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Original Article

Paediatrics Section

Effect of 6-12 Weeks of Systemic Glucocorticoids on Bone Mineral Density in Children

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ABSTRACT

Introduction: Prolonged use of systemic steroids in children is associated with many side-effects including effect on Bone Mineral Density (BMD). Effect of more than three months of systemic steroids on BMD has been studied in children but not the effect of 6-12 weeks duration of steroid.

Aim: To evaluate the effect of 6-12 weeks of systemic glucocorticoids on BMD in children.

Materials and Methods: A longitudinal observational study was conducted at a Tertiary Care Hospital. Dual Energy X-ray Absorptiometry (DEXA) of Whole Body (WB), Lumbar Spine (LS) and Distal Radius (DR) were done at baseline, end of steroid therapy or third month whichever was earlier and end of six months, on 30 patients receiving systemic steroid (Nephrotic Syndrome (NS)-7, Systemic Onset Juvenile Idiopathic Arthritis (SOJIA)-12, Tubercular Meningitis-11). Age and sex adjusted values of Bone Mineral Content (BMC), BMD and Z scores were analysed. Bone densitometric parameters of Total Body Less the Head (TBLH) were derived from WB values. X-rays of whole spine (antero-posterior and lateral view) were done at baseline and follow-up. Equal number of age and sex matched healthy controls were subjected to biochemical and DEXA scans at baseline. Continuous and categorical variables were compared using Student's t-test and Fisher-exact test, respectively. Pairwise comparison over period of time was done using Bonferroni correction.

Results: Bone densitometric parameters of cases and controls were comparable at baseline. At follow-up statistically significant decrease in BMD was found at all three sites. A statistically significant negative correlation was found between cumulative dose of steroid and duration of steroid treatment with Z score of TBLH. No vertebral fractures were detected at baseline or follow-up.

Conclusion: Use of systemic glucocorticoids for 6-12 weeks negatively affects bone mineralisation, not only during therapy but even three months after stopping it.

Keywords: Bone health, Dual energy x-ray absorptiometry scan, Steroids

INTRODUCTION

Glucocorticoids, one of the most commonly used drugs for a variety of paediatric immune and non-immune disorders are associated with many side-effects, one of which is a decrease in BMD, leading to osteoporosis. It has been reported that the risk of steroid induced fractures in adults has been strongly related to the daily and cumulative steroid dose [1-3]. DEXA is currently the preferred method for measuring BMD in children, due to its speed, accuracy, safety and economy [4,5].

Though systemic steroids have been shown to cause osteoporosis in adults, only a few studies have been reported in children with varying results [6-23], some reporting negative effect of steroids on BMD [8-15,17-19,21,22] and few observing no effect [16,24]. Most of these studies have focused on the effect of cumulative dose of steroids and duration of more than 3-6 months on bone health [6,8-11,14,15,22], very few have reported the effect of steroids of three months duration on BMD [12,13,21], and none on effect of 6-12 weeks of steroids on BMD. Hence, this study was planned to evaluate the effect of 6-12 weeks of systemic steroids on BMD in children.

MATERIALS AND METHODS

This longitudinal observational study was conducted at the Departments of Paediatrics and Radiodiagnosis, at a Tertiary Care Hospital. The study was conducted for the period of 16 months (November 2013- March 2015). The study was approved by the Institutional Ethics Committee (IEC) (sanction No- 1-40/64/2013/IEC/Thesis/PGIMER.RMLH/10278, date Nov 16th 2013, Chairperson- Dr K Satyanarayana ICMR).

Sample size was calculated, taking the study by Trapani S et al., as reference, in which 20 patients of juvenile systemic lupus erythematosus receiving steroids, revealed a LS mean BMD of 0.978 gm/square cm±0.165 Standard Deviation (SD) at baseline and 0.947 gm/square cm±0.184 SD a year later [6]. The mean difference in BMD at two point interval was 0.031. However, the data on SD of the mean difference between the two values was not provided. Hence, to detect a mean difference of 0.031 with an assumed SD of the mean difference 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. Thirty patients in paediatric age group who were to receive systemic glucocorticoids for at least 6-12 weeks were enrolled for the study. Thirty age and sex matched healthy children of nurses and paramedic staff of the hospital were enrolled as controls.

Informed consent was obtained from parents or guardians or care giver of all children enrolled in study and assent was taken where ever necessary. Children with chronic malabsorption, malnutrition, rickets, chronic renal, liver and endocrinal disease or those who received vitamin D and/or calcium supplementation in last six months or receiving glucocorticoid as replacement were excluded from study.

The following data were recorded for each patient at the time of study: Age, sex, diagnosis, Body Mass Index (BMI), Sexual Maturity Rating (SMR) stage [25,26] date of start of steroid, dose of steroid, date of stoppage of steroid, total duration of steroid received, cumulative dose of steroid.

At baseline, for both cases and controls, daily calcium and vitamin D intake in diet, daily sunlight exposure and frequency of weight bearing physical activity per week, prior to illness were calculated as per the method described by Dey S et al., [7]. Thereafter, the patients were advised to take adequate calcium and Vitamin D in

diet or supplemented if deficient and also to have adequate sunlight exposure and do weight bearing physical activity of one hour per day at home as far as possible in fully ambulatory patients. Adequacy of intake of calcium (800-1000 mg/day) and vitamin D (600 IU/day), sunlight exposure and frequency of weight bearing exercise per week were assessed every week. Cases and controls, who had deficient serum vitamin D levels were given 6 lacs IU of vitamin D2 once by intramuscular route. NS patients received prednisolone as per the standard protocol [27]. In patients who received systemic steroids other than prednisolone, the prednisolone equivalent of those steroids was calculated for determining the cumulative dose.

Serum calcium, phosphorus and alkaline phosphatase were estimated by an automated analyser- Vitros Chemistry 350. Serum 25(OH) Vitamin D3 and parathyroid hormone levels were also measured by an automated machine by ELISA chemiluminescence. All the biochemical parameters were estimated at baseline, at the end of steroid therapy or three months (whichever was earlier) i.e., first follow-up and at the end of six months of study i.e., second follow-up. A HOLOGIC (Discovery QDR series S/N 84571, Hologic, USA) bone densitometer was used to perform the 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 following three sites on each of the patients and controls- WB, Postero-anterior LS, Non-dominant DR. The densitometric measurement of the TBLH was also derived as per International Society of Clinical Densitometric Official Position statement [4]. Subject positioning was done as per manufacturer guidelines.

BMC and aBMD values were obtained as a machine generated printed report for each of the above skeletal sites. The unit used for expressing BMC was gram (gm) and that for aBMD was gram/cm^2. Z-score of the BMD values at each of the above four sites, was calculated for patients as well as controls using the following formula [7,18].

Z score of BMD (at specific skeletal site)=(Measured BMD-Mean BMD of control population)/Standard Deviation (SD) of BMD of control population.

In patients, DEXA scans were performed thrice viz., start of study (baseline), first (third month) and second (end of sixth month) follow-up. In order to detect asymptomatic vertebral fractures, X-rays of whole spine of patients, antero-posterior and lateral views were taken along with DEXA scan. In controls clinical, laboratory assessment and DEXA scans were performed at baseline only.

STATISTICAL ANALYSIS

For continuous variables, mean with SD and for categorical variables, frequency with proportions were used. Scale variables between cases and controls were compared using Student's t-test. Chi-square/Fisher's-exact test was used for determining statistical significance between qualitative variables. Since, different physiological and pathological factors are known to have a relation with bone densitometric measurements, hence a multiple linear regression analysis was done at baseline for assessing the effect of age, sex, weight, height and BMI on BMD. Thereafter, mixed method repeated measures ANOVA was used to see the overall effect of predictor variables like age, sex and disease on different biochemical and bone densitometric parameters over time.

Within subject, pair-wise comparison over the follow-up period for different parameters was done using Bonferroni correction to avoid confounding of alpha error. The p-value <0.05 were considered as statistically significant. The statistical software IBM PASW (version 22.0) was used for entire analysis. The Pearson's and Spearman's correlation coefficient were applied to find correlation between bone densitometric data and cumulative dose and duration of steroid.

RESULTS

Of the 30 patients enrolled, seven were suffering from NS, 12 Systemic Onset Juvenile Idiopathic Arthritis (SOJIA) and 11 Tuberculous Meningitis (TBM). The mean age of the patients and controls was 9.20±3.90 years and 8.80±2.92 years, respectively (p-0.655). The cases and controls comprised of 17 and 19 males, respectively. The male to female ratio was 1.3:1 in cases and 1.7:1 in controls, difference not being significant (p-0.278). NS patients received prednisolone at the dose of 2 mg/kg/day for six weeks (maximum 60 mg/day) followed by same dose alternate day for next six weeks as per the standard protocol. SOJIA patients received prednisolone at the dose of 2 mg/kg/day for 2-3 weeks followed by a taper over next 2-4 weeks to a minimum dose of 2.5 mg alternate day. In these patients, the duration of prednisolone treatment was calculated from the start of prednisolone till the time patients started receiving prednisolone 2.5 mg alternate day (i.e., lower than the physiological dose) [2]. Patients having TBM received prednisolone at the dose of 2 mg/kg/day initially for 2-3 weeks followed by gradual tapering over next 3-4 weeks and stopped.

Cases and controls were comparable with respect to age, and BMI [Table/Fig-1]. Amongst cases 56.66%, 16.66%, 20%, and 6.6% belonged to Tanner pubertal stage I, II, III and IV respectively whereas 63.33%, 13.33%, 20% and 3.3% of controls were in stage I, II, III, IV, respectively. Serum calcium, alkaline phosphatase and PTH level were significantly reduced in cases [Table/Fig-1]. The daily dietary calcium and vitamin D intake and mean weekly frequency of weight bearing activity was significantly greater in controls as compared to cases [Table/Fig-2]. At baseline, seven cases and nine controls had deficient 25(OH) Vit D3 level (below 20 nmol/L). They were treated with Vitamin D3 to avoid any confounding influence. At each follow-up visit, mean serum level of all the biochemical parameters were within normal range.

On multiple regression analysis and mixed method repeated measures of ANOVA, it was observed that age and sex had an association with BMD parameters over time, hence subsequent analysis was done with age and sex adjusted values of bone densitometric measurements.

At baseline, no significant differences was found between the cases and controls in the age and sex adjusted values of BMC, BMD and Z scores at all the four skeletal sites i.e., WB, TBLH, LS, and DR.

Parameter	Cases		Controls		t-value	p-value
	Range	Mean (SD)	Range	Mean (SD)		
Age (years)	1-14	9.20 (3.90)	1-14	8.80 (2.92)	0.450	0.655
BMI (kg/m^2)	13.10-23.80	16.63 (2.46)	12.90-24.10	16.89 (2.61)	-0.400	0.693
Serum Calcium (mg/dL)	5.7-9.8	8.78 (0.90)	8.7-10.5	9.56 (0.47)	-4.200	<0.001
Serum Phosphorus (mg/dL)	3.2-6.8	4.98 (0.69)	4.1-6.1	5.22 (0.41)	-1.670	0.101
Serum ALP (U/L)	85-398	157.87 (76.42)	112-607	288.63 (114.13)	-4.500	<0.001
Serum 25(OH) Vitamin D3 (nmol/L)	5.40-53.60	29.61 (9.00)	11.4-63.4	26.95 (12.61)	1.040	0.303
Serum PTH (pg/ml)	7.60-70.20	25.72 (14.63)	16-92	52.73 (23.30)	3.130	0.003

[Table/Fig-1]: Anthropometric profile and baseline biochemical parameters of cases (N=30) and controls (N=30).
BMI: Body mass index; SD: Standard deviation; ALP: Alkaline phosphatase; PTH: Parathyroid hormone
p-value (student's t-test)

Characteristics	Cases		Controls		t-value	p-value
	Range	Mean (SD)	Range	Mean (SD)		
Calcium Intake (mg/day)	308-869	628.83 (159.83)	300-1000	773.33 (247.09)	-2.490	0.016
Vitamin D intake (IU/day)	213-387	306.97 (62.10)	211-562	358.87 (80.48)	-2.580	0.012
Sunlight exposure (min×m^2/day)	34-78	54.20 (10.48)	30-104	60.17 (19.37)	-1.480	0.145
Frequency of physical activity (no. of times/week)	1-7	3.77 (1.68)	4-6	5.37 (0.73)	-4.76	<0.001

[Table/Fig-2]: Comparison of dietary calcium and vitamin D intake, sunlight exposure and physical activity among cases (N-30) and controls (N-30) at baseline.
SD: Standard deviation, p<0.05 considered significant (Student t-test)

Site	Bone densitometry value	Cases Mean (SD)	Controls Mean (SD)	t-value	p-value
WB	BMC (g)	828.51 (318.14)	830.72 (240.69)	-0.03	0.976
	BMD (g/sq.cm)	0.71 (0.13)	0.68 (0.09)	0.92	0.363
	Z score (BMD)	0.20 (1.0)	-0.02 (0.99)	0.99	0.327
TBLH	BMC (g)	544.05 (247.20)	581.87 (197.76)	-0.65	0.51
	BMD (g/sq.cm)	0.56 (0.13)	0.57 (0.10)	-0.29	0.813
	Z score (BMD)	0.09 (0.75)	-0.07 (0.87)	0.77	0.445
LS	BMC (g)	18.28 (8.30)	18.90 (6.79)	-0.32	0.752
	BMD (g/sq.cm)	0.52 (0.14)	0.52 (0.11)	0.01	0.996
	Z score (BMD)	0 (1.0)	0.04 (0.9)	-0.16	-0.873
DR	BMC (g)	3.10 (2.11)	3.95 (1.80)	-1.69	0.096
	BMD (g/sq.cm)	0.327 (0.058)	0.317 (0.053)	0.75	0.459
	Z score (BMD)	0.33 (0.06)	0.32 (0.05)	0.86	0.392

[Table/Fig-3]: Baseline comparison of bone densitometry measurements between cases (N=30) and controls (N=30).
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, p<0.05 considered significant (Student t-test)

Moreover, the Z scores were within the normal range of greater than-1 SD [Table/Fig-3].

Mean cumulative dose and mean duration of treatment of systemic glucocorticoids received by cases were 3.95±1.7 gm (range 1.2-7.2 gm) and 2.7±0.5 months (range 1.5-3 months), respectively.

Though BMC and BMD declined progressively at each follow-up at all the four skeletal sites, a significant reduction of BMC values of LS and DR and of BMD values of WB, LS and DR were observed at the second follow-up as compared to baseline and first follow-up [Table/Fig-4a,b]. The mean BMD of WB, LS and DR at second follow-up decreased by 3.76%, 6.94% and 6.17%, respectively [Table/Fig-4a].

At the first follow-up a significant negative correlation was observed between duration of steroids with Z score of TBLH and LS and BMD LS and between cumulative dose of steroid with BMC DR and Z score TBLH. At the second follow-up, a significant negative correlation was observed between cumulative dose of steroid and Z score TBLH and between duration of treatment and Z score TBLH [Table/Fig-5a,b].

Analysis of the disease subgroups revealed similar decrease in bone densitometric parameters at all sites over time. In patients of NS after an initial increase in BMC and BMD at WB, TBLH and LS at first follow-up, there was a decline at second follow-up. At second follow-up, at DR, BMC and BMD were significantly decreased as compared to baseline in patients with NS and at DR and LS in patients of SOJIA and TBM [Table/Fig-6a-c].

X-rays of whole spine (antero-posterior and lateral views) done for all cases at baseline and follow-up, did not show any vertebral fractures.

DISCUSSION

The present longitudinal study was, designed to evaluate the effect of systemic steroids of 6-12 weeks duration on BMD at four sites viz., WB, TBLH, LS and DR, using adjusted values of BMC, BMD, Z score, after accounting for all the possible factors influencing bone mass accrual (age, sex, weight, height, BMI, sexual maturity, calcium and vitamin D intake, sunlight exposure, weight bearing physical activity and disease; which can be taken as strength of the study). The study revealed few significant findings: i) bone densitometric parameters showed a gradual decline at three and six months after start of steroid therapy at all the skeletal sites, though a significant decline was observed only in BMC of DR at three months and in BMD of WB, LS and DR at six months, meaning thereby that the decline in BMD continued even after stoppage of steroids; ii) at six months, though a negative correlation was observed between the bone densitometric parameters and duration of treatment and cumulative

	Bone densitometric values	Baseline Mean (SD)	First follow-up Mean (SD)	Second follow-up Mean (SD)	Percentage change between follow-up		
					First and baseline	Second and first	Second and baseline
WB	BMC (g)	828.51 (318.14)	820.89 (306.35)	804.10 (309.53)	0.92	-2.05	-2.95
	BMD (g/sq.cm)	0.71 (0.13)	0.71 (0.12)	0.68 (0.12)	0.00	-3.53	-3.76
TBLH	BMC (g)	544.05 (247.20)	538.79 (242.86)	530.85 (255.47)	-0.97	-1.47	-2.43
	BMD (g/sq.cm)	0.56 (0.13)	0.55 (0.13)	0.54 (0.14)	-1.00	-1.88	-2.87
LS	BMC (g)	18.28 (8.30)	17.75 (8.68)	17.06 (9.01)	-2.88	-3.91	-6.68
	BMD (g/sq.cm)	0.52 (0.14)	0.51 (0.13)	0.49 (0.14)	-2.17	-4.87	-6.94
DR	BMC (g)	3.10 (2.11)	2.62 (1.64)	2.47 (1.71)	-15.50	-5.71	-20.32
	BMD (g/sq.cm)	0.78 (1.0)	0.32 (0.06)	0.31 (0.06)	-0.89	-5.33	-6.17

[Table/Fig-4a]: Percentage change of bone densitometric measurements between baseline and different follow-up after receiving systemic glucocorticoid among cases (N=30).
BMC: Bone mineral content; BMD: Bone mineral density; WB: Whole body; TBLH: Total body less the head; LS: Lumbar spine; DR: Distal radius

Bone densitometric value		Observations over time (I)	(J)	Mean difference (I-J)	Standard error	p-value
WB	BMC (g)	1	2	5.703	16.039	1.000
		2	3	16.046	9.490	0.307
		1	3	21.749	21.948	0.992
	BMD (g/sq.cm)	1	2	1.975	0.008	1.000
		2	3	0.025	0.007	0.006
		1	3	0.025	0.011	0.074
	Z score (BMD)	1	2	-0.007	0.062	1.000
		2	3	0.205	0.06	0.006
		1	3	0.198	0.086	0.088
TBLH	BMC (g)	1	2	4.093	12.38	1.000
		2	3	8.478	7.784	0.857
		1	3	12.571	17.334	1.000
	BMD (g/sq.cm)	1	2	0.005	0.005	0.948
		2	3	0.010	0.008	0.568
		1	3	0.016	0.011	0.542
	Z score (BMD)	1	2	0.258	0.221	0.762
		2	3	0.062	0.053	0.765
		1	3	0.319	0.231	0.536
LS	BMC (g)	1	2	0.461	0.476	1.000
		2	3	0.730	0.241	0.016
		1	3	1.191	0.607	0.180
	BMD (g/sq.cm)	1	2	0.010	0.013	0.007
		2	3	0.026	0.008	0.007
		1	3	0.037	0.015	0.054
	Z score	1	2	0.081	0.098	1.000
		2	3	0.190	0.057	0.008
		1	3	0.271	0.108	0.055
DR	BMC (g)	1	2	0.429	0.149	0.023
		2	3	0.138	0.116	0.744
		1	3	0.566	0.201	0.027
	BMD (g/sq.cm)	1	2	0.002	0.006	1.000
		2	3	0.018	0.006	0.024
		1	3	0.019	0.008	0.079
	Z score (BMD)	1	2	0.033	0.095	1.000
		2	3	0.299	0.104	0.023
		1	3	0.333	0.142	0.079

[Table/Fig-4b]: Pair-wise comparison of bone densitometric measurements in different follow-up over time after receiving systemic glucocorticoid among cases using Bonferroni correction.
BMC: Bone mineral content; BMD: Bone mineral density LS: Lumbar spine; DR: Distal radius; 1=Baseline, 2=1st follow-up, 3=2nd follow-up. p-value <0.05 considered significant-Greenhouse-Geisser test

dose of steroids, the negative correlation reached a significant level between the Z score TBLH and the duration and cumulative doe of steroid; iii) no vertebral fractures were observed during the study period. No similar study was available for comparison.

Many cross-sectional and few longitudinal studies have reported negative effect of three months or longer duration of steroids on bone health [6-23], and most of these studied the effect on LS only [10-15,18,19,21-24]. Two studies have evaluated BMD of total body, LS and DR in children [8,9] who received steroids for more than six months; one revealing lower bone mass gains at WB and DR [8] and the other showing decreased bone mass accrual at LS [9]. A decline in BMD up to six months at all four sites was observed in the present study. In contrast Phan V et al., reported an initial decline of LS BMD at three months followed by an increase at six months [14].

Site	Bone densitometric value	Correlation coefficient at first follow-up	p-value at first follow-up	Correlation coefficient at second follow-up	p-value at second follow-up
WB	BMC (g)	0.045	0.815	-0.034	0.858
	BMD (g/sq.cm)	0.085	0.655	-0.124	0.514
	Z score (BMD)	-0.023	0.902	-0.037	0.847
TBLH	BMC (g)	0.011	0.952	0.132	0.486
	BMD (g/sq.cm)	0.135	0.478	0.025	0.895
	Z score (BMD)	-0.692	<0.001	-0.692	<0.001
LS	BMC (g)	-0.111	0.560	0.077	0.685
	BMD (g/sq.cm)	0.106	0.577	-0.073	0.702
	Z score (BMD)	0.048	0.803	-0.079	0.677
DR	BMC(g)	-0.408	0.025	-0.238	0.205
	BMD (g/sq.cm)	0.129	0.498	-0.238	0.206
	Z score (BMD)	0.168	0.376	-0.239	0.203

[Table/Fig-5a]: Correlation of cumulative dose of systemic glucocorticoids with bone densitometric measurements at first and second follow-up among cases.
BMC: Bone mineral content; BMD: Bone mineral density; WB: Whole body; TBLH: Total body less the head; LS: Lumbar spine; DR: Distal radius
p-value <0.05 considered significant-Pearson correlation

Site	Bone densitometric value	Correlation coefficient at first follow-up	p-value at first follow-up	Correlation coefficient at second follow-up	p-value at second follow-up
WB	BMC (g)	0.006	0.974	-0.015	0.936
	BMD (g/sq.cm)	-0.182	0.335	0.224	0.235
	Z score (BMD)	-0.101	0.595	0.164	0.388
TBLH	BMC (g)	0	0.999	0.067	0.726
	BMD (g/sq.cm)	-0.197	0.296	0.066	0.727
	Z score (BMD)	-0.367	0.046	-0.362	0.049
LS	BMC (g)	-0.233	0.216	-0.293	0.116
	BMD (g/sq.cm)	-0.413	0.023	0.316	0.089
	Z score (BMD)	-0.398	0.029	0.318	0.087
DR	BMC (g)	0.081	0.670	-0.065	0.731
	BMD (g/sq.cm)	-0.169	0.372	0.171	0.366
	Z score (BMD)	-0.182	0.335	0.172	0.364

[Table/Fig-5b]: Correlation of duration of treatment with systemic glucocorticoid with bone densitometric measurements at first and second follow-up among cases.
BMC: Bone mineral content; BMD: Bone mineral density; WB: Whole body; TBLH: Total body less the head; LS: Lumbar spine; DR: Distal radius, p-value <0.05 considered significant-Pearson correlation

On sub-group analysis, it was found that in cases of NS, BMC and BMD values of WB, TBLH and LS were increased initially at first follow-up and then declined at second follow-up, whereas BMD of DR showed a consistent decline and reached significant levels at the second follow-up as compared to baseline. A logical explanation of this discordance of gain of BMD at three sites and loss at one site initially and then decline later at all sites, could not be found. Tsampalieros A et al., in contrast reported that the glucocorticoid increased cortical BMD and decreased trabecular BMD and attributed it to greater muscle mass and suppressed cortical modeling [28]. A significant decrease in spine BMD in patients of NS on steroids in the present study was in concordance to other studies [10,12-14,20-22]. Studies with larger samples would be required to clarify this discordance.

Among the cases of SOJIA, though there was decline in BMC and BMD at all four sites over time but a statistically significant decline was seen in BMC and BMD of LS and DR. The results of the present study were similar to prior studies which showed decreased BMD LS in patients with SOJIA who received steroids [7,9,11,15,17,18].

In the absence of any published study, the results of decreased bone densitometric parameters in TBM patients in the present study could not be compared. A statistically significant negative correlation

	Bone densitometric values	Baseline mean (SD)	First follow-up mean (SD)	Second follow-up mean (SD)	Percentage change between follow-up (p-value)		
					First and baseline	Second and first	Second and baseline
WB	BMC (g)	476.66 (219.21)	492.82 (216.24)	484.93 (210.70)	3.39 (1.0)	-1.60 (0.15)	1.74 (1.0)
	BMD (g/sq.cm)	0.56 (0.10)	0.58 (0.11)	0.56 (0.09)	3.81 (0.76)	-3.61 (0.06)	0.05 (1.0)
TBLH	BMC (g)	300.64 (183.15)	304.05 (163.77)	296.24 (165.48)	1.14 (1.0)	-2.57 (1.0)	-1.46 (1.0)
	BMD (g/sq.cm)	0.43 (0.11)	0.43 (0.11)	0.42 (0.10)	-0.60 (1.0)	-1.50 (0.81)	-2.09 (1.0)
LS	BMC (g)	9.96 (4.91)	10.39 (5.31)	10.20 (5.02)	4.35 (0.42)	-1.88 (1.0)	2.38 (1.0)
	BMD (g/sq.cm)	0.40 (0.10)	0.43 (0.07)	0.41 (0.10)	6.59 (0.73)	-3.54 (1.0)	2.82 (1.0)
DR	BMC (g)	1.86 (2.11)	1.53 (0.38)	1.57 (0.83)	-17.84	-3.09 (1.0)	-15.30 (0.28)
	BMD (g/sq.cm)	1.53 (0.38)	0.28 (0.06)	0.24 (0.03)	-3.45 (0.03)	-0.39 (0.05)	-3.86 (0.03)

[Table/Fig-6a]: Percentage change of bone densitometric measurements between baseline and different follow-up after receiving systemic glucocorticoid among cases of Nephrotic syndrome (NS) (N=7).
BMC: Bone mineral content; BMD: Bone mineral density; WB: Whole body; TBLH: Total body less the head; LS: Lumbar spine; DR: Distal radius

	Bone densitometric values	Baseline mean (SD)	First follow-up mean (SD)	Second follow-up mean (SD)	Percentage change between follow-up (p-value)		
					First and baseline	Second and first	Second and baseline
WB	BMC (g)	914.39 (202.22)	896.18 (198.60)	873.24 (236.44)	-1.99 (1.0)	-2.56 (0.95)	-4.50 (1.0)
	BMD (g/sq.cm)	0.75 (0.08)	0.75 (0.07)	0.71 (0.09)	-0.56 (1.0)	-4.30 (0.06)	-4.84 (0.34)
TBLH	BMC (g)	592.61 (161.89)	577.61 (167.79)	570.94 (194.59)	-2.53 (1.0)	-1.15 (1.0)	-3.66 (1.0)
	BMD (g/sq.cm)	0.60 (0.11)	0.59 (0.11)	0.57 (0.12)	-1.40 (1.0)	-3.62 (0.55)	-4.97 (0.66)
LS	BMC (g)	19.65 (5.16)	18.70 (5.48)	17.63 (5.61)	-4.82 (0.98)	-5.75 (0.03)	-10.30 (0.01)
	BMD (g/sq.cm)	0.56 (0.11)	0.54 (0.09)	0.51 (0.11)	-2.27 (1.0)	-5.91 (0.05)	-8.05 (0.04)
DR	BMC (g)	3.40 (1.87)	2.80 (1.32)	2.33 (1.21)	-17.62 (0.27)	-16.75 (0.11)	-31.42 (0.05)
	BMD (g/sq.cm)	0.34 (1.87)	0.33 (0.04)	0.31 (0.05)	-3.61 (0.37)	-6.29 (0.05)	-9.68 (0.04)

[Table/Fig-6b]: Percentage change of bone densitometric measurements between baseline and different follow-up after receiving systemic glucocorticoid among cases of SOJIA (N=12).
BMC: Bone mineral content; BMD: Bone mineral density; WB: Whole body; TBLH: Total body less the head; LS: Lumbar spine; DR: Distal radius

	Bone densitometric values	Baseline mean (SD)	First follow-up mean (SD)	Second follow-up mean (SD)	Percentage change between follow-up (p-value)		
					First and baseline	Second and first	Second and baseline
WB	BMC (g)	958.74 (324.87)	947.54 (317.72)	931.77 (307.79)	-1.17 (0.94)	-1.66 (0.30)	-2.81 (0.43)
	BMD (g/sq.cm)	0.76 (0.12)	0.74 (0.13)	0.73 (0.13)	-1.79 (0.53)	-2.62 (0.65)	-4.37 (0.23)
TBLH	BMC (g)	645.98 (269.30)	645.81 (266.48)	636.41 (0.12)	-0.03 (1.0)	-1.46 (1.0)	-1.48 (1.0)
	BMD (g/sq.cm)	0.59 (0.13)	0.59 (0.13)	0.59 (0.15)	-0.74 (1.0)	-0.15 (1.0)	-0.89 (1.0)
LS	BMC (g)	22.08 (9.46)	21.40 (10.72)	20.81 (11.69)	-3.06 (1.0)	-2.79 (0.96)	-5.76 (0.05)
	BMD (g/sq.cm)	0.57 (0.14)	0.54 (0.17)	0.51 (0.17)	-5.95 (0.55)	-4.42 (0.62)	-10.11 (0.04)
DR	BMC (g)	3.56 (2.66)	3.11 (2.16)	3.19 (2.30)	-12.50 (0.35)	2.37 (1.0)	-10.43 (0.14)
	BMD (g/sq.cm)	0.35 (0.07)	0.35 (0.07)	0.32 (0.07)	-0.32 (0.13)	-6.91 (0.05)	-7.21 (0.04)

[Table/Fig-6c]: Percentage change of bone densitometric measurements between baseline and different follow-up after receiving systemic glucocorticoid among cases of TBM (N=11).
BMC: Bone mineral content; BMD: Bone mineral density; WB: Whole body; TBLH: Total body less the head; LS: Lumbar spine; DR: Distal radius; TBM: Tuberculous meningitis

was observed between cumulative dose and duration of systemic glucocorticoids and bone densitometric measurements in the present study. The negative correlation of cumulative dose of steroid and BMD was in accordance with many studies [6-8,15,17,19-21,23] but contrary to some [11,16,24]. No study could be found in literature which delineated any association of duration of steroid use and bone densitometric parameters.

Limitation(s)

Since muscle mass and muscle traction forces have also been reported to influence bone mass accrual [27], these could have been confounding variables. Authors could not completely negate these variables in statistical adjustments in the study. This could be considered as a limitation of this study.

CONCLUSION(S)

To conclude this study was the first one to show that steroids used for a period for 6-12 weeks adversely affect bone mass accrual in both cortical and trabecular bones as revealed by decreased BMD at WB, LS, DR and TBLH, effect being more pronounced three months after stopping steroids but not to the extent of causing vertebral fractures. A negative correlation was observed between cumulative dose and duration of treatment with Z score TBLH.

More follow-up studies would be required to determine the duration up to which negative effect of steroid on bone health persists or whether duration of less than six weeks of steroid use could adversely affect bone health.

REFERENCES

[1] Canalis E, Mazziotti G, Giustina A, Bilezikian JP. Glucocorticoid-induced osteoporosis: Pathophysiology and therapy. Osteoporos Int. 2007;18:1319-28.
[2] Gupta P, Bhatia B. Corticosteroid physiology and principles of therapy. Ind J Paed. 2008;75:1039-44.
[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;730-41.
[4] Bain S, Leonard MB, Bianchi M, Hans DB, Kalkwarf HJ, Langman CB. Official Position of the International Society for Clinical Densitometry and Executive Summary of the 2007 ISCD Paediatric Position Development Conference. J Clin Densitometry: Assessment of Skeletal Health. 2008;11:06-21.
[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 Paediatric Official Positions. J Clin Densitom. 2008;11:43-58.

[6] 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. Rheumatol Int. 1998;18:45-49.
[7] 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 absorptiometery. Ind J Ped. 2014;81:126-32.
[8] Lilleby V, Lien G, Frey Froslie K, Haugen M, Flato B, Forre O. Frequency of osteopenia in children and young adults with childhood- Onset systemic lupus erythematosus. Arth Rheum. 2005;52:2051-59.
[9] 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. Arth Rheum. 2005;52:833-40.
[10] Bak M, Serdaroglu E, Guclu R. Prophylactic calcium and vitamin D treatments in steroid-treated children with nephrotic syndrome. Paediatr Nephrol. 2006;21:350-54.
[11] Valta H, Lahdenne P, Jalanko H, Aalto K, Makitie O. Bone health and growth in glucocorticoid treated patients with juvenile idiopathic arthritis. J Rheumatol. 2007;34:831-36.
[12] Chaudhary S, Aggarwal I, Sheshadri MS. Calcium and vitamin D for osteoprotection in children with new onset nephrotic syndrome treated with steroids: A randomised controlled interventional study. Paediatric Nephrol. 2014;6:1025-32.
[13] 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. J Clin Diagnos Res. 2017,9:SC18-SC21.
[14] 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 glucocoticoid therapy for paediatric nephrotic syndrome. Osteoporosis Int. 2014;2:627-37.
[15] Stagi S, Cavalli L, Signorini C, Bertini F, Cerinic MM, Brandi ML, et al. Bone mass and quality in patients with juvenile idiopathic arthritis: Longitudinal evaluation of bone-mass determinants by using dual-energy X-ray absorptiometry, peripheral quantitative computed tomography and quantitative ultrasonography. Arthr Res & Therap. 2014;16:83-96.
[16] Abdwani R, Abdulla E, Yaroubi S, Berehi H, Al-Zakwani I. Bone mineral density in juvenile onset systemic lupus erythematosus. Ind Ped. 2015;52:38-40.
[17] Falcini F, Trapani S, Civinini R, Capone A, Ermini M, Bartolozzi G. The primary role of steroids on the osteoporosis in juvenile rheumatoid patients evaluated by dual energy X-ray absorptiometry. J Endocrinol Invest. 1996;19:165-69.
[18] Okumus O, Erguven M, Deveci M, Yilmaz O, Okumus M. Growth and bone mineralisation in patients with juvenile idiopathic arthritis. Ind J Paed. 2008;75:239-43.
[19] 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;24:282-87.
[20] Basiratnia M, Fallahzadeh MH, Derakhshan A, Hosseini-Al-Hashemi G. Bone mineral density in children with relapsing nephrotic syndrome. Iran J Med Sci. 2006;31:82-86.
[21] Kosan C, Ayar G, Orbak Z. Effects of steroid treatment on bone mineral metabolism in children with glucocorticoid sensitive nephrotic syndrome. West Indian Med J. 2012;61:627-30.
[22] Rodd C, Lang B, Ramsay T, Alos N, Huber AM, David A, et al. Incidental vertebral fractures among children with rheumatic disorders 12 months after glucocorticoid initiation: A national observational study. Arth Care & Research. 2012;64:122-23.
[23] 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. Eur J Pediiatr. 2014;27:123-25.
[24] Mishra OP, Meena SK, Singh SK, Prasad R, Mishra RN. Bone mineral density in children with steroid sensitive nephrotic syndrome. Ind J Ped. 2009;76:1237-39.
[25] Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child. 1970;45:13-23. doi:10.1136/adc.45.239.13. PMC 2020414. PMID 5440182.
[26] Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child. 1969;44:291-303. doi:10.1136/adc.44.235.291. PMC 2020314. PMID 5785179.
[27] Indian Paediatric Nephrology Group, Indian Academy of Paediatrics, Bagga A, Ali U, Banerjee S, Kanitkar M, et al. Management of steroid sensitive nephrotic syndrome: Revised guidelines. Indian Paediatr. 2008,45(3):203-14. PMID 18367765.
[28] Tsampalieros A, Gupta P, Denburg MR, Shults J, Zemel BS, Mostoufi-Moab S, et al. Glucocorticoid effects on changes in bone mineral density and cortical structure in childhood nephrotic syndrome. J Bone Min Res. 2013;28:480-88.

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