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Original article

Feasibility of measurement of bone turnover markers in female patients with systemic lupus erythematosus



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ABSTRACT

Objective: To investigate the feasibility of bone turnover markers for the assessment of bone metabolism in patients with systemic lupus erythematosus, according to the guidelines of the International Osteoporosis Foundation and the International Federation of Clinical Chemistry and Laboratory Medicine.

Methods: The study included 43 female systemic lupus erythematosus patients. Serum procollagen type I N propeptide, C-terminal telopeptide of type I collagen, osteocalcin, parathyroid hormone, 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3, anti-cardiolipin, anti-dsDNA, and anti-nucleosome levels were measured.

Results: Procollagen type I N propeptide and C-terminal telopeptide of type I collagen levels were elevated in systemic lupus erythematosus patients aged >45 in comparison to those aged <45, although with borderline significance ($p=0.05$, respectively). Correlations were found between bone turnover markers: the strongest being between procollagen type I N propeptide and osteocalcin ($\tau=0.69$, $p<0.05$). Procollagen type I N propeptide and osteocalcin were found to be associated with parathyroid hormone ($\tau=0.3$, $\tau=0.29$, respectively, $p<0.05$). Age correlated with procollagen type I N propeptide ($\tau=0.23$, $p<0.05$). Elevated procollagen type I N propeptide was found more frequently than elevated osteocalcin or C-terminal telopeptide of type I collagen, both in patients aged <45 ($p=0.001$) and >45 ($p<0.001$). No significant difference in procollagen type I N propeptide, osteocalcin or C-terminal telopeptide of type I collagen levels was found with respect to season, neither in the entire systemic lupus erythematosus group nor in the under-45 or over-45 groups. Previous glucocorticoid treatment was not associated with difference in bone turnover markers.

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Conclusions: Increased bone turnover markers in systemic lupus erythematosus appear to predominantly reflect the pattern of bone remodeling related to age. Increased procollagen type I N propeptide is expected to be the most frequent outcome among bone turnover markers. Better diagnoses of bone disturbances with bone turnover markers performed in accordance with international reference standards need to be included in the approach to systemic lupus erythematosus patients, in addition to bone mineral density assessment.

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Viabilidade da mensuração de marcadores de remodelação óssea em mulheres com lúpus eritematoso sistêmico

R E S U M O

Palavras-chave:

Remodelação óssea
Lúpus eritematoso sistêmico
Procolágeno
Osteocalcina
Vitamina D

Objetivo: Investigar a viabilidade dos marcadores de remodelação óssea (MRO) na avaliação do metabolismo ósseo em pacientes com lúpus eritematoso sistêmico (LES), de acordo com as diretrizes da International Osteoporosis Foundation e da International Federation of Clinical Chemistry and Laboratory Medicine.

Métodos: O estudo incluiu 43 pacientes do sexo feminino com LES. Foram medidos os níveis séricos de propeptídeo N-terminal do procolágeno tipo I (PINP), telopeptídeo C-terminal do colágeno tipo I (CTX), osteocalcina, HPT, 25(OH)D, anticorpos anticardiolipina, antidsDNA e antinucleossomo.

Resultados: Os níveis de PINP e CTX estavam elevados em pacientes com LES com idade >45, em comparação com aqueles com idade <45 anos, embora com significância estatística limítrofe ($p=0,05$). Foram encontradas correlações entre os MRO: a mais forte foi entre o PINP e a osteocalcina ($\tau=0,69$, $p<0,05$). Encontrou-se que o PINP e a osteocalcina estão correlacionados com o HPT ($\tau=0,3$, $\tau=0,29$, respectivamente, $p<0,05$). A idade estava correlacionada com o PINP ($\tau=0,23$, $p<0,05$). Valores elevados de PINP foram encontrados em maior frequência do que valores elevados de osteocalcina ou CTX, tanto em pacientes com idade <45 ($p=0,001$) quanto >45 ($p<0,001$). Não houve diferença estatisticamente significativa nos níveis de PINP, osteocalcina ou CTX com relação à estação do ano, nem em todo o grupo de pacientes com LES, nem naqueles com mais ou menos de 45 anos. O uso prévio de glucocorticoides não esteve associado a diferenças nos MRO.

Conclusões: O aumento nos MRO no LES parece refletir predominantemente o padrão de remodelação óssea relacionado com a idade. Pode-se esperar que o PINP aumentado seja o desfecho mais comumente encontrado entre os MRO. É necessário incluir melhores diagnósticos de distúrbios ósseos com MRO, feitos de acordo com as normas internacionais de referência, na abordagem de pacientes com LES, além de avaliar a densidade mineral óssea.

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Introduction

In 2011, the International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) stated that assessment of a marker of bone formation, serum procollagen type I N propeptide (PINP), and a marker of bone resorption, serum C-terminal telopeptide of type I collagen (CTX), provided reference parameters for bone turnover markers (BTMs) in clinical studies.¹ Increased serum concentration of BTMs may predict fracture risk in postmenopausal women, independent of bone mineral density (BMD) measurements.¹ High bone turnover may be associated not only with bone loss, resulting in a low BMD, but also with the deterioration of bone architecture not detected in bone mass assessment.¹ Bone strength is determined by both BMD and bone quality.² Apart from BMD, bone quality depends mainly on micro-architecture and bone turnover.²

Osteoporosis, and consequently indication for treatment, is diagnosed either clinically on the basis of fractures following low energy trauma, or in the pre-fracture stage by assessment of clinical risk factors associated with densitometry and bone metabolism.³

In a recent study of Mak et al. conducted on 45 patients with systemic lupus erythematosus (SLE), a high 10-year fracture risk was found in 16% of patients and in 2% of healthy controls.⁴ Demonstration of a high (>20%) individual 10-year absolute fracture risk is the criterion for initiation of pharmacological treatment.³ As pregnancy is an absolute contraindication to dual X-ray absorptiometry (DXA) in the assessment of BMD, and female SLE patients of child-bearing age may be apprehensive of densitometry, compliance might be limited. Under such circumstances, BTM analysis would appear to be a practical alternative, as samples of blood are easily collected and the procedure is relatively noninvasive.¹ BTMs have been used in clinical researches for many years,

but there is still a need for stronger evidence on their usage in SLE.

Due to the sparse evidence addressing PINP and CTX in lupus patients, the aim of the study was to investigate BTMs, including those recommended by IOF-IFCC, and to assess their feasibility as clinical markers in patients with SLE in remission. To our knowledge, this is the first study concerning the simultaneous assessment of PINP and CTX, in female patients with SLE. As no data regarding the newer biochemical parameters of bone metabolism has so far been published, osteocalcin (OC), parathyroid hormone (PTH) and vitamin D levels are also investigated. Since atraumatic metatarsal stress fractures have been reported to occur in SLE, particularly in association with the antiphospholipid syndrome, anti-cardiolipin (aCL) antibodies are also investigated.⁵

Materials and methods

The study included a limited number of 43 female patients with SLE, aged 27–75 (mean 46.09 ± 12.87). The diagnosis of SLE was based on the classification criteria for SLE updated in 1997 by the American College of Rheumatology.⁶ The duration of SLE ranged from 2 to 24 years (mean 10.32 ± 5.47 years). At the time of the study, the entire group of SLE patients were found to have a disease activity <6 , as indicated by SLEDAI.⁷ Exclusion criteria for the SLE patients in this study were pregnancy; the presence of disease known to affect bone turnover not related to SLE, such as chronic renal failure, chronic liver disease, inflammatory bowel disease, hyperparathyroidism, hypogonadism; any medication known to affect bone turnover with the exception of calcium or vitamin D supplements; glucocorticoids or the drugs used for the treatment of SLE. Any treatment with prednisolone or equivalent, ≥ 5 mg/day in the preceding 6 months, was recorded. The study was approved by the local Ethics Committee.

The studied individuals were inhabitants of the Lodz region, which is located between the 51° and 52° northern latitudes. The solar spectrum in absolute units of the area measured on June 30, 2010, 10.47 GMT is given in detail elsewhere.⁸ As the study population was located in the northern hemisphere, the seasonal variation of vitamin D status was determined thus: the cold season was defined as the period between November and April while the warm one included the remaining months.

Serum was collected in the morning and stored at -70°C until assayed. PINP, N-MID Osteocalcin, B-Cross Laps (CTX), PTH and 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3 (25(OH)D) were measured with reagents, including calibration and control sera, obtained from Roche Diagnostic, Mannheim, Germany. Electrochemiluminescence immunoassay (ECLIA) was performed using an Elecsys 2010 automated analyzer. For the evaluation of bone formation, PINP and serum OC concentrations were measured automatically using chemiluminescence immunoassays (Elecsys; Roche Diagnostics). According to the manufacturer's guidelines, the normal range of serum concentration of PINP is <30 ng/mL in individuals aged <45 , and <37 ng/mL in those aged >45 . The normal range

of serum concentration of OC is <31 ng/mL in subjects aged <45 , and <41 ng/mL in those aged >45 .

For the evaluation of bone resorption, the concentration of serum CTX was assayed automatically using chemiluminescence immunoassay. The normal range of serum concentration of CTX is known to be <0.3 ng/mL at age <45 , and <0.6 ng/mL at age >45 . PTH (pg/mL) was measured in a routine procedure. Serum 25(OH)D concentrations were determined by immunochemiluminescence (Elecsys, Roche Diagnostics), controlled and certified by The International Vitamin D Proficiency – Testing Program (DEQAS). Vitamin D status was defined as follows: deficiency <20 ng/mL (<50 nmol/L), insufficiency 20 – 29 ng/mL (50 – 72.5 nmol/L) and recommended range 30 – 80 ng/mL (72.5 – 200 nmol/L).⁹

Autostat II ACA IgM and IgG kits were used to detect aCL antibodies (Hycor, USA), while ELISA QUANTA Lite® dsDNA kit (INOVA, USA) and Nucleosome IgG ELISA kit (D-tek, Belgium) were used for assessment of anti-dsDNA and anti-nucleosome (aNuc) antibodies, respectively. The levels of anti-dsDNA, aNuc and aCL antibodies were variables in the assessment of lupus activity.

Statistical analysis was performed using Statistica software version 10.0 (Statsoft, Poland). As the distribution of the measured variables was not Gaussian, according to the Shapiro–Wilk test, the nonparametric tests were used. Mann–Whitney U test was employed to compare variables between two independent groups. The Kendall tau rank correlation coefficient was used to estimate correlation and validity, and the Cochran's Q test was employed to estimate the reliability of the results. The Fisher's exact test was used in the assessment of the significance of the association between categorical data, i.e. results of BTMs out of the reference range, according to age, and other studied parameters, i.e. renal involvement, menopause, any treatment with prednisolone or equivalent, ≥ 5 mg/day in the preceding 6 months, and vitamin D deficiency. In descriptive statistics means and standard deviations were used. In all calculations, $p < 0.05$ was regarded as statistically significant.

Results

Comparison of BTMs, PTH, 25(OH)D, aCL, anti-DNA and aNuc antibodies obtained in patients with SLE according to age <45 and >45 are shown in Table 1.

PINP and CTX levels were elevated in SLE patients aged >45 in comparison to those at the age <45 , however, only with borderline significance (42.4 ± 43.8 vs. 48.8 ± 29.1 ng/mL; 0.2 ± 0.1 vs. 0.3 ± 0.2 ng/mL; $p = 0.05$, respectively).

In SLE, all BTMs were significantly positively correlated one with another, with the strongest correlation being between PINP and OC ($p < 0.05$) (Table 2).

PINP and OC were also correlated with PTH ($p < 0.05$). Age was correlated with PINP. Anti-dsDNA level was correlated with aNuc and aCL IgG antibodies ($p < 0.05$).

In a subgroup of SLE patients aged <45 , 3 (14.28%) patients had a CTX level elevated above the recommended range (>0.3 ng/mL); one patient (4.76%) displayed an elevated OC level (>31 ng/mL), and 9 (42.85%) patients displayed an increased PINP concentration (>30 ng/mL). No association

Table 1 – Procollagen type I N propeptide (PINP), osteocalcin (OC), C-terminal telopeptide of type I collagen (CTX), parathyroid hormone (PTH), 25(OH)D, anti-cardiolipin (aCL), anti-dsDNA and anti-nucleosome (aNuc) antibodies in patients with systemic lupus erythematosus (SLE).

Parameter	SLE		p
	<45 years old N = 21	>45 years old N = 22	
PINP [ng/mL]	42.4 ± 43.8	48.8 ± 29.1	0.05 ^a
OC [ng/mL]	14.8 ± 9.3	19.2 ± 13.3	0.16
CTX [ng/mL]	0.2 ± 0.1	0.3 ± 0.2	0.05 ^a
PTH [pg/mL]	37.5 ± 20.2	45.6 ± 26.8	0.23
25(OH)D [ng/mL]	27.3 ± 7.0	31.0 ± 11.6	0.29
aCL IgM [U/mL]	16.0 ± 13.6	10.1 ± 11.9	0.08
aCL IgG [U/mL]	24.2 ± 24.1	21.6 ± 19.0	0.94
Anti-dsDNA [IU/mL]	311.9 ± 397.0	315.0 ± 382.9	0.77
Anti-Nuc [U/mL]	1.2 ± 1.4	0.9 ± 0.9	0.81
SLE duration [years]	8.4 ± 5.4	12.3 ± 4.9	0.02

^a Mann-Whitney U test.

was found between results of BTMs out of the reference range, according to age, and renal involvement (2/21; 9.52%), menopause (0; 0%), any treatment with prednisolone or equivalent, ≥ 5 mg/day in the preceding 6 months (13/21; 61.9%) and vitamin D deficiency (2/21; 9.52%) in a subgroup of SLE patients aged <45.

In the subgroup of SLE patients aged >45, 3 (13.63%) patients were found to have an increased CTX level (>0.6 ng/mL); one patient (4.54%) had an elevated OC level (>41 ng/mL), and 13 (59.09%) patients had an increased PINP concentration (>0.6 ng/mL). No association was found between results of BTMs out of the reference range, according to age, and renal involvement (2/22; 9.09%), menopause (16/22; 72.72%), any treatment with prednisolone or equivalent, ≥ 5 mg/day in the preceding 6 months (13/22; 59.09%) and vitamin D deficiency (2/22; 9.09%) in a subgroup of SLE patients aged >45.

According to an analysis of the differences between the frequencies of elevated results, i.e. between those inside and those outside the normal range by the Cochran's Q test, increases in PINP were significantly more common than elevations in OC and CTX in all subjects: both those aged <45

($p = 0.001$) and those aged >45 ($p < 0.001$). The results are shown in Fig. 1.

Measurements in the warm and cold seasons did not reveal any significant difference in levels of PINP (38.58 ± 27.98 ng/mL vs. 51.39 ± 42.17 ng/mL, respectively), OC (16.49 ± 13.18 vs. 17.59 ± 10.51 ng/mL) or CTX (0.26 ± 0.22 vs. 0.27 ± 0.17 ng/mL) in SLE patients. In addition, no significant difference between warm and cold was found in the SLE subgroup aged <45 for PINP (26.86 ± 11.89 vs. 56.6 ± 57 ng/mL), OC (11.31 ± 3.79 vs. 18.03 ± 11.6 ng/mL) or CTX (0.17 ± 0.07 vs. 0.23 ± 0.11 ng/mL), nor in those aged >45 with PINP (51.58 ± 35.21 vs. 46.98 ± 25.57 ng/mL), OC (22.23 ± 17.44 vs. 17.21 ± 9.96 ng/mL), and CTX (0.36 ± 0.29 vs. 0.31 ± 0.21 ng/mL).

No significant difference was revealed between SLE patients not given steroid treatment and those treated within the previous 6 months with glucocorticoids at a dosage ≥ 5 mg prednisolone daily, or equivalent, with regard to levels of PINP (47.97 ± 45.52 vs. 41.72 ± 17.72 ng/mL, respectively), OC (17.43 ± 13.86 vs. 16.36 ± 7.94 ng/mL), and CTX (0.27 ± 0.22 vs. 0.29 ± 0.13 ng/mL). Similarly, no relationship was observed in those aged <45: PINP (45.53 ± 54.72 vs. 36.67 ± 18.78 ng/mL);

Table 2 – Correlations of bone turnover markers, PTH, 25(OH)D, aCL, anti-DNA and aNuc antibodies obtained in patients with SLE.

Variable	PINP	OC	CTX	PTH	25(OH)D	aCL IgM	aCL IgG	Anti-dsDNA	Anti-Nuc	SLE duration	Age
PINP	–	0.69 ^a	0.50 ^a	0.30 ^a	0.04	0.15	0.11	0.02	–0.04	0.12	0.23 ^a
OC	0.69 ^a	–	0.48 ^a	0.29 ^a	–0.01	0.05	0.06	0.06	–	0.12	0.21
CTX	0.50 ^a	0.48 ^a	–	0.11	–0.01	0.07	0.02	0.16	0.18	0.15	0.18
PTH	0.30 ^a	0.29 ^a	0.11	–	0.09	0.10	–0.04	–0.02	–0.08	0.09	0.11
25(OH)D	0.04	–0.01	–0.01	0.09	–	0.20 ^a	0.15	0.07	0.05	–0.04	0.06
aCL IgM	0.15	0.05	0.07	0.10	0.20 ^a	–	0.14	0.19	0.09	–0.05	–0.09
aCL IgG	0.11	0.06	0.02	–0.04	0.15	0.14	–	0.30 ^a	0.03	0.24	0.10
Anti-dsDNA	0.02	0.06	0.16	–0.02	0.07	0.19	0.30 ^a	–	0.43 ^a	0.16	–0.03
Anti-Nucleosome	–0.04	–0.16	0.18	–0.08	0.05	0.09	0.03	0.43 ^a	–	0.12	–0.12
SLE duration	0.12	0.12	0.15	0.09	–0.04	–0.05	0.24	0.16	0.12	–	0.31 ^a
Age	0.23	0.21	0.18	0.11	0.06	–0.09	0.10	–0.03	–0.12	0.31 ^a	–

^a $p < 0.05$ according to Kendall τ rank correlation coefficient.

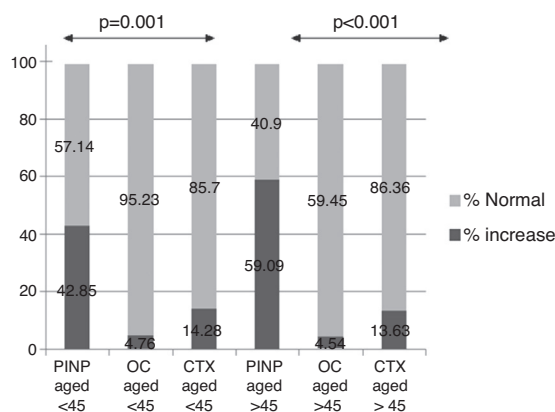


Fig. 1 – Increased outcomes of procollagen type I N propeptide were found significantly more frequently in all systemic lupus erythematosus patients both in those aged <45 and those aged >45 ($p = 0.001$ and $p < 0.001$, respectively; Cochran's Q test). Results are displayed as percentage.

OC (14.83 ± 10.58 vs. 14.23 ± 7.62 ng/mL); CTX (0.19 ± 0.11 vs. 0.2 ± 0.06 ng/mL); nor in those aged >45: PINP (50.41 ± 36.18 vs. 48.79 ± 15.08 ng/mL); OC (20.03 ± 15.55 vs. 19.35 ± 8.21 ng/mL); or CTX (0.35 ± 0.29 vs. 0.4 ± 0.1 ng/mL).

Discussion

Despite the fact that serum PINP and CTX were recommended in 2011 to be included in all future studies of osteoporotic fracture risk or treatment as reference markers of bone resorption and formation, there is a lack of studies addressing their role in SLE.¹ Three studies addressing BTMs in SLE have so far been conducted.¹⁰⁻¹² However, most of the investigated BTMs are not included in the IOF-IFCC recommendations, such as procollagen type I C propeptide (PICP), OC, alkaline phosphatase, carboxy-terminal cross-linking telopeptide of type I collagen (ICTP), and deoxypyridoline excretion.¹⁰⁻¹² Korczyńska et al. report a significant increase of CTX in SLE patients, and Bhattoa et al. note a significant decrease in CTX levels between baseline and all subsequent visits after one-year transdermal estrogen replacement therapy in 15 osteopenic postmenopausal SLE patients.^{11,12} Due to sparse evidence, it is not possible to perform any meta-analyses of literature data or draw any convincing conclusions of their feasibility in lupus. However, an understanding of BTMs should be rooted in the knowledge of the roles played by them in bone metabolism and the clinical picture of SLE.^{13,14}

An imbalance in bone turnover results in changes in bone structure, strength and mass.^{13,14} Bone mass can be easily measured by DXA, in contrast to bone structure and strength, which are difficult to assess *in vivo*.^{13,14} BTMs represent a promising tool in the diagnosis of imbalances in bone turnover measurement.^{13,14} However, international reference standards of measurements are required, as reference ranges are not universally defined, and in addition, it is difficult to determine precise thresholds or cut-off values

for practical use in individual patients.^{1,14} In our study, the reference ranges according to age given by the manufacturer were employed. We have found positive correlations among the levels of all three BTMs, with the strongest correlation between PINP and OC; PTH was also found to correlate with PINP and OC, and age correlated with PINP. Of all the BTMs tested, PINP, a bone formation marker, was the one most frequently found to increase. The observed increase in PINP level in relation to age seems to stand in sharp contrast to the fact that PINP is a marker of bone formation, although it is important to remember that PINP provides information regarding the rate of bone remodeling for the entire skeleton.¹⁵ Since a molecule of PINP is enzymatically cleaved off and secreted into the extracellular space after synthesis of procollagen by osteoblasts, PINP level quantitatively reflects the amounts of newly synthesized collagen.¹³ However, as only the simultaneous formation and resorption of bone determines the rate of bone remodeling at one point in time *in vivo*, the elevation of serum PINP in SLE appears to reflect the continuous process of bone formation intended to counter bone loss.

It may be speculated that PINP level should be decreased in SLE as a result of glucocorticoid treatment. Baker-LePain et al. report that serum OC, another bone formation marker, is negatively correlated with glucocorticoid dose in childhood-onset systemic lupus.¹⁶ Accordingly, Uaratanawong et al. note that BMD measurements were found to be significantly lower in premenopausal SLE patients who had corticosteroid treatment than those who had not.¹⁷ They also identified a negative correlation between BMD and corticosteroid therapy, but not with disease activity.¹⁷ In pre-menopausal Mexican women with SLE, chronic disease damage, low body mass index, and cumulative corticosteroid dose were found to be risk factors for low BMD.¹⁸ On the other hand, Bhattoa et al. found that bone mass in men with SLE was not decreased despite having undergone corticosteroid therapy, and biochemical markers of bone turnover were within the reference range.¹² In accordance with the study of Bhattoa et al. our present comparison of PINP with respect to age and glucocorticoid use within previous 6 months did not reveal any significant difference in female patients. However, our group of SLE patients was small and only Caucasian females were enrolled in the study protocol. The present study also assesses relationships with glucocorticoid treatment according to a dichotomic, weak variable: no treatment or any treatment in the preceding 6 months with prednisolone or equivalent at a dosage of ≥ 5 mg daily. Thus, it is difficult to univocally state that PINP level in SLE is not related to glucocorticoid treatment and studies on larger group of patients are required.

Nevertheless, the key limitation of our study is the lack of BMD measurement. As a result, it could not be verified whether the subjects who did not report osteoporosis had PINP and CTX within normal limits, or whether they were elevated due to a subclinical manifestation of the bone disorder. By finding a positive correlation between PINP and PTH and between PINP and the age of SLE patients, it may be speculated that the elevation of PINP observed in SLE is likely to be connected with sex steroid deficiency and physiological secondary hyperparathyroidism. However, the levels of sex

hormones were not assessed and it was impossible to confirm this hypothesis. On the other hand, one may also use BTMs in assessing the impact of new treatment regimens on bone metabolism in lupus patients. A recent study by Mendoza Pinto et al. conducted on 30 patients with SLE found that a one-year course of treatment with rituximab, surprisingly, resulted in lower BMD at both femoral neck and lumbar spine, compared with patients without such therapy.¹⁸ However, PINP and CTX analyses were not performed.

The present study has several limitations which must be emphasized. Firstly, the number of patients included in the study was relatively low, and studied individuals were only female Caucasians with SLE in remission. The main variables in the assessment of lupus activity were the level of anti-dsDNA, aNuc and aCL antibodies, which were found not to correlate with BTMs. Interestingly, Sangle et al. found that atraumatic metatarsal stress fractures may occur in SLE, particularly in association with antiphospholipid syndrome.⁵ Our results confirm those of Uaratanawong et al. who did not reveal any correlation between BMD and disease activity.¹⁷ Surprisingly, in childhood-onset SLE, disease activity was found to be a negative predictor of bone resorption, suggesting that lupus disease activity is not the primary factor contributing to the bone deficits.¹⁶ Secondly, as mentioned before, BMD was not performed, which defeats any attempts to estimate the risk of bone fracture in relation to BTMs. Such algorithms should also be assessed and further validated in male and non-Caucasian populations of SLE patients. Finally, our study was performed at one point in time. With no doubt, follow-up assessment and longitudinal observation would make a valuable contribution to the understanding of the rate of bone metabolism and risk of fracture in the clinical course of SLE. However, the key strength of our study is that it employs markers of both bone formation and resorption recommended by the IOF-IFCC, thus making results more comparable and reproducible and leading to meta-analyses of future studies conducted on larger populations of SLE patients from different sites.

Several clinical conclusions can be drawn from this study. First of all, the increased levels of BTMs observed in SLE appear to be associated with an age-related pattern of bone remodeling. Of all BTMs, increased PINP is expected to be the most frequently observed. Efforts aimed at a better diagnosis of bone disturbances using an assessment of bone turnover in accordance with international reference standards, in addition to BMD assessment, need to be included in the diagnostic approach to SLE patients.

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Conflicts of interest

The authors declare no conflicts of interest.

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