Bone mineral density among systemic lupus erythematosus patient age 5-18 years with glucocorticoid treatment in child and adolescent outpatient clinic, Cipto Mangunkusumo Hospital, Jakarta

N Indriyani, B Tridjaja, B E Medise and N Kurniati*
Department of Pediatric, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
*E-mail: nia.kurniati@ui.ac.id

Abstract. Systemic lupus erythematosus (SLE) is an autoimmune disease affecting children; its morbidity and mortality rates are significant. One risk factor for morbidity is chronic corticosteroid use. The aim of this study is to determine the occurrence rate of low bone mineral density; discuss the characteristics, including cumulative and daily doses of corticosteroid, body mass index, Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), calcium, and vitamin D intake; and assess bone metabolism laboratory parameters, including serum calcium, vitamin D, alkaline phosphatase (ALP), phosphorus, and cortisol among children with SLE receiving corticosteroids. This was a descriptive, cross-sectional study involving 16 children with SLE attending the child and adolescent outpatient clinic at Cipto Mangunkusumo Hospital in November–December 2016. Low bone mineral density occurred among 7/16 patients. The mean total bone mineral density was 0.885 ± 0.09 g/cm². Children with SLE receiving corticosteroid had low calcium (8.69 ± 0.50 mg/dl), vitamin D (19.3 ± 5.4 mg/dl), ALP (79.50 [43.00–164.00] U/l), and morning cortisol level (1.20 [0.0–10.21] ug/dl), as well as calcium (587.58 ± 213.29 mg/d) and vitamin D (2.9 [0–31.8] mcg/d) intake. The occurrence of low bone mineral density was observed among children with SLE receiving corticosteroid treatment. Low bone mineral density tends to occur among patients with higher cumulative doses and longer duration of corticosteroid treatments.

1. Introduction
Systemic lupus erythematosus (SLE) is an autoimmune disease that especially affects double-strand deoxyribonucleic acid (ds-DNA). In Indonesia, the incidence of SLE is about 20 cases/100,000 children [1]. SLE has higher prevalence in women at the age after puberty and before menopause. To diagnose this disease, at least 4 of 11 criteria established by the American College of Rheumatology (1982) must be met [2]. Quality of life and musculoskeletal (muscle and bone) issues are closely related, as most SLE cases are associated with musculoskeletal problems. SLE patients tend to lose their jobs or decide not to engage in the workforce due to their illness [3]. Children and adolescents with SLE in the population have a greater risk of musculoskeletal morbidity, especially osteoporosis. This occurs because in these patients, SLE appears before they have achieved optimum bone mass [4]. Reaching the optimum bone mineral density during the period of growth and development of the bones is important for bone health in adulthood. Normally, there is an increase in bone mineral density during puberty of 8% per year; however, children with SLE only show an increase of 3.4% per year.
As a result, these children are vulnerable to bone fracture, especially asymptomatic vertebral fracture, which occurs in 23% of pediatric and adolescent SLE patients [5]. In one study, it was found that pediatric SLE patients in the United States had lower bone mineral density than the healthy age-matched controls, even after vitamin D supplementation [6-8]. Moreover, a decreasing in bone mineral density of as much as 8.2% has been reported after the use of glucocorticoids for 20 weeks (5 months) [6].

Osteoporosis is defined as a systemic bone disease characterized by low bone mineral density and worsening of the bone tissue microarchitecture, resulting in increased vulnerability to fracture. Currently, bone mineral density examination using dual X-ray absorptiometry (DXA) is the gold standard for diagnosing osteoporosis. However, this examination is unable to illustrate all processes related to the turnover of bone tissue, such as the worsening of bone microarchitecture processes. Thus, the turnover of bone tissue can be examined based on a bone tissue examination of biochemical parameters in serum, including alkaline phosphatase (ALP) as a bone formation marker, vitamin D, phosphorus, calcium serum, and parathyroid hormone [9]. The levels of calcium and phosphorus in plasma are a reflection of the bone formation and resorption processes; homeostasis is illustrated from the level of bone metabolism regulation hormones, such as parathyroid hormone, calcitonin, and vitamin D [10].

Nutrition intake especially that of calcium and vitamin D, is especially important for children with chronic disease [11]. Sufficient vitamin D intake is considered extremely important, and this is illustrated by the level of vitamin D in blood. With sufficient vitamin D, the calcium level can also be maintained, as vitamin D plays a role in the absorption of calcium in intestines [12]. Other risk factors related to bone mineral density include age and low body mass index (BMI) [13]. Research that evaluates bone mineral density and the factors that affect it in pediatric SLE patients receiving corticosteroid treatment is ongoing. This is because different research conclusions are still being generated, and it is not clear whether there is a relationship between the use of corticosteroid and bone mineral density. Another hypothesis suggest that the use of corticosteroids does not cause low bone mineral density, but instead results in cumulative damage that can be assessed using the disease damage index (DDI) value [7,14,15]. Given this lack of clarity in the literature, the researchers wanted to investigate bone mineral density characteristics as bone health parameters in Indonesian pediatric and adolescent patients with SLE.

2. Materials and Methods

This is a preliminary descriptive study seeking to determine the density of bone mass in SLE pediatric patients receiving glucocorticoid treatment. It adopts a cross-sectional study design to assess SLE patients receiving treatment at the Child and Adolescent Outpatient Clinic of the Cipto Mangunkusumo Hospital (RSCM). The descriptive data used include laboratory parameters that describe bone metabolism, such as the level of calcium in blood, vitamin D, phosphorus, ALP, and morning cortisol. These data were considered in conjunction with the risk factors for low bone mineral density, such as the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score, BMI, and calcium and vitamin D intake.

The target population in this research was pediatric and adolescent SLE outpatients aged 5–18 years attending pediatric polyclinics at the RSCM. The inclusion criteria were pediatric and adolescent patients aged 5–18 years with SLE, as diagnosed based on the American College of Rheumatology (1982) criteria, who had been receiving glucocorticoid treatment for at least 5 months.

All data were numbered in research report forms, which were prepared and entered into the computer database using the SPSS program version 22 for Windows; this software was employed for data analysis. The statistical analyses involved the Shapiro-Wilk test, Z scores for different characteristics and laboratory parameters related to bone mineral density, and scatterplots of the bone mineral density Z scores according to the cumulative dose of corticosteroids. This study was approved by the Commission of Ethics Research, Medical Faculty Universitas Indonesia.
3. Results and Discussion

3.1 Results

Sixteen subjects were included in this research, 14 of whom were female. The average age of the subjects was 13.31 ± 3.02 years, and the patients had been receiving steroid treatment for an average of 28.0 ± 16.3 months. Nine subjects had SLEDAI scores in mild/moderate flare category. The characteristics of the research subject are listed in Table 1.

Table 1. Characteristics of the subjects

| Characteristic                        | Value          | Normal values | Unit   |
|---------------------------------------|----------------|---------------|--------|
| Age                                   | 14 (8–17)      | 30-100        | years |
| Female sex                            | 14/16          |               |        |
| Body mass index                       | 20.51 ± 4.32   | 9.2–11.0      | kg/m²  |
| Duration of corticosteroid treatment  | 24 (8–63)      |               | month  |
| Daily corticosteroid dosage           | 0.58 (0.26–0.95)|              | mg/kg  |
| Cumulative dose of corticosteroid     | 351.22 ± 165.7 |               | mg/kg  |
| SLEDAI score                          | 4 (0–12)       | 5–15          |        |
| Normal                                | 7/16           |               |        |
| Mild/moderate flare                   | 9/16           |               |        |
| Laboratory parameters                 |                |               |        |
| 25-OHD                                | 19.3 ± 5.4     | 92–110        | ng/ml  |
| Calcium                               | 8.69 ± 0.50    | 2.5–6.0       | mg/dl  |
| Phosphorus                            | 4.05 (2.90–5.20)|              | mg/dl  |
| Alkaline phosphatase                  | 79.50 (43.00–164.00)| 92–336 | U/l    |
| Morning cortisol                      | 1.20 (0.0–10.21)| 4.3–22.4      | ug/dl  |
| Micronutrient intake                  |                |               |        |
| Calcium                               | 587.58 ± 213.29| 1,000–1,200   | mg/day |
| Vitamin D                             | 2.9 (0–31.8)   | 5–15          | mcg/day|

Data were obtained from the patients in the form of bone whole body mineral density (total body less head; TBLH) and lumbar vertebrae, and the Z scores were calculated. The Z scores for TBLH and lumbar vertebrae were −1.46 ± 1.30 and −1.75 ± 1.24, respectively. Six subjects had a Z score ≤ −2.0 for TBLH bone mineral density, while seven subjects had a Z score of ≤ −2.0 for lumbar vertebral bone mineral density (Table 2).

Table 2. Dual X-ray absorptiometry (DXA) examination of the subjects

| DXA                                      | Mean ± standard deviation |
|------------------------------------------|---------------------------|
| Total bone mineral density (TBLH)        | 0.885 ± 0.09 g/cm²        |
| Z score of TBLH                          | −1.46 ± 1.30              |
| Z score of vertebrae                     | −1.75 ± 1.24              |

There were different variable characteristics of steroid treatment duration and cumulative steroid dose obtained with the Z scores for TBLH bone mineral densities of ≤ −2.0 and > −2.0 (40.17 ± 13.00 months vs. 20.70 ± 13.78 months; 502.85 ± 155.37 mg/kg vs. 260.25 ± 88.58 mg/kg). Meanwhile, the cumulative steroid doses was different between the subjects with Z scores for the lumbar vertebrae of ≤ −2.0 and > −2.0 (459.30 ± 182.74 mg/kg vs. 267.17 ± 91.04 mg/kg). The duration of steroid treatment for subjects with Z scores for the lumbar vertebrae of ≤ −2.0 tended to be longer than it was
for subjects with a score > −2.0. There was no difference in the SLEDAI score or the intake of either vitamin D or calcium.

**Table 3.** Characteristics and laboratory parameters based on the bone mineral density Z scores

| Characteristic                  | Total-body-less-head (TBLH) bone mineral density Z score | Lumbar vertebral bone mineral density Z score |
|--------------------------------|----------------------------------------------------------|---------------------------------------------|
|                                | ≤ −2.0 (n = 6)                                           | > −2.0 (n = 10)                             |
| Age (years)                    | 15.0 ± 1.5                                              | 12.3 ± 3.3                                  |
| Body mass index (BMI; kg/m²)   | 1.32 ± 6.71                                             | 21.23 ± 2.15                                |
| Duration of corticosteroid use (months) | 40.17 ± 13.00                                        | 20.70 ± 13.78                               |
| Daily corticosteroid dose (mg/kg) | 0.48 ± 0.26                                         | 0.66 ± 0.16                                 |
| Cumulative corticosteroid dose (mg/kg) | 502.85 ± 155.37                                  | 260.25 ± 88.58                              |
| SLEDAI score                   | 4.5 (2–12)                                              | 4 (0–6)                                    |
| Vitamin D level (ng/dl)        | 21.18 ± 5.42                                            | 18.17 ± 5.33                                |
| Blood calcium level (mg/dl)    | 8.52 ± 0.40                                             | 8.80 ± 0.54                                 |
| Serum alkaline phosphatase (ALP; U/l) | 99.33 ± 53.89                                    | 78.30 ± 30.37                               |
| Morning cortisol level (ug/dl) | 4.67 (0.0–10.21)                                       | 1.12 (0.0–7.44)                            |
| Phosphorus level (mg/dl)       | 3.90 ± 0.71                                             | 4.19 ± 0.75                                 |
| Calcium intake (% of daily needs) | 45.47 ± 2.61                                           | 54.95 ± 16.74                               |
| Vitamin D intake (% of daily needs) | 18.7 (0–212.0)                        | 41.7 (7.0–276.0)                            |

### 3.2 Discussion

This research included 16 SLE patients from the Child and Adolescent Outpatient Clinic of Cipto Mangunkusumo Hospital, Jakarta. This is the first study from the RSCM pediatric department to measure the density of bone mass in SLE patients. The main objective of this research was to determine the density of bone mass, as assessed by DXA, among patients receiving corticosteroid treatment. Nearly half of the subjects in this research had low SLEDAI scores; only one subject had a SLEDAI score >10. One limitation of this research was that the bone mineral density was calculated only once, and there were no baseline data from before corticosteroid therapy. Baseline data could help to explain the ongoing relationship between corticosteroid treatment and bone mineral density changes in SLE patients. In addition, the researchers did not find a relationship between the risk factors for osteoporosis and bone mineral density because of the limited number subjects. This research is only used descriptive data for SLE patients who received corticosteroid treatment.

This research represents the first study in Indonesia to analyze the relationship between the various risk factors for low bone mineral density among SLE children and elucidate the tendency toward decreased bone mineral density along with an increasing cumulative dose of corticosteroids received by patients. Thus, this research can become the basis for a larger study including more subjects focusing on the relationships among osteoporosis risk factors in SLE patients. The average of whole body bone mineral density obtained in this research was 0.885 g/cm². This was lower than the reference bone mineral density for the population of female Southeast Asian children in the age group of 14–15 years (i.e., 1.043 g/cm²) [16] The researchers focused on bone mineral density examination results using Z scores, which represent a comparison of the bone mineral density with the standard deviation from healthy children of Asian race adjusted for gender and age. DXA examination was carried out on the TBLH and lumbar vertebra. Compared with research by So et al. [17], this study obtained lower Z scores for lumbar vertebrae. The bone mineral density of the lumbar vertebrae was lower than that of the TBLH; this finding is supported by Lilleby et al. [18] results. The effect of corticosteroid is greater on bones that contain a larger trabecular area, including the lumbar vertebrae [19, 20], as higher metabolic activity is evident in trabecular bones [6]. A case control study conducted by Li et al. [21] in China compared the differences in Z scores for bone mineral density between
female SLE patients and controls in various bones (whole body, lumbar vertebrae, neck, intertrochanter, trochander, and total hip). The greatest difference in Z scores was found in the lumbar vertebrae.

In So et al. [17] study, only 3 of 20 SLE patients had Z scores ≤ −2.0; in contrast, in this research, 7 of 16 patients had such Z scores. This can be associated with the spectrum of this research population (Indonesian population). The population of Indonesia especially that of young women who has been reported to have the lowest bone mineral density compared with the populations of six other countries in Southeast Asia [22]. Kruger et al. associated the low bone mineral density in Indonesia with lower calcium and vitamin D intake compared with other Southeast Asian countries [22,23]. In this research, all subjects’ calcium intake levels were below the daily needs for this nutrient. Meanwhile, most subjects exhibited lower intake of vitamin D than their daily needs. As shown in Table 1.3, the subjects with low bone mineral density tended to be older and have lower BMI. Meanwhile, no differences were found in the SLEDAI scores between the subjects with and without low bone mineral density. Age and low BMI are known to be independent risk factors for osteoporosis in patients with SLE. Compeyrot-Lasagne et al. [24], also found that patients with low bone mineral density are likely to be older.

In this research, no subjects were included in the “severe” category based on the SLEDAI score. There appeared to be no differences in SLEDAI scores in subjects with and without low bone mineral density. Lilley et al. and Dhillon et al. concluded that the corticosteroid dose has a greater association with bone mineral density than the SLEDAI score does [18,25]. Patients with low bone mineral density seem to have a slightly lower BMI. Rocher et al. [26], explained that children with higher BMI levels exert a greater burden related to bone weight support, so they have better bone mineral density. However, this interpretation needs to be adjusted according to the bone mass to body weight ratio. Rocher et al. [26], concluded that the bones of children with higher BMIs are not strong enough to support their body weight.

Lu et al. [27] carried out a longitudinal analysis of bone mineral density values, especially those of the TBLH and lumbar vertebrae, in young patients. That study found that a linear relationship between BMI, body weight, and height is evident up to a certain point (inflection point), which is reached around the age of 13 years for girls and 16 years for boys. After this point, there is no correlation between BMI and bone mineral density. In this research, 14/16 subjects were female, and 10 were ≥13 years old; it is assumed that they had passed the inflection point, as there were no striking differences related to BMI between subjects with and without low bone mineral density. The age of 10–16 years represents the period exhibiting the fastest increase in bone mineral density during growth [28].

In general, low average levels of 25-OHD, calcium, ALP, and morning cortisol serum were found in SLE patients. As a comparison, Lilley et al. [18] obtained an average ALP serum level in SLE children of 50.2 U/L/U/L. For all subjects in this research, the level of 25-OHD was below the laboratory reference value of 30 ng/dl. A 25-OHD level > 30 ng/dl is needed to maintain the optimum homeostasis of systemic calcium [29]. As noted above, the Indonesian population has the lowest bone mineral density in Southeast Asia; interestingly, Indonesian children also have lower levels of 25-OHD than children from Malaysia, Vietnam, and Thailand. The factors related to low 25-OHD levels in Indonesian children are female sex and older age. Although Indonesia is located in a tropical region, long exposure to sunlight was not related to the level of 25-OHD in this research. Moreover, the children in Java had significantly lower 25-OHD levels than children from other islands did [30].

Although pediatric SLE patients are given supplements of vitamin D (133–266 IU) and calcium (500–1,000 mg/day), low levels of serum 25-OHD and calcium were still found. The low total intake of vitamin D and calcium in the Indonesian population described above could be seen in the subjects in this research. Until now, there has been no specific protocol regarding recommendations for vitamin D and calcium supplementation in patients with SLE who undergo continuous high-dose corticosteroid treatment. Calcium supplementation is required for all patients with corticosteroid treatment, as corticosteroids reduce the absorption of calcium in the gastrointestinal tract and increase the excretion of calcium through urine. For adult populations, the American College of Rheumatology Ad Hoc
Committee on Osteoporosis (2001) recommended that patients on corticosteroid treatment should maintain a calcium intake of 1,000–1,500 IU/day or higher and a vitamin D intake of 800 IU/day, both in the form of supplements and dietary calcium and vitamin D. Patients who are candidates for supplementation are those who take corticosteroids equal to 5 mg/day for more than 3 months. In addition to supplements, other suggestions are to avoid smoking and alcohol, take bisphosphonate or calcitonin (second-line bisphosphonate), and receive hormone therapy if low values are identified [31,32]. In their new recommendations, the American College of Rheumatology (2010) increased the recommended intake of calcium to 1,200–1,500 mg/day and vitamin D to 800–1,200 IU/day or higher, as corticosteroids can decrease the absorption of vitamin D in the gastrointestinal tract [31]. The effect of adequate calcium and vitamin D supplementation intake was observed in Buckley et al.’s research on patients with rheumatoid arthritis and corticosteroid treatment [30]. In that study, the researchers divided the patients undergoing low-dosage corticosteroid treatment into three groups, as follows: a calcium carbonate (1,000 mg/day) group, a vitamin D (500 IU/day) group, and a placebo group. After 2 years, it was found that the placebo group lost 2% per year of lumbar vertebral bone mineral density, while the supplementation groups showed an increase of 0.72% per year [30]. However, Moghadam-Kia and Werth stated that calcium and vitamin D supplementation is not enough to prevent decreasing bone mass in patients with high-dose corticosteroid treatment regimens [29].

Comparing the subjects with and without low bone mineral density from Table 3, it is apparent that there is no difference in calcium, vitamin D, or phosphorus levels. Meanwhile, patients with low bone mineral density have higher levels of ALP and morning cortisol. Relative hypercortisolism conditions in patients with corticosteroid treatment are known to have a negative effect on bone mass, whether directly or indirectly. This condition can increase bone resorption rates [33]. The description of the ALP level was an interesting finding in this research. In general, a lower than normal level of ALP was found; this is in accordance with the theory that osteoporosis is associated with corticosteroid therapy. However, there were differences in ALP levels between the subjects with and without low bone mineral density. The higher level of ALP in patients with low bone mineral density can be explained by suggesting that these patients had increased rates of bone resorption and decreased bone formation. ALP is a marker of bone formation, so that its level will decrease with the long-term use of corticosteroids, and bone resorption will become more dominant than bone formation. As explained in previous study, initially, there are decreases in osteocalcin and ALP in General Inter-ORB Protocol (GIOP) [33]. Meanwhile, although a decreasing level of vitamin D is expected, this study conveyed that the levels of Parathyroid hormone (PTH), vitamin D, phosphorus, and calcium can also be normal [33]. Another study observed calcium serum, osteocalcin, and ALP in series during corticosteroid therapy [34]. Along with the tapering dosage of corticosteroid, serum osteocalcin and ALP, which first decreased, began to increase again, although they did not reach the baseline levels [35]. Meanwhile, these researchers found that the levels of PTH and calcium do not change much during corticosteroid therapy. It can also be noted that ALP is not specific because it is also produced by other tissues besides bones. Because this was a cross-sectional study, changing levels of ALP during corticosteroid therapy could not be monitored carefully. The higher ALP in patients with low bone mineral density may have been due to a lower tapering dosage of corticosteroids compared to patients with good bone mineral density.

The researchers did not observe any difference in vitamin D intake in a day based on the Z scores of the TBLH and lumbar vertebrae. Meanwhile, the calcium intake was not greatly different between subjects with and without low bone mineral density. Research on SLE patients also showed that calcium intake is not related to low bone mineral density. In that research, the corticosteroid dose was related to low Z scores on DXA measurements. Research by Steingrimsdottir et al. [12] found that vitamin D intake has a greater effect on PTH levels than calcium intake does. Adequate intake of vitamin D can maintain PTH levels even if the calcium intake is lower. In contrast, even if calcium intake is excessive, with lower vitamin D intake, increased PTH levels will still be evident. In line with this research, patients with low bone mineral density clearly exhibit low vitamin D intake, while there is no difference between the calcium intake levels between those with and without low bone
mineral density. However, since this research did not examine PTH subjects, the comparison of these results is limited.

This research found a difference in the cumulative corticosteroid dose between subjects with bone mineral density Z scores of \( \leq -2.0 \) and those with scores of \( \geq -2.0 \). The cumulative corticosteroid dose was higher in subjects with low bone mineral density. These finding also support the results of Compeyrot-Lasagne et al., in which subjects with low Z scores for lumbar vertebral bone mineral density had a higher cumulative dose of corticosteroids \( (629.9 \pm 381.5 \text{ mg/kg vs. } 506.2 \pm 413.6 \text{ mg/kg}) \) [24]. Thus, in terms of the duration of corticosteroid treatment, patients with low bone mineral density consumed corticosteroids longer, which is in accordance with this research. This finding is also in accordance with the results of SLE patient observation in other studies, namely those of Pelase et al. and Lilleby et al.; these researchers also found a negative correlation between cumulative dose and duration of corticosteroid treatment and the bone mineral density of SLE patients [17,18,24]. So et al. experienced limitations in calculating the cumulative corticosteroid dose per kilogram of body weight because the research design used retrospective medical records and monitoring of subjects, where annual calculations had already been carried out. The present research tried to overcome this limitation by calculating the cumulative dose of corticosteroids in mg/kg [17].

4. Conclusion
In this study, low bone mineral density \( (Z \text{ score } \leq -2.0) \) was found in 7/16 of pediatric SLE patients included as research subjects. The characteristics of SLE children with low bone mineral density exhibited a higher cumulative dose with longer duration of the corticosteroid treatment. In addition, SLE children with low bone mineral density tended to be older and have lower BMI and vitamin D intake. There was no tendency toward differences in SLEDAI score and calcium intake in SLE children with low bone mineral density. In general, SLE patients taking corticosteroids had low levels of vitamin D, calcium, ALP, and morning cortisol. Especially, levels of ALP and cortisol were found to be higher in SLE patients with low bone mineral density.

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