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ORIGINAL ARTICLE

A randomized double-blind placebo-controlled trial of vitamin D supplementation in juvenile-onset systemic lupus erythematosus: positive effect on trabecular microarchitecture using HR-pQCT

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Abstract

Summary In this randomized double-blind placebo-controlled 24-week trial, cholecalciferol supplementation at 50,000 IU/week effectively improved bone microarchitecture parameters in juvenile-onset systemic lupus erythematosus (JoSLE) patients, as assessed by high-resolution peripheral quantitative computed tomography (HR-pQCT) at tibia site. An increase in the trabecular number and a decrease in the trabecular separation were observed, suggesting that vitamin D supplementation may be recommended for JoSLE patients with its deficiency.

Introduction Vitamin D has an important effect on bone but there are no trials that directly address the boosting of serum levels of 25-hydroxyvitamin D (25OHD) in bone microarchitecture in JoSLE patients. The aim of this study was to evaluate the effect of vitamin D supplementation on bone microarchitecture parameters using HR-pQCT in JoSLE patients.

Methods This study was a randomized double-blind placebo-controlled 24-week trial. Forty female JoSLE patients were randomized (1:1) to receive oral cholecalciferol at 50,000 IU/week (JoSLE-VitD) or placebo (JoSLE-PL). The medications remained stable throughout the study. Serum levels of 25OHD were measured using a radioimmunoassay. The bone microarchitecture and volumetric bone density were analyzed using HR-pQCT at tibia site.

Results At baseline, the groups were similar with respect to their age, body mass index, organ involvement, glucocorticoid dose, immunosuppressant use, serum 25OHD levels, and HR-pQCT parameters. After 24 weeks, higher 25OHD levels were observed in the JoSLE-VitD group compared to the JoSLE-PL group [31.3 (8.6) vs. 16.5 (5.8) ng/mL, $p < 0.001$]. An increase in the trabecular number [ΔTb.*N* 0.16 (0.24) vs. 0.03 (0.19) 1/mm, $p = 0.024$] and a decrease in the trabecular separation [ΔThSp −0.045 (0.067) vs. 0.001 (0.009) mm, $p = 0.017$] were found in the JoSLE-VitD group compared to the JoSLE-PL group at tibia site. No differences were observed in other structural parameters [trabecular (Tb.Th) or cortical thickness (Ct.Th)], volumetric bone mineral densities, cortical porosity, and biomechanical parameters ($p > 0.05$).

Conclusion This study suggests that cholecalciferol supplementation for 24 weeks effectively improved the bone microarchitecture parameters, mainly the trabecular number, in JoSLE patients.

Trial Registration NCT01892748

Keywords Bone density · Bone microarchitecture · Cholecalciferol · Juvenile systemic lupus erythematosus · Vitamin D

Introduction

Vitamin D plays an important role in bone health. The maintenance of calcium levels in the body is organized by a balanced system, with vitamin D acting to produce sufficient gastrointestinal absorption and inhibit the renal excretion of calcium to satisfy bone turnover [1–4].

Thus, adequate vitamin D levels are critical for bone formation [4]. In juvenile patients, a low bone mass is associated

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with a failure to achieve a peak bone mass and, consequently, may increase the fragility fracture risk [5].

Vitamin D levels are reduced in patients with systemic lupus erythematosus [6–8]. These patients have several risk factors, including the use of drugs, such as glucocorticoids (GC) and hydroxychloroquine (HCQ), as well as sun avoidance or photoprotection [9]. With regard to juvenile systemic lupus erythematosus (JoSLE), there is some evidence in the literature that they have a higher frequency of vitamin D deficiency [10, 11].

Previous studies describe a low bone mass in adult SLE patients, with or without an association with glucocorticoid use, but the role of vitamin D has not been evaluated [12, 13]. Our group demonstrated an association between vitamin D deficiency (< 20 ng/mL) and lower spine and total body bone mineral density, supporting the notion that vitamin D supplementation could be beneficial for SLE patients [10].

Recently, we demonstrated reduced parameters of density and strength, as well as a microarchitecture alteration of the cortical and trabecular bone, in JoSLE patients using high-resolution peripheral quantitative computed tomography (HR-pQCT) [14], although the effect of 25-hydroxyvitamin D (25OHD) serum levels in these parameters was not assessed [14].

There are a few vitamin D supplementation studies in systemic lupus erythematosus [15–18], but these did not evaluate the bone microarchitecture in adolescents/young patients. Therefore, the aim of this study was to evaluate the effect of cholecalciferol supplementation on the bone parameters in female JoSLE patients using HR-pQCT.

Patients and methods

This study was a randomized, double-blind, placebo-controlled study (Clinical Trial Registry NCT01892748) that was conducted at the Hospital das Clínicas da Universidade de Sao Paulo, Brazil.

Study participants

From July 2012 to August 2013, 60 JoSLE patients were followed at the Juvenile Rheumatology Outpatient Clinic, University of São Paulo. Among them, 45 female patients with JoSLE up to the age of 25 years old, who fulfilled the American College of Rheumatology (ACR) classification criteria for SLE [19] and began exhibiting symptoms before the age of 16, were consecutively selected. The exclusion criteria were a SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) score higher than 12, other autoimmune disease or infectious conditions, renal impairment (serum creatinine > 2.5 mg/dL), a history of nephrolithiasis, hypercalciuria, intestinal malabsorption, liver disease, bisphosphonates use, pregnancy at the start of the study, and refusal to participate.

Randomization and blinding

The patients were randomized into two parallel groups as follows: vitamin D supplementation (JoSLE-VitD) and placebo (JoSLE-PL). All patients and physicians were blinded to the group assignments and treatment allocations. The first group received oral cholecalciferol at 50,000 IU/week, and the second group received identical placebo tablets for 6 months. All the subjects were evaluated for clinical and laboratory parameters at baseline and after the end of the supplementation.

Adherence to vitamin D supplementation was assessed by pill counts of the returned vitamin D tablets and bi-weekly phone calls to the patients.

Assessment and treatment protocol

The demographic characteristics and clinical/laboratory/treatment data were obtained using a specific questionnaire and the electronic medical record database established in 2001 and were carried out at 1–6 months intervals. These data included the relevant clinical features for this study [diagnostic criteria, disease duration, body mass index (BMI), and medication use including the mean daily dose of glucocorticoid (GC) and the use of immunosuppressant drugs].

Race was defined based on a self-reported patient's race of two generations of their ancestors, as previously validated for the Brazilian population [20]. Those with four grandparents that were self-reported Caucasians were classified as white. The presence of mixed African and Caucasian ancestors, commonly referred to as mixed race, was classified as non-Caucasian. In the absence of the racial information for the grandparents, the participant's race was similarly determined by the race of their parents.

Photoprotection was recommended to all the patients. Both groups were allowed to continue their ongoing standard therapy [GC, hydroxychloroquine (HCQ), and immunosuppressants] and only minimal changes in the GC doses were accepted. None of the patients had taken vitamin D for at least 3 months prior to entering the study.

Laboratory evaluation

Serum levels of 25 hydroxyvitamin D (25OHD) were measured using a radioimmunoassay technique (DiaSorin, Stillwater, MN, USA), with a lower detection limit of 5 ng/mL. The normal levels of vitamin D ranged from 30 to 100 ng/mL. Serum levels lower than 30 ng/mL were classified as a vitamin D insufficiency, and serum levels lower than 20 ng/mL were classified as a vitamin D deficiency [21]. The inter-

and intra-assay coefficients of variation were 7.8 and 5.6%, respectively.

Assessment of volumetric bone mineral density and bone microarchitecture

The bone parameters were measured at tibia site using a 3D HR-pQCT device (XtremeCT, Scanco Medical AG, Brüttisellen, Switzerland). The entire volume of interest was automatically separated into the cortical and trabecular components, yielding an average bone density (Tt.vBMD), a trabecular bone density (Tb.vBMD), and a cortical bone density (Ct.vBMD) in milligram hydroxyapatite (HA)/cm^3. The mean cortical thickness (Ct.Th) was defined as the mean cortical volume divided by the outer bone surface. Using 3D HR-pQCT datasets, the metric indices of the topological features of the trabecular bone structure were directly assessed by measuring the distances in 3D space. The trabecular number (Tb.*N*) was taken as the inverse of the mean distance between the mid-axes of the observed trabecular structure. Combining the Tb.*N* and the trabecular bone volume fraction (BV/TV) allowed for the calculation of the trabecular thickness [(Tb.Th) = BV/TV divided by Tb.*N*] and the trabecular separation [(Tb.Sp) = (1 – BV/TV) / Tb.*N*]. Likewise, an advanced analysis of the cortical region provided measures of the cortical porosity [14, 22–24].

Finite element analysis

Linear μFE models were created directly from the HR-pQCT images of the tibia using the software provided by the manufacturer (Scanco Medical AG) to assess the biomechanical bone strength. The following biomechanical properties were analyzed using the microfinite element analysis (μFEA): stiffness (S, kN/mm), estimated failure load (F.ult, *N*), and apparent modulus (E.app, *N*/mm^2) [22].

The HR-pQCT precision measurement from our laboratory, expressed as the coefficient of variation, ranged from 0.25 to 1.16% for the density parameters and was 0.78–6.35% for the morphometric parameters at tibia site [14].

Safety and tolerability were also assessed at every visit. Treatment-related adverse events, reported by the patients, were collected at each visit. A treatment-related adverse event was defined as any reported event first occurring or worsening in severity during the vitamin D or placebo treatment compared to the baseline period.

Statistical analysis

The data are expressed as the mean (SD) or numbers (percentages). The continuous variables between the two groups were compared using a Student's *t* test or Mann-Whitney test. The categorical variables were compared using a chi-squared test and Fisher's exact test, as appropriate. Statistical significance was defined as a two-sided p value < 0.05.

Ethics committee approval

The participants, or their legal guardians, signed an informed consent, and the study was approved by the Local Ethics Committee.

Results

Forty-five female subjects were initially screened for participation. These patients were randomly assigned to the JoSLE-VitD group ($n = 22$) or the JoSLE-PL group ($n = 23$). Five patients withdrew for personal reasons or were lost in the follow-up. Therefore, 40 subjects completed the trial and were analyzed. The compliance to supplementation was similar in both groups (85 vs. 75%, $p = 0.69$).

The baseline parameters of both groups are described in Table 1. The anthropometric, clinical, and laboratory disease parameters were similar in the JoSLE-VitD and JoSLE-PL groups ($p > 0.05$). All patients included in the study had already reached menarche. No difference was observed in the JoSLE-VitD vs. JoSLE-PL groups regarding menarche age ($p = 0.17$), estradiol serum levels ($p = 0.23$), breast Tanner stage ($p = 1.00$), and pubic Tanner stage ($p = 0.97$). Also, no difference was observed between JoSLE-VitD and JoSLE-PL groups regarding oral contraceptives use (35 vs. 25%, $p = 0.503$).

In relation to ACR classification criteria for SLE fulfilled for each patient at the time of diagnosis, the two groups (JoSLE-VitD vs. JoSLE-P) were similar, as following described: serositis (80 vs. 80%, $p = 1.00$), oral ulcers (15 vs. 10%, $p = 0.643$), arthritis (90 vs. 95%, $p = 0.560$), photosensitivity (85 vs. 100%, $p = 0.075$), hematological involvement (50 vs. 30%, $p = 0.206$), renal involvement (15 vs. 25%, $p = 0.442$), anti-nuclear antibodies (95 vs. 95%, $p = 1.00$), immunologic criteria (100 vs. 100%, $p = 1.00$), neurologic disorder (10 vs. 10%, $p = 1.00$), malar rash (80 vs. 75%, $p = 0.714$), and discoid rash (5 vs. 10%, $p = 0.560$). At the study entry, no differences were observed in JoSLE-VitD vs. JoSLE-PL groups regarding skin manifestations (25 vs. 30%, $p = 0.801$), as described in Table 1.

The mean 25OHD serum level at baseline was 19.1 (6.4) in the JoSLE-VitD group vs. 19.5 (4.5) ng/mL in the JoSLE-PL group ($p = 0.82$) (Table 2). The overall prevalence of vitamin D insufficiency in all the JoSLE patients at baseline was 95%.

During the study period, only two patients required minimal changes in treatment. One patient in the JoSLE-VitD group needed an increase in the prednisone dose from 5 to

Table 1 Baseline parameters of JoSLE patients according to treatment group

Parameters	JoSLE-VitD $N = 20$	JoSLE-PL $N = 20$	p
Age, years	18.7 (3.4)	19.3 (3.3)	0.619
Menarche age, years	13.2 (1.0)	12.6 (1.3)	0.174
Race			
Caucasian (%)	70	75	0.501
Season			
Winter (%)	45	40	0.766
Spring (%)	40	35	0.751
Summer (%)	15	25	0.442
Weight (kg)	56.21	59.92	0.393
Height (cm)	156.43	156.45	0.993
Body mass index, kg/m^2	22.6 (4.2)	24.1 (5.3)	0.283
Breast Tanner stage > 2, (%)	95	100	1.000
Pubic Tanner stage > 2, (%)	95	85	0.974
Skin involvement (%)	25	30	0.801
Polyarthritis (%)	5	5	1.000
Hematological (%)	45	55	0.647
Renal disease (%)	10	20	0.424
Glucocorticoid current use (%)	80	85	0.686
Glucocorticoid current dose, mg/day	11.90 (9.4)	14.10 (13.6)	0.614
Oral contraceptives current use (%)	35	25	0.503
Hydroxychloroquine current use (%)	80	85	0.636
Immunosuppressant current use (%)	85	75	0.514
Azatioprine (%)	65	50	0.350
Mycophenolate mofetil (%)	15	25	0.442
Methotrexate (%)	15	15	1.000
Serum estradiol, pg/mL	107.4 (111.3)	70.7 (47.1)	0.231
Serum calcium, mg/dL	9.4 (0.5)	9.1 (0.5)	0.121
Serum creatinine, mg/dL	0.64 (0.1)	0.70 (0.2)	0.222
Serum PTH, pg/mL	33.78 (15.6)	28.6 (10.7)	0.233

Data are expressed as the mean (SD) and percentage

JoSLE juvenile-onset systemic lupus erythematosus, *JoSLE-VitD* treatment group that received oral cholecalciferol 50,000 IU/week, *JoSLE-PL* placebo group, *PTH* parathormone

Table 2 Hydroxyvitamin D (25OHD) serum levels at baseline and after 6 months of intervention in JoSLE patients according to treatment group

	JoSLE-vitD $N = 20$	JoSLE-PL $N = 20$	p
Baseline			
25OHD, ng/mL	19.1 (6.4)	19.5 (4.5)	0.821
25OHD < 30 ng/mL (%)	90	100	0.154
25OHD < 20 ng/mL (%)	60	45	0.354
24 weeks			
25OHD, ng/mL	31.3 (8.6)	16.5 (5.8)	< 0.001
25OHD < 30 ng/mL (%)	30	100	< 0.001
25OHD < 20 ng/mL (%)	10	75	< 0.001

Data are expressed as the mean (SD) or percentage

10 mg/day due to articular activity refractory to a non-steroidal anti-inflammatory drug. In another patient from the JoSLE-PL group, prednisone was increased from 2.5 to 10 mg/day, also due to articular activity.

Concerning the HR-pQCT parameters at baseline, no differences were observed between the JoSLE-VitD and JoSLE-PL groups in the volumetric bone mineral density, structural parameters, cortical porosity, and finite element analysis variables at tibia site ($p > 0.05$) (Table 3).

After 24 weeks of supplementation, the JoSLE-VitD patients presented higher levels of 25OHD than those in the JoSLE-PL group [31.3 (8.6) vs. 16.5 (5.8) ng/mL, $p < 0.001$]. Moreover, in the JoSLE-VitD group, 70% of the patients reached 25OHD levels > 30 ng/mL compared to 0% in the JoSLE-PL group ($p < 0.001$) (Table 2).

Table 3 Density, structural, cortical porosity, and strength parameters analyzed using HR-pQCT at distal tibia in JoSLE patients in baseline and after 24 weeks of oral cholecalciferol 50,000-IU/week supplementation

Tibia	JoSLE-VitD	JoSLE-PL	*p*
	N = 20	*N* = 20	
Volumetric bone density			
Tt.vBMD, mg HA/ccm			
Baseline	291.7 (61.9)	309.7 (62.4)	0.364
24 weeks	291.6 (62.9)	309.6 (61.3)	0.368
Δ	−0.16 (6.9)	−0.18 (6.7)	0.990
Tb.vBMD, mg HA/ccm			
Baseline	162.1 (35.2)	166.8 (42.0)	0.706
24 weeks	161.8 (36.0)	166.5 (43.9)	0.715
Δ	−0.29 (7.0)	−0.29 (4.4)	0.995
Ct.vBMD, mg HA/ccm			
Baseline	903.5 (35.8)	911.7 (51.2)	0.562
24 weeks	903.7 (36.3)	910.4 (49.1)	0.662
Δ	0.22 (13.9)	−1.31 (15.3)	0.643
Structural parameters			
Tb.*N*, 1/mm			
Baseline	1.73 (0.32)	1.90 (0.34)	0.111
24 weeks	1.89 (0.32)	1.93 (0.39)	0.912
Δ	0.16 (0.24)	0.03 (0.19)	**0.024**
Tb.Th, mm			
Baseline	0.078 (0.016)	0.075 (0.019)	0.558
24 weeks	0.075 (0.015)	0.075 (0.020)	0.993
Δ	−0.003 (0.605)	0.000 (0.007)	0.114
Tb.Sp, mm			
Baseline	0.516 (0.108)	0.462 (0.100)	0.107
24 weeks	0.471 (0.098)	0.463 (0.100)	0.800
Δ	−0.045 (0.067)	0.001 (0.009)	**0.017**
Ct.Th, mm			
Baseline	1.103 (0.296)	1.180 (0.330)	0.772
24 weeks	1.104 (0.305)	1.194 (0.318)	0.571
Δ	0.001 (0.443)	0.013 (0.465)	0.359
Cortical porosity			
Ct.Po, %			
Baseline	0.0098 (0.0013)	0.0092 (0.0015)	0.210
24 weeks	0.0095 (0.0012)	0.0095 (0.0015)	0.930
Δ	−0.0020 (0.0078)	0.0002 (0.0013)	0.127
Finite element analysis			
Stiffness, *N*/*k*m			
Baseline	179,806 (33087)	189,520 (44202)	0.456
24 weeks	180,371 (33926)	187,599 (42698)	0.573
Δ	564 (14540)	−1921 (21792)	0.687
Estimated failure load, *N*			
Baseline	8581 (1466)	9068 (1936)	0.396
24 weeks	8625 (1499)	8977 (1889)	0.535
Δ	43 (629)	90 (833)	0.585
Apparent modulus, N/mm^2			
Baseline	2388 (563)	2472 (646)	0.677
24 weeks	2392 (517)	2431 (624)	0.839
Δ	3 (342)	−41 (420)	0.721

Data are expressed as the mean (SD)

Statistically significant, $p < 0.05$

HR-pQCT high-resolution peripheral quantitative computed tomography, *JoSLE* juvenile-onset systemic lupus erythematosus, *Tt.vBMD* total bone density, *Tb.vBMD* trabecular bone density, *Ct.vBMD* cortical bone density, *HA* hydroxyapatite, *Tb.N* trabecular number, *Tb.Th* trabecular thickness, *Tb.Sp* trabecular separation, *Ct.Th* cortical thickness, *Ct.Po* cortical porosity

Regarding bone microarchitecture, after 24 weeks in the JoSLE-VitD group, a higher increase in the trabecular number at tibia site was detected compared to the JoSLE-PL group [ΔTb.*N* = 0.16 (0.24) vs. 0.03 (0.19), $p = 0.024$]. Moreover, after 24 weeks, a decrease in the trabecular separation at tibia site was observed in the JoSLE-VitD group [ΔTb.Sp = −0.045 (0.067) vs. 0.001 (0.009), $p = 0.017$]. Regarding the volumetric bone mineral density, there were no differences in the two groups after supplementation (Table 3).

After 24 weeks of vitamin D supplementation, no differences were found comparing the two groups regarding the

cortical porosity and the finite element analysis parameters ($p > 0.05$) at tibia site (Table 3).

The supplementation was well tolerated with no serious side effects recorded in the two groups. Six patients (four in the intervention group and two in the placebo group) reported epigastric pain but without the discontinuation of therapy.

Discussion

This study demonstrated, for the first time, that vitamin D supplementation (cholecalciferol 50,000 IU/week for 6 months) in juvenile lupus patients improved the bone microarchitecture parameters at tibia site using HR-pQCT.

At baseline, the JoSLE patient groups were comparable with respect to weight, BMI, hydroxychloroquine, and glucocorticoid treatment. In fact, weight can be an important confounding factor since 25OHD is fat soluble and lower levels of this hormone in overweight individuals may be a consequence of a larger volume of this vitamin in body fat compartments [25, 26].

Furthermore, glucocorticoids can influence vitamin D serum levels and counteract some 25OHD effects [26]. Glucocorticoids (GCs) inhibit calcium absorption in the gut by opposing the action of vitamin D and decrease specific calcium channels. GCs also inhibit renal tubular calcium reabsorption [27].

In addition to the action of glucocorticoids (GCs) on vitamin D, lupus patients have several factors that contribute to vitamin D deficiency including avoiding sun exposure [28], anti-vitamin D antibodies [29], and the use of medication. It is demonstrated that chronic anti-convulsant therapy results in the accelerated conversion of vitamin D and its active metabolite, 25-hydroxycholecalciferol, to inactive metabolites by inducing liver microsomal enzymes [30]. Moreover, the usual SLE treatment impacts active vitamin D since hydroxychloroquine inhibits the conversion of 25OH vitamin D to its active form 1,25(OH)2 vitamin D [31].

Another advantage of this study was that the treatment of the JoSLE patients remained stable during the 6-month follow-up, allowing for a more accurate analysis of the effect of vitamin D supplementation in this rheumatic condition.

Vitamin D is relevant for bone health and calcium homeostasis [1–4]. However, its action in bone metabolism seems to be dose dependent. A meta-analysis of controlled randomized trials shows that oral vitamin D supplementation between 700 to 800 IU/day appears to reduce the risk of hip and non-vertebral fractures in elderly persons. An oral vitamin D dose of 400 IU/day is not sufficient for fracture prevention [27]. In the present study, the vitamin D dose used was 50,000 IU/week, which is in accordance with Holick et al., showing that after 8 weeks, there was an increase in vitamin serum levels in most individuals [32]. The "Endocrine Society Clinical Practice Guideline to Evaluation, Treatment, and Prevention of Vitamin D Deficiency" recommends that the 25(OH)D blood level should be above 30 ng/mL to maximize vitamin D's effect on calcium, bone, and muscle metabolism in children and adults [21]. Petri et al. previously conducted a study showing the benefits of supplementation with 50,000-UI vitamin D2 weekly with Ca/D3 200 UI twice daily in SLE patients with low levels of 25-hydroxyvitamin D (< 40 ng/mL) in decreasing SLEDAI scores, but these authors did not analyze the bone parameters [17].

Vitamin D levels declined over the course of the study, which could be due to the intra-assay variability of the 25OHD measurement, as well as the season of the year in which vitamin D was evaluated. However, there was no significant difference between the two groups (JoSLE-PL baseline vs. JoSLE-PL after 24 weeks, $p = 0.08$) Table 2.

Our study demonstrated that vitamin D supplementation might be associated with improving trabecular bone, as reflected by the significant increase in the trabecular number (Tb.*N*) and a decrease in the trabecular separation (Tb.Sp) at tibia site. In contrast, a cross-sectional study in a cohort of healthy individuals from Alberta, Canada, demonstrated that medium/high serum levels of 25OHD were associated with a low trabecular number at the tibia. The authors suggest that their findings could be related to an increase of trabecular thickness with a better microarchitecture. However, the Canadian study had some limitations, including a wide variation in the duration of the participation of each subject in the program and a convenience cohort comprising people who were all taking high levels of supplementation [23]. Additionally, the present study comprises young adult patients, and the vitamin D supplementation could have a different effect by increasing the trabecular number in the non-mature skeleton.

The relevance of a microarchitecture analysis using HR-pQCT is well documented [33–35]. The data from literature demonstrate that bone density does not explain all fragility fractures. A bone-quality evaluation using the microarchitecture parameters (bone trabecular number, thickness, and connectivity) is fundamental to better understand bone impairment [36, 37]. In fact, this method separately evaluates the trabecular and cortical bone compartments, as well as the strength proprieties, providing additional information to better understand bone quality [22]. This is mainly important in rheumatologic conditions because fragility fractures are more prevalent, even in children and young adults, secondary to several factors, such as inflammation, vitamin D deficiency, and glucocorticoid use [14, 38, 39]. It is particularly notable that an impairment of the bone trabecular microarchitecture correlates with glucocorticoid dose use [40]. This knowledge could better orient future target therapies. Additionally, previous data suggests that an optimal serum 25 (OH) vitamin D concentration may lead to a further reduction in the bone loss at the hip in patients on bisphosphonates [41], reinforcing the

importance of the maintenance optimal serum levels of vitamin D in these patients.

In conclusion, vitamin D replacement is well tolerated and may improve bone microarchitecture in patients with juvenile-onset systemic lupus erythematosus. A therapeutic intervention may be recommended for patients with deficient levels of 25OHD. However, large multicenter trials are still necessary to better assess these findings.

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Compliance with ethical standards The participants, or their legal guardians, signed an informed consent, and the study was approved by the Local Ethics Committee.

Conflicts of interest None.

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