Renal Data from Asia–Africa

Bone Mineral Density in Children with Relapsing Nephrotic Syndrome: A Hospital-Based Study

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ABSTRACT. This cross-sectional analytical study was conducted from January 2012 to November 2014 in the Department of Pediatric Nephrology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, to evaluate the bone mineral density (BMD) values in children with relapsing nephrotic syndrome (NS). Thirty relapsing nephrotic patients were enrolled in this study. They were divided into two groups: Group I - Frequent Relapse (FR) with 21 patients and Group II - Infrequent Relapse (IFR) with nine patients. Children included were both males and females aged between four and 15 years with relapsing NS with normal renal function. Steroid-resistant NS or those with abnormal renal functions or who were on cyclosporine and calcium supplement with Vitamin D or children with secondary NS were excluded from the study. All the study population underwent dual-energy X-ray absorptiometry scan to see the BMD value. Mean age of the patients of Group I (8.43 ± 2.61 years) was lower than that of Group II (9.41 ± 2.94 years (P = 0.4043). Mean BMD Z-scores of Group I was significantly lower than that of Group II (−2.70 ± 1.28 vs. −1.30 ± 1.54, respectively; P = 0.0317). A significantly higher cumulative dose of prednisolone was administered to Group I compared with Group II (P = 0.00003). On multivariate analysis, the total dose of prednisolone (P = 0.03693), body mass index (BMI) (P = 0.00703), and age of onset of disease (P = 0.03465) had a linear relationship with dependent variable BMD Z-score. On univariate regression analysis, statistically significant inverse relationship was observed between cumulative dose of prednisolone (in grams) (P = 0.049) and BMI (P = 0.00) with BMD Z-score, but no relation was observed with duration of illness. Children with relapsing NS, especially those receiving higher doses of steroids, were at risk for low BMD.

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Introduction

Corticosteroid is the drug of choice for the initial treatment of nephrotic syndrome (NS). About 90% of children with NS require a high dose of oral prednisolone (60 mg/m²/day) for complete clinical and biochemical remission,
and thereby, they have an excellent long-term prognosis. Even in resistant cases, alternate-day steroids are advised along with steroid-sparing drugs.

The immediate consequence of corticosteroid is the loss of bone mineral density (BMD). Steroid-induced metabolic bone disease (MBD), i.e., osteopenia, osteoporosis, and osteonecrosis are major problems for nephrotic children. These children are at risk for MBD, not only because of disease state (biochemical derangements) but also because of repeated courses of steroid therapy. Corticosteroid particularly affects the trabecular bone (axial skeleton i.e., spine) more than the cortical bone (i.e., femur). The earliest signs of corticosteroid-induced osteoporosis are seen in the lumbar spine because of its high content of trabecular bone.

Corticosteroid-induced osteoporosis is the most common form of secondary osteoporosis. Doses and the duration of glucocorticoids (GC) use correlates with a decrease in bone mass and rapid increase in fracture risk. Five milligrams or more of prednisolone or its equivalent per day decreases BMD and rapidly increases the risk of fracture over three to seven months. The risk is mainly associated with recent and prolonged GC use, more than to remote or short courses. Gulati et al also showed that children with idiopathic NS may be at risk for low bone mass, especially who received higher doses of steroids. The correlation of low BMD score with steroid therapy also has been well documented in patients with asthma and rheumatoid arthritis.

A BMD test is the best way to determine the bone health. The most widely recognized BMD test is called dual-energy X-ray absorptiometry (DEXA) test. Due to its noninvasive nature, DEXA is a common methodology used to quantify BMD. This test can identify osteopenia and osteoporosis, determine the risk of fracture, assess growth retardation, and measures the response to treatment. Z-score is used to compare a child’s BMD with an age- and gender-matched norm, with appropriate adjustments for bone age or pubertal status often needed.

However, very few studies have been carried out to assess the BMD or show the correlation of steroid therapy with low BMD in such patients and even exact value of BMD (Z score) has not been studied among this group of patients.

This study was conducted with the objective of determining the BMD value in children with relapsing NS who had a normal renal function. This study also assessed the relationship of BMD with age of onset of illness, duration of diseases, and cumulative doses of steroid.

Methodology

This cross-sectional analytical study was done in the Department of Pediatric Nephrology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, from January 2012 to November 2014.

Study Population

Thirty children with steroid-sensitive relapsing NS (SSNS) attending in the pediatric nephrology department were enrolled in the study. Based on the response to steroid therapy, children were divided into two groups: Group I [frequent relapse (FR)] and Group II [infrequent relapse (IFR)]. Individuals enrolled in the study were aged four to 15 years with relapsing NS with normal renal function and were on alternate-day steroid therapy. Patients who were steroid resistant, had never experienced relapse or receiving any 2nd line drugs, prior calcium (Ca) and Vitamin D supplementation for the last three months, and those with underlying structural bone abnormalities (osteogenesis imperfecta and juvenile osteoporosis) were excluded from this study. Age group below four years was excluded from study as a measurement of BMD value was not possible with the existing BMD machine.

NS was defined by edema, massive proteiniuria (>40 mg/m²/h), hypoalbuminemia (<2.5 g/dL), and hyperlipidemia. FR was defined as ≥2 relapses within the first six months of presentation or ≥4 relapses within any 12-
month period. Steroid dependency was defined as two consecutive relapses at least 14 days after steroid withdrawal or when on alternate-day steroid therapy, while IFR was defined as <2 relapses within the first six months of presentation or <4 relapses within any 12 months period. A relapse was considered when bedside urine albumin was present for three consecutive days in patients who were on remission. Relapse was treated by daily dose of prednisolone 60 mg/m²/day up to protein free for three consecutive days. Then, 40 mg/m² every alternate day for four week for IFR, and gradually, the dose was tapered by 5 mg every two weeks and stopped within six months for FR and steroid-dependent patient.

Obesity was defined when body mass index (BMI)-for-age Z-score above +2.0 standard deviation (SD), according to the WHO growth reference 2007.

All patients were initially evaluated by detailed history taking and physical examination. Findings were collected and recorded in the preformed data collection sheet. An estimate of the cumulative steroid dose in each of the children was prepared. Then, all the cases were numbered chronologically.

Demographic data (age of onset of disease, duration of disease number of relapses, cumulative, or total doses of the prednisolone) and clinical characteristics [height (cm), weight (kg), and BMI] were recorded. The cumulative doses of prednisolone that each patient received during therapy were calculated from their medical records.

Before the commencement of this study, the protocol was approved by the Institutional Review Board of BSMMU, Dhaka. Informed written consent was taken from legal guardians of individual patients before enrolling their child in the study. Patient’s name and particulars were recorded in the case record file.

Bone mineral density test and its interpretation

BMD of the lumbar spine was measured with DEXA by thin mode scan (lunar GE Medical Systems) using pencil beam, and the patient’s data values were expressed as the Z-score (number of SDs from the mean values of healthy children matched for sex and chronological age). The result was reported as Z-scores and Z Score = (P-Mam)/SDam

Where P is patient’s bone density, Mam is bone density of age-matched controls, and SDam is SD age-matched controls. Here, Mam is based on manufacturer’s database.

Based on BMD value, osteoporosis is defined as a BMD z score of 2.5 SD less than the mean for age and sex, and osteopenia is defined as bone density value of the AP lumbar spine (L1 to L4) of 1 SD less than normal for age (z scores).

**Statistical Analysis**

Statistical analysis of results was performed using window-based software devised with IBM SPSS Statistics for Windows version 24.0 (IBM Corp., Armonk, NY, USA). For all statistical tests, *P* <0.05 was considered as statistically significant. Continuous variable was presented as Mean ± SD. Continuous variable was compared through Student’s *t*-test, and categorical variable by Chi-square test. Pearson’s correlation coefficient method was used to study the correlation of BMD Z-score with other parameters. Subsequently, multivariate analysis was performed to evaluate factors predictive of a low BMD Z-score. Variables with a significant correlation were entered into a stepwise linear regression model where greatest *R* value was finally considered.

**Results**

Thirty patients were enrolled who fulfilled the inclusion criteria and Group I [Frequently relapsing NS (FRNS), FR/steroid dependent] had 21 patients and Group II [Infrequently relapsing NS (IFRNS)] had nine patients. There were 22 (73%) boys and eight (17%) girls with mean age of patients as 8.73 ± 2.70. Gender, age, onset of illness, body weight, body height, and nutritional status based on BMI between two groups were comparable. Mean age of onset of Group I was significantly lower than that of Group I (*P* = 0.0201). Group I had significantly longer duration of illness,
more number of relapses, and greater cumulative steroid doses in comparison to Group II. Though males were predominant among both groups, the relationship was insignificant in two groups ($P=0.09$) (Table 1).

In the present study, a significant difference of BMD Z scores among the two groups was observed ($P = 0.0317$). BMD Z-score was observed below $-2.5$ SD for 16 patients. Children in Group I had lower Z-scores of BMD compared to Group II, but the difference was statistically significant (Table 2). However, none of them experienced fracture in two groups.

On univariate regression analysis, statistically significant inverse relationship was observed between cumulative dose of prednisolone (in grams) ($P =0.049$) and BMI ($P = 0.00$) with BMD Z score, but no relation was observed with duration of illness (Figures 1-3).

On multivariate analysis, the total dose of prednisolone, BMI, and age of onset of disease had a linear relationship with dependent variable BMD Z-score (Table 3).

### Discussion

Corticosteroid is the choice of treatment for children with INS; these children are prone to low BMD because of both biochemical derangements caused by the renal diseases and corticosteroid therapy. Low BMD has been described in many other pediatric disorders with the correlation of steroid therapy though underlying inflammatory diseases also play a major role. However, there is conflicting evidence on the risk of low bone mass regarding BMD in children with NS.\textsuperscript{16,17}

In the present study, enrolled patients were grouped into two groups. Group I (FRNS)

| Parameter (mean ±SD) | Group I FRNS and SDNS ($n = 21$) | Group II IFRNS ($n = 9$) | $P$  |
|----------------------|---------------------------------|--------------------------|------|
| Age (year)           | 8.43±2.61                       | 9.41±2.94                | 0.4043|
| Sex (M/F)            | 17/4                            | 5/4                      | 0.0900*|
| Age of onset (year)  | 4.16±1.89                       | 6.57±2.42                | 0.0201|
| Number of relapses   | 10.90±4.23                      | 4.33±1.50                | 0.0000|
| Duration of disease (year) | 4.27±2.24                      | 2.83±1.04                | 0.0234|
| Weight (kg)          | 29.43±9.21                      | 30.33±11.38              | 0.8364|
| Height (cm)          | 119.86±15.06                    | 131.89±16.68             | 0.0837|
| BMI Kg/m$^2$         | 21.00±4.80                      | 16.76±2.72               | 0.0052|
| GFR (mL/min/1.73 m$^2$) | 132.58±38.80                    | 136.35±56.33             | 0.8580|
| Serum albumin (g/L)  | 25.00±3.58                      | 26.58±4.14               | 0.3374|
| Serum creatinine (mg/dL) | 0.51±0.12                      | 0.52±0.11                | 0.7659|
| Cumulative dose of prednisolone (g) | 18.08±4.72                      | 8.69±2.87                | 0.00003|

Data presented as mean±SD. *Chi-square tests were used to analyze data, Student’s $t$-test was carried in other cases, $P \leq 0.05$ was considered as significant. SD: Standard deviation, BMI: Body mass index, GFR: Glomerular filtration rate, FRNS: Frequently relapsing nephrotic syndrome, IFRNS: Infrequently relapsing nephrotic syndrome.

### Table 1. Comparison of demographic, clinical, and biochemical parameter among Group I and II.

| Z Score | Group I FRNS/SDNS ($n=21$) | Group II IFRNS ($n=9$) | $P$  |
|----------|-----------------------------|------------------------|------|
| Mean BMD Z score* | $-2.70±1.28$                | 1.30±1.54               | 0.0317|
| Osteoporosis (Z score $<-2.5$) | 14 (46.67%)              | 2 (6.67%)               |      |
| Osteopenia (Z Score $<-1$ and $\geq -2.5$) | 4 (13.33%)              | 4 (13.33%)              | 0.0821*|
| Normal (Z Score $>-1$) | 3 (10%)                | 3 (10%)                 |

BMD: Bone mineral density, FRNS/SDNS: Frequently relapsing nephrotic syndrome/steroid-dependent nephrotic syndrome, IFRNS: Infrequently relapsing nephrotic syndrome.

*Chi-square test used to analyze data, $P \leq 0.05$ considered as statistically significant.
Univariate regression analysis was conducted between bone mineral density (Z-score) and cumulative dose of prednisolone (in grams) and a significant inverse relationship was observed ($P = 0.049$). Above figure shows the relationship.

Univariate regression analysis was conducted between bone mineral density (Z-score) and duration of disease, and an inverse relationship was observed although it was not significant ($P = 0.28$).

Univariate regression analysis was conducted between bone mineral density (Z-score) and body mass index and an inverse relationship was observed, which was statistically significant ($P = 0.00$).
Table 3. The correlations of bone mineral density with influencing parameters in study subjects (n=30).

| Independent variables of regression | Coefficients | P       | Lower 95.0% | Upper 95.0% |
|-------------------------------------|--------------|---------|-------------|-------------|
| Intercept                           | -2.48678     | 0.40665 | -8.58267    | 3.60910     |
| Age of onset of disease             | -0.22964     | 0.03465 | -0.44747    | -0.01183    |
| Total dose of prednisolone          | -0.02555     | 0.03693 | -0.06202    | 0.11312     |
| BMI                                 | -0.10536     | 0.00703 | -0.21454    | 0.00382     |
| Weight                              | 0.073893     | 0.417878| -0.1114     | 0.259191    |
| Height                              | -0.07547     | 0.182761| -0.18912    | 0.038178    |
| Dose/year                           | -0.00021     | 0.257605| -0.00059    | 0.000167    |

Dependent Variable Z score. Adjusted R² value for the model 0.53; F=5.75; P=0.0007 (analysis of variance). Multivariate analysis was performed to identify factors predictive of a low bone mineral density Z-score among relapsing nephrotic children. BMI: Body mass index.

consists of 21 patients (70%) and Group II (IFRNS) consists of nine patients (30%). The mean age of Group I (8.43 ± 2.61) was lower than that of Group II (9.41 ± 2.94), although the difference was insignificant (P = 0.4043). Nurmalia et al. also conducted a similar study with 44 patients (22 FRNS and 22 IFRNS) and found mean age of patients were 8.7 years in FRNS group and 6.6 years in IFRNS. In the present study, the majority of the children were males although P value was insignificant (P = 0.09). Mishra et al. were also observed male predominance in their studies.

Corticosteroid induced obesity was associated with low bone mass. It is supported by this present study where BMI had an inverse relationship with BMD value on multivariate analysis. A similar finding was also shown by Nina et al., where the prevalence of obesity was 29% and 14% in the SSNS and SRNS groups, respectively, and the overall prevalence of central obesity was 50%, with 54% and 46% in the SSNS and SRNS groups, respectively. However, this result was in contrasted to Mishra et al where they could not establish any relationship between bone density and BMI.

NS patients may not reach normal peak bone mass and may be at risk for low bone mass due to not only for disease state but also for the repeated course of steroid therapy. Patients receiving >7.5 mg of prednisolone per day for one to six months duration or cumulative steroid dose >500 mg or steroid exposure >12 months and ≥4 courses of high dose prednisone are at risk of significant loss of trabecular bone in axial skeletons such as spine, hips, and ribs. The early changes can be detected in the spine and femoral neck. In this study, cumulative dose of prednisolone was more (18.08 ± 4.72 g) in Group I in comparison to Group II (8.69 ± 2.87 g), and the difference was statistically significant (P = 0.0003). Nurmalia et al. had also observed statistically significant differences (P <0.001) in cumulative dose of steroid among both groups which were 13.47 ± 8.88 and 4.649 ± 4.142, respectively.

Regional bone mineral content and BMD of lumbar spine is more preferred than whole body measurement due to various confounding factors like skull size, total body fat, and height of patients. In the present study, BMD value in L₁-L₂ was observed as −2.70 ± 1.28 for Group I patients, while it was observed as −1.30 ± 1.54 for Group II patients and statistically significant relationships were observed (P = 0.0317) in two groups. Hence, it is likely that the difference of BMD value between two groups was caused by a greater cumulative dose of steroids although mean duration of disease was not same for the two groups. Several studies also reported the relationship between low BMD value and cumulative dose of steroids and found low bone density in children with steroid-dependent NS (SDNS) and FRNS patients. Although Nurmalia et al., observed that children in SDNS (Group I) had lower mean Z-scores of BMD L₁-L₄ compared to that of IFRNS (Group II), the difference was not statistically significant.

This study has reported the adverse effect of steroid therapy on BMD. Corticosteroid the-
Therapy was associated with decreased BMD Z-score and osteoporosis. Factors predictive of low bone mass were BMI ($P = 0.007$), a total dose of prednisolone ($P = 0.036$) and a linear correlation was observed in this study. The correlation of low BMD value with steroid therapy has been also well documented in patients with asthma and rheumatoid arthritis. Aceto et al showed corticosteroid reduced BMD Z-score in SSNS patients and BMD Z-score was significantly correlated with total dose of prednisolone. However, duration of disease was not significantly associated with low BMD scores. The similar outcome is also supported by Gulati et al, Naglax et al, Basiratnia et al and El-Mashad et al. However, older age of onset of NS was also predictive factor for low bone mass in study conducted by Gulati et al. Moreover, this finding was similar to the present study where we found low BMD values was related to older age of onset of disease. However, this finding was contradictory to the study conducted by Basiratnia et al.

Fracture is one of the important sequelae of steroid therapy. Among the nephrotic children, fracture risk is increased who require more than four courses of oral corticosteroid. El-Mashad et al had also observed risk of fracture among 44% patients. In the present study, our study population did not experience fracture though 53.33% patients had osteopenosis and 26.67% had osteopenia. Gulati et al also observed osteopenia in 61% patients and osteoporosis in 22% of their patients.

**Limitation**

The limitations of this study are the level of Vitamin D of the patient was not measured, and dietary Ca chart was not prepared which could act as confounding factors. A longitudinal study could yield more set of data and will be more helpful for such studies.

**Conclusion**

Low BMD assessed by DEXA was frequent in nephrotic children, especially those administered a higher dose of steroid. Older age at onset and higher number of relapses are more prone to low bone mass. Regular BMD evaluation and appropriate therapeutic approach with Ca and Vitamin D supplements are recommended for these children. A longitudinal study with a larger sample size along with longer follow-up is needed for getting a clearer picture of this problem in such patients.

**Conflict of interest:** None declared.

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