinical Practice* 2006; **102**(3-4): c81-c87.
https://doi.org/10.1159/000089664
PMid: 16282699

23. Yadav VK, Sharma S, Debata PK, Patel S, Kabi BC, Aggarwal KC. Change in bone mineral density and role of vitamin D and calcium supplementation during treatment of first episode of nephrotic syndrome. *Journal of Clinical and Diagnostic Research* 2017; **11**(9):SC18-SC21.
https://doi.org/10.7860/JCDR/2017/27030.10657
PMid: 29207799 PMCid: PMC5713821

24. Trapani S, Civinini R, Ermini M, Paci E, Falcini F. Osteoporosis in juvenile systemic lupus erythematosus: A longitudinal study on the effect of steroids on bone mineral density. *Rheumatology International* 1998; **18**: 45–9.
https://doi.org/10.1007/s002960050056
PMid: 9782532

25. Phan V, Blydt-Hansen T, Feber J, Alos N, Arora S, Atkinson S, *et al*. Skeletal findings in the first 12 months following initiation of glucocorticoid therapy for paediatric nephrotic syndrome. *Osteoporosis International* 2014; **25**(2): 627-37.
https://doi.org/10.1007/s00198-013-2466-7
PMid: 23948876 PMCid: PMC4100956

26. Rudge S, Hailwood S, Horne A, Lucas J, Wu F, Cundy T. Effects of once-weekly oral alendronate on bone in children on glucocorticoid treatment. *Rheumatology* 2005; **44**: 813-8.
https://doi.org/10.1093/rheumatology/keh538
PMid: 15695300

27. Lien G, Selvaag AM, Flato B, Haugen M, Vinje O, SorsKaar D, *et al*. A two year prospective controlled study of bone mass and bone turnover in children with early juvenile idiopathic arthritis. *Arthritis and Rheumatology* 2005; **52**(3): 833-40.
https://doi.org/10.1002/art.20963
PMid: 15751052

28. Indian Pediatric Nephrology Group, Indian Academy of Pediatrics. Management of steroid sensitive nephrotic syndrome: Revised guidelines. *Indian Pediatrics* 2008; **45**(3): 203-14.

29. Dalle Carbonare L, Arlot ME, Chavassieux PM, Roux JP, Portero NR, Meunier PJ. Comparison of trabecular bone microarchitecture and remodeling in glucocorticoid-induced and postmenopausal osteoporosis. *Journal of Bone and Mineral Research* 2001; **16**(1); 97-103.
https://doi.org/10.1359/jbmr.2001.16.1.97
PMid: 11149495

30. Gafni RI, Mccarthy EF, Hatcher T, Meyers JL, Inoue N, Reddy C, *et al*. Recovery from osteoporosis through skeletal growth: early bone mass acquisition has little effect on adult bone density. *FASEB Journal* 2002; **16**(7): 736-8.
https://doi.org/10.1096/fj.01-0640fje
PMid: 11923218