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Factors Affecting Bone Mineral Density in Children and Adolescents with Systemic Lupus Erythematosus

Running title: Factors Affecting Bone Mineral Density in Juvenile-onset Systemic Lupus Erythematosus

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Abstract

Purpose: Patients with juvenile-onset systemic lupus erythematosus (JSLE) are at a high risk of entering adulthood with disease-related morbidities such as reduced bone mass and osteoporosis. This study aimed to evaluate the clinical characteristics of JSLE and to analyze the factors associated with low bone mineral density (BMD) in these patients.

Methods: Children and adolescents diagnosed with JSLE at a single hospital in Korea were included. Demographic, clinical, and laboratory data and use of glucocorticoids and disease-modifying anti-rheumatic drugs were collected. Lumbar spine BMD Z-score was measured using dual energy x-ray absorptiometry, and lumbar spine radiographic data were collected.

Results: A total of 29 patients with JSLE were included in this study. Of these patients, seven had a lumbar spine Z-score of -2.0 or lower and were designated as the low BMD group. The differences in the clinical parameters and treatment variables between the low BMD and non-low BMD groups were compared. Higher cumulative glucocorticoid dose, longer glucocorticoid exposure, and higher cumulative hydroxychloroquine dose were associated with low BMD; the main factor was the duration of exposure. There was no significant correlation between BMD and clinical profile, SLE disease activity, or bone metabolism markers.

Conclusion: The duration of glucocorticoid exposure, cumulative glucocorticoid dose, and cumulative hydroxychloroquine dose were risk factors for low BMD in patients with JSLE, with the main factor being duration of glucocorticoid exposure. Thus, patients with JSLE should be routinely monitored for low BMD and potential fracture risks, and glucocorticoid-sparing treatment regimens should be considered.

Keywords: bone density; bone diseases, metabolic; glucocorticoids; juvenile osteoporosis; lupus erythematosus, systemic

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder characterized by chronic inflammation and damage to various organs, including the skin, joints, blood cells, brain, and kidneys (1). Juvenile-onset SLE (JSLE) represents 15-20% of all SLE cases, and the course of JSLE is often more severe than adult SLE, with a higher frequency of aggressive renal disease and a higher requirement for steroids and immunosuppressive drugs (2). In recent studies, the overall prognosis for SLE has improved to more than 90% 10-year survival (3). However, longer survival has meant that patients with SLE now experience more complications, and that patients with JSLE are at a higher risk of entering adulthood with disease-related morbidities such as reduced bone mass and osteoporosis (4). Furthermore, patients with JSLE are at considerable risk for developing low bone mass since they are affected by the disease before reaching peak bone mass, which serves as a future bone bank.

Several factors may adversely affect bone health in patients with JSLE, including systemic inflammation, hormonal factors, decreased physical activity, limited sunlight exposure, and inadequate calcium and vitamin D intake (5, 6). Treatments, primarily glucocorticoids (GCs) and possibly some disease-modifying anti-rheumatic drugs (DMARDs), may also have a negative impact on bone health (7). GCs are well known to reduce bone formation and increase bone resorption. However, they might also have favorable effects on bone mass through the reduction of systemic inflammation (8). Several cross-sectional studies assessed the effects of GC use on bone mass in adult patients with SLE, and although there are still some controversies, GCs were reported to be a risk factor for low bone mass and fractures (9-13).

However, there have been few studies concerning bone health in patients with JSLE. A few cross-sectional studies on bone health in children with rheumatic disorders have demonstrated low bone mass and fractures in this population (14-17). Trapani et al. documented a significant inverse correlation between bone mineral density (BMD) and cumulative GC dose in patients with JSLE (14), while Valta et al. reported no correlation between BMD and cumulative GC dose in patients with juvenile idiopathic arthritis (17). A prospective study from the Canadian Steroid-Associated Osteoporosis in the Pediatric Population consortium reported that every 0.5 mg/kg increase in the average daily GC dose was associated with a two-fold increased fracture risk among children with rheumatic disorders, including juvenile dermatomyositis, juvenile idiopathic arthritis, systemic vasculitis, and JSLE (18).

This study aimed to evaluate the clinical characteristics of patients with JSLE and to analyze the factors associated with low BMD in these patients.

Materials and Methods

1. Subjects

Children and adolescents diagnosed with JSLE from January 1, 2009 to April 30, 2022 at a single institution in Korea were included. The diagnosis was made by pediatric rheumatologists, based on the American College of Rheumatology and Systemic Lupus International Collaborating Clinics' classification criteria (19-21). In this study, patients with JSLE were defined according to Silva et al.'s definition, which consists of SLE onset prior to age 18 years, a threshold based on different gender distribution, clinical course and disease activity from adult SLE (22). Only patients who had undergone dual energy x-ray absorptiometry (DXA) and thoracolumbar spine radiography were considered eligible. Patients who had received GC treatment for less than 3 months were excluded. This study was approved by the Institutional Research Board (IRB No. KC22RISI0496). Written

informed consent was waived due to the retrospective nature of the study.

2. Clinical and laboratory data of SLE

Demographic, clinical, and laboratory data, including age, height, weight, body mass index (BMI), pubertal stage, course of disease, bone metabolism markers, serologic markers of SLE activity, and use of GCs and DMARDs, were collected. All data were collected from each patient at two time points: diagnosis and follow-up (the time when the latest DXA was performed).

The clinical manifestations and disease course were evaluated. Organ involvement was assessed in five categories: skin, joint, hematologic, and renal involvement, and neuropsychiatric SLE. Skin involvement was categorized based on the presence of malar rash or photosensitivity. Joint involvement was defined as the presence of swelling or effusion in two or more joints. Hematologic involvement was defined by the presence of one of the following: hemolytic anemia (Hemoglobin < 10.0 g/dL with evidence of hemolysis), leukopenia (white blood cell count < 4.0 x 10^9 /L), and thrombocytopenia (platelet count < 100 x 10^9 /L). Renal involvement was defined as histological renal damage or the presence of proteinuria (> 0.5 g within 24 hours). Neuropsychiatric SLE was designated according to the American College of Rheumatology nomenclature (23). Disease activity was assessed using the revised version of the SLE Disease Activity Index (SLEDAI) (24). SLE flare was defined as new or worsening clinical symptoms with escalation of treatment (i.e., new immunosuppressant use, a prednisone increase of 0.5 mg/kg/d, intravenous methylprednisolone, or hospitalization). Serological markers related to SLE disease activity were collected. Low C3 and C4 complement levels and high titers of anti-dsDNA antibodies were considered reflective of higher SLE activity (25).

The cumulative GC dose (expressed as prednisolone equivalent) was calculated for each patient's mean body weight (from diagnosis to follow-up) and presented in grams per kilogram. The average

daily dose was presented as grams per kilogram per day. The duration of exposure was assessed, excluding periods when GC was discontinued due to improvement or remission of the disease. The use of hydroxychloroquine (HCQ) and other DMARDs (azathioprine, methotrexate, mycophenolate mofetil, and cyclosporine) was recorded from diagnosis to follow-up.

3. Bone assessment

Lumbar spine (LS) BMD (L1-L4) was measured in all patients using DXA (Horizon W DXA system®, Hologic Inc., Marlborough, MA, USA). All DXA data from diagnosis to recent follow-up were collected. The BMD Z-score was calculated and compared with 1,650 healthy age- and sex-matched Korean controls (26). Lateral thoracolumbar spine radiographs were collected from diagnosis to follow-up, when the latest DXA was performed. Spine radiographs were scored independently by two pediatric radiologists according to the modified Genant semiquantitative method (27). Vertebral bodies were graded according to the extent of reduction in height ratios: 20-25% (mild), 25-40% (moderate), and > 40% (severe). Bone metabolism markers included calcium, phosphorous, alkaline phosphatase, 25-hydroxyvitamin D, and parathyroid hormone at diagnosis and follow-up.

4. Statistical analysis

Results are reported as medians (interquartile range [IQR]) for continuous variables and as proportions for categorical variables. Anthropometric data, clinical features, disease-related serological markers, bone metabolism markers, cumulative dose and duration of GCs, and cumulative HCQ dose were compared with respect to an LS BMD of -2.0 using the non-parametric Mann-Whitney test. The proportion of DMARDs use was compared with respect to a -2.0 LS BMD using the chi-square test. Linear regression analysis and univariate binominal logistic regression were performed to identify risk factors for low BMD. Variables identified as significant in univariate

analysis were entered into a multiple logistic regression model. Statistical calculations were performed using the Statistical Package for the Social Sciences (SPSS) Statistics Software v.27.0 (SPSS Inc., Chicago, IL, USA). Two-tailed *p* values less than 0.05 were considered significant.

Results

1. Demographic and clinical characteristics

A total of 29 patients with JSLE (25 females and 4 males) were included in this study. SLE was diagnosed at a median age of 12.7 years (Interquartile range [IQR] 11.5–14.8), and the median age at follow-up was 15.8 years (IQR 13.6–17.5). All patients were treated with GCs at a median daily dose of 9.9 mg, with a median cumulative dose of 14.6 g, during their median follow-up period of 4.5 years [IQR 2.2–6.9]. The median (IQR 25%-75%) LS BMD Z-score at follow-up was -0.9 (-1.8–0.1). The prevalence of vertebral fractures (VF) at follow-up was 52%, with mild, moderate, and severe fractures representing 24%, 21%, and 10% of these, respectively. In view of the fact that presence of 1 or more vertebral compression fracture in the absence of local disease or high-energy trauma meets the definition of osteoporosis in children and adolescents, prevalence of osteoporosis in the present study was 52%. The demographic data, clinical characteristics, and laboratory characteristics of the subjects at diagnosis and at the time of the latest DXA are summarized in Table 1.

2. Comparison of clinical parameters with respect to a -2.0 LS BMD

Based on the latest DXA, patients with an LS BMD Z-score of -2.0 or lower were classified as the low BMD group, while others were classified as the non-low BMD group. Of the 29 patients, seven had a LS BMD Z-score of -2.0 or lower and were designated as the low BMD group. The differences in the clinical parameters between the low BMD and non-low BMD groups are summarized in Table 2 and Table S1.

Comparison of anthropometric data at diagnosis and follow-up revealed that the low BMD group had a lower height Z-score at both diagnosis (-0.043 vs. -1.651, $p = 0.014$) and follow-up (-0.504 vs. -1.843, $p = 0.013$) compared to the non-low BMD group. There were no significant differences in weight and BMI. There was no difference between the clinical profiles (skin, joint, hematologic, and renal involvement, and neuropsychiatric SLE), SLEDAI scores, and flare-up episodes between the two groups. The serological markers reflecting SLE disease activity and bone metabolism markers showed no difference between the two groups at both diagnosis and follow-up. The low BMD group had a higher prevalence of a -1.0 or lower initial LS BMD Z-score (27% vs. 100%, $p < 0.001$) compared to the non-BMD group. The prevalence of moderate VF (9% vs. 43%, $p < 0.001$) and severe VF (0% vs. 43%, $p < 0.001$) was higher in the low BMD group than in the non-low BMD group.

3. Comparison of medication use with respect to a -2.0 LS BMD

Medication use was compared with respect to an LS BMD Z-score of -2.0 (Table S2). All patients with JSLE used GCs and HCQ from the onset of the disease. Duration of GC exposure was significantly longer in the low BMD group (2.9 years vs. 6.9 years. $p = 0.002$) than in the non-low BMD group. Total cumulative dose (12.3 g vs. 26.8 g, $p = 0.021$) and cumulative dose per mean body weight (0.23 g/kg vs. 0.54 g/kg, $p = 0.027$) was significantly higher in the low BMD group than in the non-low BMD group. However, daily GC dose showed no difference between the two groups (Fig. 1).

Tapering or discontinuation of medication was attempted with GCs but not with HCQ throughout the disease course of the present cohort. Four out of the 29 patients discontinued using GCs, although one of them restarted GC treatment due to increased disease activity. In contrast, all patients continued on HCQ from diagnosis to follow-up, and discontinuation or tapering was not attempted in any patient. This is consistent with the 2019 EULAR recommendations prescribing HCQ for all patients with SLE,

unless contraindicated. In contrast, GC discontinuation is recommended whenever possible (28). As the duration of HCQ was not a modifiable factor, we compared the cumulative HCQ dose between the two groups. Cumulative HCQ dose was 4.64 g/kg and 10.10 g/kg in the non-low BMD and low BMD groups, respectively ($p = 0.003$) (Fig. 1).

Other DMARDs used in the cohort were azathioprine (55%), methotrexate (34%), mycophenolate mofetil (31%), and cyclosporine (10%). The use of DMARDs other than HCQ showed no significant difference between the two groups. Regarding anti-osteoporosis treatment, bisphosphonate use was significantly higher in the low BMD group (0% vs. 57%, $p < 0.001$) than in the non-low BMD group.

4. Association between GC, HCQ and low BMD

Considering that the cumulative dose and duration of GCs and cumulative HCQ dose were higher in the low BMD group, we further analyzed the association between GC, HCQ use, and LS BMD. Linear regression analyses demonstrated that cumulative GC dose, duration of GC exposure, and cumulative HCQ dose had a statistically significant inverse relationship with the LS BMD Z-score (Fig. 2).

The three treatment variables (cumulative dose and duration of GCs, and cumulative HCQ dose) were entered into univariate logistic regression analyses for low BMD (LS BMD Z-score ≤ -2.0). The duration of GC exposure was significantly associated with low BMD (odds ratio [OR] 3.17, $p = 0.020$). The cumulative GC dose (OR 1.005, $p = 0.043$) and HCQ dose (OR = 1.000, $p = 0.017$) were also statistically significant, but with low relevance to the LS BMD Z-score ≤ -2.0 compared to the duration of GC exposure. We performed a multivariate logistic regression analysis, including the three variables. However, the Pearson's correlation test revealed that the three variables were highly correlated, making the model unstable. Duration of GCs and cumulative HCQ dose were particularly interrelated, with a Pearson correlation coefficient of 0.92 ($p < 0.001$). Therefore, we performed three

separate analyses using two of these three variables at a time for low BMD (Table 3). The best model for low BMD was the model including the duration of GCs and cumulative GC dose, and the results of this analysis demonstrated that the duration of GCs best predicted low LS BMD (OR 4.486, 95% confidence interval [CI] [1.035-19.445], $p = 0.045$).

5. Association between other clinical variables and low BMD

Since the low BMD group had lower height Z-score than the non-low BMD group, we further analyzed whether height deficit is a risk factor for low BMD. We adjusted the LS BMD Z-score for body size (26) in two children with short stature (height Z-score < -2.0) and performed a univariate logistic regression for low BMD. We found that height at diagnosis ($p = 0.093$) and follow-up ($p = 0.108$) were not risk factors for low BMD. As mentioned above, the low BMD group had a higher prevalence of a ≤ -1.0 initial LS BMD. Another logistic regression analysis was performed; however, a ≤ -1.0 initial LS BMD was not a relevant risk factor for low BMD ($p = 0.994$).

Discussion

The present study focused on low BMD in patients with JSLE and showed that longer duration of GC exposure, higher cumulative GC dose, and higher cumulative HCQ dose were associated with low BMD in patients with JSLE, with the main risk factor being duration of GC exposure. We found no significant correlation between LS BMD and clinical profile, SLE disease activity, or bone metabolism markers. There was no significant difference in the use of DMARDs, other than HCQ, between the low and non-low BMD groups.

Although a recent meta-analysis failed to show a correlation between GC use and low BMD in adult patients with SLE (9), several studies have demonstrated an association between GC use and low

BMD (10-13). However, the results are inconsistent regarding whether the cumulative dose, duration, or both, are risk factors for low BMD. Davidson et al. (11) reported that the cumulative steroid dose was significantly associated with osteoporosis (OR 1.60, 95% CI [1.07-2.41]), whereas the duration of GC exposure was not. A recent meta-analysis of secondary osteoporosis in adult patients with SLE revealed that both the cumulative GC dose and duration of GC therapy were significantly different between patients with and without osteoporosis (13). Studies concerning the pediatric SLE population are scarce and mostly focus on the daily or cumulative doses of GCs rather than the duration of GC exposure. Nakhla et al. reported that the significant risk factors for VF in patients with JSLE include cumulative GC dose, but the duration of GC exposure was not analyzed (15). Reduction in LS BMD was significantly associated with higher cumulative GC doses in the study by Lilleby et al., but the duration of GC exposure was assessed as "current GC use or not" and did not include a specific duration (4). Furthermore, an increase in the average daily GC dose was shown to be associated with increased VF risk (HR 1.95, 95% CI 1.08-3.51), whereas GC intensity and duration of GC therapy were not (29). Our study investigated both the effect of cumulative GC dose and the effect of the duration of GC exposure on BMD and revealed that the duration of GC exposure is a notable risk factor for low BMD in patients with JSLE. This result is clinically meaningful because it may support the applicability of a more aggressive use of intravenous methylprednisolone pulses upon diagnosis, which might allow for faster tapering and discontinuation of oral GCs, shortening the duration of GC exposure. Another approach may include the early initiation of immunosuppressants to facilitate tapering and discontinuation of GCs. These two approaches may minimize the duration of GC exposure, which may be beneficial to bone health in patients with JSLE.

HCQ is an antimalarial agent given to all patients with SLE. HCQ treats skin disease, minimizes flare-ups, and decreases autoantibody production by inhibiting Toll-like receptor pathways (30). In the present study, all patients used HCQ, and the cumulative HCQ dose was higher in the low BMD

group, although it was not a significant risk factor for low BMD in multivariate analyses. Data regarding the effects of HCQ on bone health are scarce, and the results are conflicting. Two cross-sectional studies documented higher spinal BMD associated with HCQ use, suggesting a protective effect of HCQ on bone (31, 32). In contrast, a 6-year Dutch study reported that hip BMD loss was associated with HCQ use (10). A more recent study involving 1807 adult patients with SLE showed no correlation between HCQ use and BMD (33). The impact of immunosuppressant drugs on bone health is also controversial, and it is difficult to clearly determine their effect on bone because their use usually implies a more severe SLE disease status. Methotrexate and azathioprine use is considered in patients when trials with GC and HCQ or HCQ alone are insufficient to control symptoms. However, although there have been reports of patients who developed multiple insufficiency fractures while on prolonged methotrexate therapy, commonly known as methotrexate osteopathy, the effects of methotrexate on bone loss are not fully understood (34, 35). An observational study on 60 patients with rheumatic arthritis did not reveal a significant difference in BMD between methotrexate users and non-users (36). There are minimal data on azathioprine and BMD, but a study concerning patients with Crohn's disease demonstrated that azathioprine did not affect the BMD itself; however, it seemed to have a protective effect on bone mass via steroid sparing (37). Furthermore, a recent large cross-sectional study by Cramarossa et al. showed no association between immunosuppressant use and BMD (33). The association between DMARDs use and bone loss requires further investigation.

A recent meta-analysis of secondary osteoporosis in SLE showed that among nine studies that reported SLEDAI scores, there was no significant difference in SLEDAI between patients with or without osteoporosis and SLE (13). This result was consistent with that of our study, which showed no correlation between SLEDAI and low BMD. In a large 5-year study of adult female patients with SLE, Zhu et al. reported that SLE flares during follow-up were significantly associated with a larger decrease in LS BMD (38). We also investigated the relationship between flare-ups and BMD. In our

study, 71% of the low BMD group and 32% of the non-low BMD group experienced flare-ups, but the difference was not statistically significant. In short, in our study, there was no significant correlation between disease activity and low BMD. In addition to SLEDAI and flare-ups, there was no significant correlation between the clinical profile, serological markers of SLE activity, bone metabolism markers, and low BMD. Although this is a negative finding, it may imply that clinical manifestations, SLEDAI score, or serological markers cannot predict low bone mass in patients with JSLE, and routine surveillance of BMD and VF is necessary to detect early bone mass reduction.

In the present study, the low-BMD group had a lower height Z-score at both diagnosis and follow-up. Several studies have reported that BMD increased with height and weight (39, 40). In other words, lower height and weight were associated with lower BMD. Although height deficit was not proven to be a risk factor for low BMD in our study, the fact that the low BMD group had a lower height Z-score at diagnosis and follow-up may imply that patients with JSLE with short stature should be more cautiously monitored for a decline in BMD and growth.

This study has some limitations owing to its retrospective design. First, the total number of patients with JSLE who had undergone DXA and thoracolumbar spine radiography was small. The patients did not have sufficient DXA data or spine radiographs at diagnosis, which limited further comparison of DXA data done at early stages of treatment and at follow-up for each patients. Further prospective studies are needed to determine the effects of GCs and DMARDs on low BMD. Second, the dietary calcium and vitamin D intake, amount of physical activity and sunlight exposure could not be accurately assessed by chart review. Lastly, BMD by DXA did not consider three-dimensional bone microarchitecture and volumetric BMD. We did not have access to quantitative measures assessed by computed tomography. However, the strength of this study is that we performed a comprehensive analysis of the effects of anthropometric, clinical, laboratory, and treatment-related variables on BMD in patients with JSLE.

In conclusion, longer duration of GC exposure and higher cumulative GC and HCQ doses were risk factors for low BMD in patients with JSLE, and the main risk factor was the duration of GC exposure. Disease activity markers of SLE and bone metabolism markers did not predict low BMD. Thus, patients with JSLE should be routinely monitored for low BMD and potential fracture risks, and GC-sparing treatment regimens should be considered for patients with JSLE to shorten GC exposure.

Conflicts of interest

If there are any conflicts of interest, authors should disclose them in the manuscript. If there are *no* any conflicts of interest, authors should describe following sentence. “The authors have nothing to disclose.”

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Figure Legends

Fig. 1 Comparison of GCs and HCQ with respect to a -2.0 LS BMD Z-score

The low BMD group had longer duration of GC exposure, higher cumulative GC dose, and higher cumulative HCQ dose compared to the non-low BMD group, but there was no difference in daily GC dose between the two groups.

GC, glucocorticoids; HCQ, hydroxychloroquine; LS BMD, lumbar spine bone mineral density.

Cumulative glucocorticoid doses are expressed as prednisolone equivalents.

Fig. 2 Linear regression model of treatment variables and LS BMD Z-score

The linear regression model shows an inverse relationship between LS BMD Z-score and the following factors: duration of GC exposure, cumulative GC dose, and cumulative HCQ dose.

GC, glucocorticoids; HCQ, hydroxychloroquine; LS BMD, lumbar spine bone mineral density.

Table 1. Demographics and clinical and laboratory characteristics of the study subjects

Clinical parameters	Diagnosis (*n*=29)	Follow up (*n*=29)
Age, years	12.7 (11.5–14.8)	15.8 (13.6–17.5)
Female, *n*. (%)	25 (83%)	25 (83%)
Tanner stage	3 (1–4)	5 (4–5)
Disease duration		4.5 (2.2–6.9)
Anthropometry		
Height Z-score	-0.4 (-0.9–0.7)	-0.7 (-1.3–0.4)
Δ Height Z-score		-0.1 (-0.3–0)
Weight Z-score	-0.3 (-1.2–0.8)	-0.1 (-1–1.2)
Δ Weight Z-score		0.2 (-0.4–1)
BMI Z-score	0.1 (-1.2–1.0)	0 (-0.7–1)
Δ BMI Z-score		0.3 (-0.1–1.1)
Clinical profile of SLE		
Skin involvement	15 (52%)	3 (10%)
Articular involvement	9 (31%)	3 (10%)
Renal involvement	5 (17%)	3 (10%)
Neuropsychiatric SLE	2 (7%)	2 (7%)
Hematological involvement	22 (76%)	14 (48%)
SLEDAI score	8 (6–13)	4 (2–7)
Disease activity markers of SLE		
C3, mg/dL	63 (35–93)	82 (72–100)
C4, mg/dL	6.8 (4.8–14.4)	13.1 (7.9–17.3)

Anti-ds DNA Ab, IU/mL	149 (21.4–345.9)	21.8 (10.0–161.7)
Bone assessment		
Biochemical markers		
Calcium, mg/dL	9 (8.4–9.3)	9.2 (8.8–9.5)
Phosphorous, mg/dL	3.9 (3.5–4.4)	4.3 (3.4–4.8)
Alkaline phosphatase, U/L	83 (59–109)	80 (56–102)
Parathyroid hormone, pg/mL	25.1 (23.2–31.5)	27.1 (22.4–45)
25(OH)VitD, ng/mL	22.3 (17.3–27.1)	20.1 (14.3–28.5)
Radiology		
LS BMD Z-score		-0.9 (-1.8–0.1)
Areal LS BMD, g/cm^2		0.9 (0.8–1)
Lt Femur BMD Z-score		-1 (-1.8–-0.3)
Areal Lt Femur BMD, g/cm^2		0.8 (0.7–0.9)
VF, *n.* (%)		15 (52%)
Mild		7 (24%)
Moderate		5 (21%)
Severe		3 (10%)

All values are expressed as the median, IQR (25-75%) unless specified otherwise.

BMI, body mass index; SLE, systemic lupus erythematosus; CH50, total hemolytic complement; Anti-ds DNA Ab, anti-double stranded DNA antibody; ANA, antinuclear antibody; SLEDAI, Systemic lupus erythematosus disease activity index; 25(OH)VitD, 25-hydroxy Vitamin D; LS lumbar spine; BMD, bone mineral density; VF, vertebral fracture

Table 2. Comparison of clinical parameters with respect to a -2.0 LS BMD

	LS BMD Z-score > -2.0 (*n*=22)	LS BMD Z-score ≤ -2.0 (*n*=7)	*p* value
Anthropometry			
At diagnosis			
Height	**-0.043 (-0.798–0.739)**	**-1.651 (-1.99–-0.508)**	**0.014**
Weight	-0.274 (-1.138–0.949)	-0.279 (-0.912–0.506)	0.470
BMI	-0.038 (-1.498–-0.892)	0.57 (-00.433–-1.250)	0.821
Follow up			
Height	**-0.504 (-0.861–0.719)**	**-1.843 (-2.364–-0.736)**	**0.013**
Weight	-0.226 (-1.191–1.208)	-0.021 (-0.382–0.933)	0.734
BMI	0.045 (-0.823–0.957)	0.028 (-0.075-1.849)	0.805
Clinical profile			
At diagnosis			
Skin involvement	11 (50%)	4 (57%)	0.742
Articular involvement	6 (27%)	3 (43%)	0.438
Renal involvement	4 (18%)	1 (14%)	0.812
Neuropsychiatric SLE	2 (9%)	0 (0%)	0.408
Hematological involvement	17 (77%)	5 (71%)	0.753
SLEDAI score	10 (5–11.5)	8 (7–14.5)	0.332
Follow up			
Skin involvement	3 (14%)	0 (0%)	0.302
Articular involvement	1 (4.5%)	2 (26%)	0.069

Renal involvement	3 (14%)	0 (0%)	0.302
Neuropsychiatric SLE	2 (9%)	0 (0%)	0.408
Hematological involvement	2 (9%)	3 (43%)	0.742
SLEDAI score	8 (7–14.5)	10 (5–11.5)	0.664
Flare up	7 (32%)	5 (71%)	0.064
Radiology			
Follow up			
Initial LS BMD Z-score ≤-1.0	**6 (27%)**	**7 (100%)**	**<0.001**
VF, *n.* (%)			
Mild	**7 (32%)**	**0 (0%)**	**<0.001**
Moderate	**2 (9%)**	**3 (43%)**	**<0.001**
Severe	**0 (0%)**	**3 (43%)**	**<0.001**

All values are expressed as the median, IQR (25-75%) or *n.* (%).

SLE, systemic lupus erythematosus; LS lumbar spine; BMD, bone mineral density; VF, vertebral fracture; CH50, total hemolytic complement; Anti-ds DNA Ab, anti-double stranded DNA antibody; ANA, antinuclear antibody; 25(OH) Vit D, 25-hydroxy Vitamin D; SLEDAI, systemic lupus erythematosus disease activity index

Table 3. Multiple logistic regression analysis of treatment associated factors when the LS BMD Z-score is ≤-2.0 *

	LS BMD Z-score ≤-2.0†					
	Univariate			Multivariate		
	OR (95% CI)	SE	*p*	OR (95% CI)	SE	*p*
Glucocorticoid						
Cumulative dose, mg/kg	**1.005 (1.000-1.011)**	0.002	**0.043**			
Duration, yr	**3.17 (1.198-8.383)**	0.496	**0.020**	**4.486 (1.035-19.445)**	0.748	**0.045**
Hydroxychloroquine, mg/kg	**1.000 (1.000-1.001)**	0.001	**0.017**			

* Three separate multivariate analyses were performed using two of the three interrelated variables at a time.

† Adjusted for cholecalciferol intervention.

Abbreviations: CI, confidence interval; LS BMD, lumbar spine bone mineral density; OR, odds ratio; SE, standard error

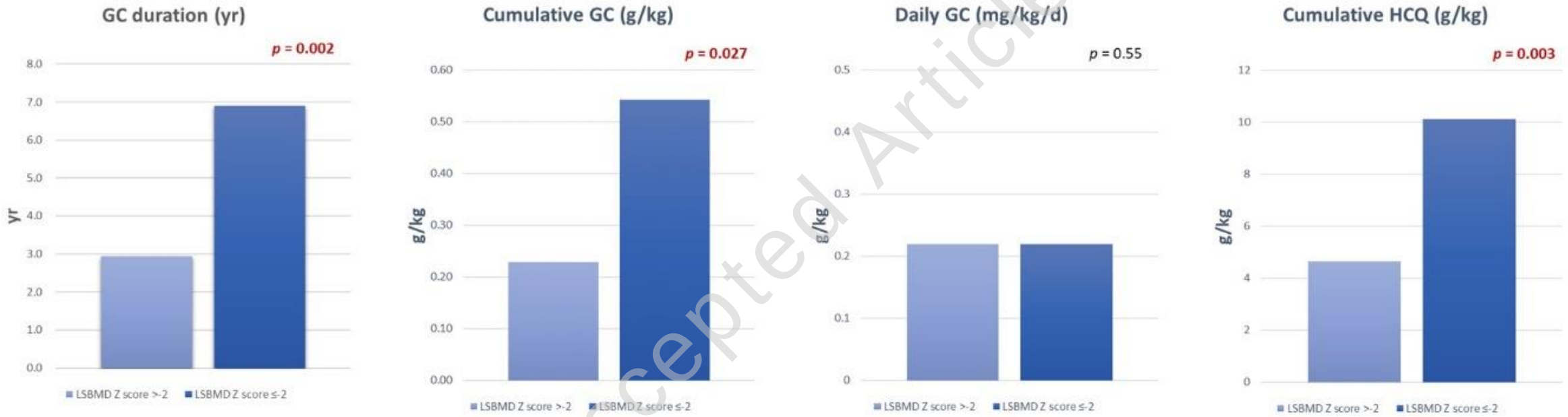
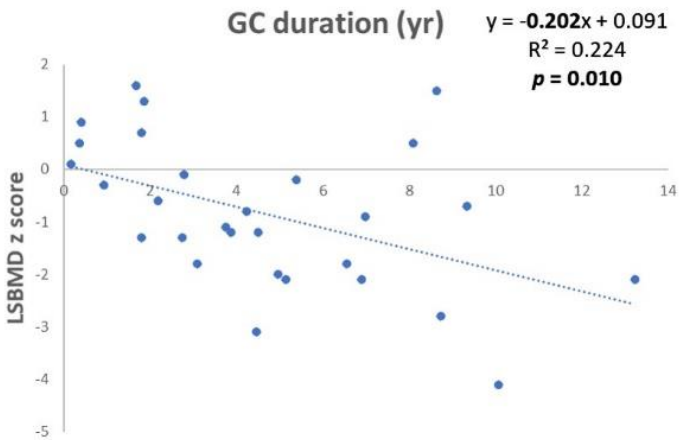
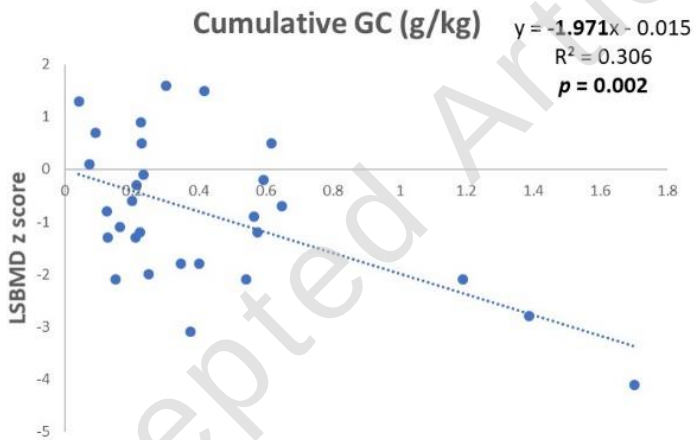


Figure 1





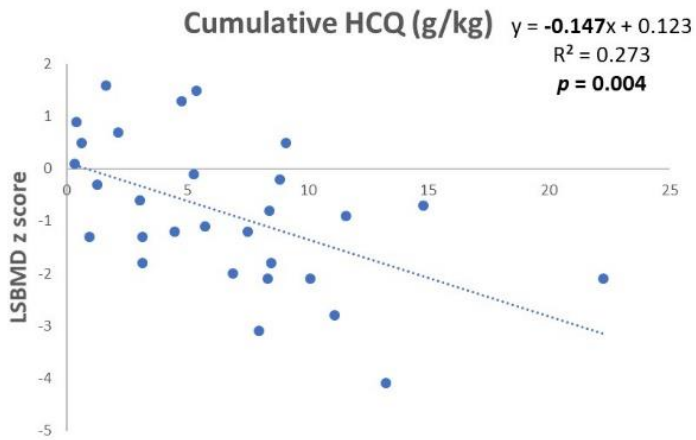


Figure 2