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Research paper

Bone mineral density in women with systemic lupus erythematosus, its association with bone turnover markers, levels of estradiol and interleukin-6

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Abstract

Introduction: Osteoporosis is frequently diagnosed in patients with systemic lupus erythematosus (SLE). Potential causes and mechanisms of the development of this disease in patients with SLE are still being studied.

Aim: To study bone mineral density (BMD) of women with SLE in Ukraine, evaluate its association with the level of bone turnover markers, interleukin-6 (IL-6) and serum estradiol levels.

Material and methods: In total, 91 SLE women and 29 healthy individuals were examined. Apart from clinical risk factors for osteoporosis development, the levels of IL-6, bone formation and resorption markers, serum estradiol and their association with reduced BMD were evaluated. The deterioration of BMD was detected by dual-energy X-ray absorptiometry.

Results and discussion: Reduced BMD in women with SLE is found in 35.2%. In the study group, 28 women with SLE (48.3%) have decreased levels of bone formation markers, while 30 women (51.7%) have increased bone resorption markers. Imbalance of bone metabolism is highly associated with the severity of the disease, IL-6, and an exposure dose of glucocorticoids. The level of estradiol in women with SLE is 1.8 times lower than in individuals from the control group. The deterioration of the BMD is closely related to the bone turnover disorder, level of IL-6 and estradiol.

Conclusions: Independent predictors of BMD disorder in SLE women are levels of osteocalcin and C-terminal telopeptide of type I collagen as well as IL-6 and decreased level of serum estradiol.

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1. INTRODUCTION

Despite significant improvement in the quality of life in patients with systemic lupus erythematosus (SLE), long-term duration of this disease is still associated with the development of permanent internal organ damage. Thus, osteoporosis and fragility fractures are one of the most frequent SLE complications. Etiology of decreased bone mineral density (BMD) in such patients is still under discussion. The potential factors for bone loss include the role of long-term drug therapy with glucocorticoids (GCs) and immunosuppressants, a systemic inflammatory process with internal organ damage and hormonal status.[1]

Osteoporosis is considered to be developed as a result of deterioration of the number or function of osteoblasts and osteoclasts. The balance between bone resorption and bone formation is supported by numerous cytokines that ensure the interaction of the body's immune and bone systems.[2] Therefore, the pathological levels of proinflammatory cytokines inherent in autoimmune diseases, in particular SLE, may be one of the key mechanisms of the development of osteoporosis.

Another, equally important mechanism of bone loss is hypoestrogenemia.[3] A potential direct effect of estrogens on bone tissue can be confirmed by the presence of specific receptors on osteocytes, osteoblasts and osteoclasts, as well as immune cells.[4] It has been shown that estrogen deficiency causes a shift in the balance of bone metabolism towards the processes of its resorption by reducing bone cell activity, calcitonin synthesis, calcium absorption, increase of proinflammatory cytokines, etc.[3] However, how BMD in SLE patients changes in conditions of hypoestrogenemia at different reproductive ages is unknown. The peculiarities of the metabolic state of bone tissue and its association with the changes in BMD in such patients need further study.

2. AIM

The aim of this research is to study BMD of women with SLE in Ukraine, evaluate its association with the level of bone turnover markers (BTMs), interleukin-6 (IL-6) and serum estradiol.

3. MATERIAL AND METHODS

The study group consisted of 91 SLE women (average age 45.11 ± 1.03 years old) and 29 individuals from the control group of the relevant age and sex (average age 46.79 ± 2.30 years old). The age range of patients in the main group was 23–65 years, in the control group 22–66 years. In total, 53 (58.2%) women with SLE were of reproductive age, 38 (41.8%) women were postmenopausal. Menopause was determined retrospectively as the last independent menstruation, followed by 12 months of amenorrhea and postmenopause was defined as the period that has lasted since the final menses. The SLE diagnosis was made on the basis of 2019 European League Against Rheumatism / American College of Rheumatology classification criteria for SLE.[5] Organs damage was determined according to Systemic Lupus International Collaborating Clinics / American College of Rheumatology damage index (SLICC/ACR DI).[6] Traditional and SLE-related risk factors for osteoporosis were studied, i.e. age of patients, menstrual status, history of fragility fractures, duration of the disease, Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). All patients were taking GCs at the time of examination. The exposure dose of glucocorticoids was calculated for each patient.

Serum levels of IL-6, BTMs – osteocalcin (OC), procollagen type I C-terminal propeptide (P1CP), pyridinoline (PYD), C-terminal telopeptide of type I collagen (CTX) and estradiol – were determined by enzyme immunoassay.

X-ray of the thoracic and lumbar spine in lateral projections as well as of both hip joints in direct projection and the affected joint in lateral projection was used to detect fragility fractures.

Dual-energy X-ray densitometry on Hologic Discovery Wi (S/N 87227) was used for the BMD study at the lumbar spine and the proximal hip. The lowest *T*- and *Z*-score values of the above-mentioned study areas were selected for the diagnosis. In postmenopausal women osteoporosis was diagnosed if the *T*-score of the lumbar spine and/or proximal hip (neck and total hip) was –2.5 standard deviation (SD) or less. Osteopenia was detected by *T*-score from –1.0 to –2.5 SD. Decrease in *Z*-score up to –2.0 SD in women of reproductive age were considered as 'below the expected range for age.'

We used standard methods for statistical analysis of the results. These included Excel 10.0 application package and the program SPSS-10.0.5 for Windows (license number 305147890). The Shapiro–Wilk test was used to determine the normality of the distribution of indicators. Thus, there was a normal distribution of data in our study. The significance of differences was determined by Student's *t*-test. The relationship between two variables was measured by Pearson's correlation coefficient. To compare the significance of the differences between the relative values, Fisher's exact test was used. Multiple linear regression was used to obtain an optimal estimate of one (dependent) variable from the others.

4. RESULTS

In postmenopausal women, osteoporosis was observed in 7 (18.4%) patients with SLE, while in the control group, it was found in 1 (6.3%) woman. Osteopenia occurred in 19 (50.0%) patients with SLE and in 4 (25.0%) individuals from the control group. In women with SLE of reproductive age 9.4% of SLE women of reproductive age had decreased BMD in both study areas. During this period, no cases of bone loss were found in the control group. Thus, a total of 32 (35.2%) SLE patients and 5 (17.2%) healthy individuals had a reduce in BMD.

The lumbar spine BMD in women with SLE was 0.90 ± 0.01 g/cm^2, the hip BMD was 0.93 ± 0.02 g/cm^2. In the control group, it was 0.97 ± 0.02 g/cm^2 and 1.02 ± 0.03 g/cm^2, respectively, and was on average 8% higher.

The estimation of the levels of BTMs showed that in 28 (48.3%) SLE patients and 4 (13.8%) individuals from the control group, there is a decrease of at least one bone formation marker. The combination of low levels of OC and P1CP was detected in 10 (17.2%) patients with SLE.

The analysis of bone resorption processes showed that increased level of CTX and/or PYD was detected in 30 (51.7%) SLE women and in 4 (13.8%) individuals from the control group. The combination of the increased level of CTX and PYD was detected in 10 (17.2%) SLE patients. The simultaneous decrease of bone formation markers and increase of bone resorption markers was detected in 15 (25.9%) SLE patients and was not detected in practically healthy individuals. Considering this fact, we formed two groups of patients. One group included 15 (25.9%) SLE patients who had deterioration of both bone formation and bone resorption; the other group included the same number of patients with normal BTMs.

Patients with bone remodeling disbalance had decreased BMD in the lumbar spine and hip (Table 1). In women who had changes in the levels of BTMs, *T*-score was 3–4 times lower ($P < 0.05$), and *Z*-score was 7 and more times lower ($P < 0.05$). BMD in this group was also 13.7%–19.3% lower than in individuals without deterioration of bone formation and resorption. In the group of patients with the signs of deviation of bone remodeling processes, there were more individuals (46.6% more often) with decreased BMD as well as 20.0% more often there were patients who had fractures.

The course of the disease and pharmacotherapy approaches also revealed a clear correlation with biochemical processes in bone tissue. Thus, the course and severity of the disease, exposure dose of GCs were higher in patients with the signs of decreased bone formation and increased bone resorption than in the group with normal BTMs.

Analysis of serum estradiol showed that in the control group, its average content was 110.2 ± 15.8 pg/mL. In patients with SLE, estradiol levels were 1.84 times (45.6%) lower than those in the control group and equaled 59.9 ± 5.6 pg/mL. Hypoestrogenia was associated with the deterioration of bone tissue condition (Table 2). In particular, in patients of premenopausal age with low levels of estradiol, *T*- and *Z*-scores as well as lumbar BMD were lower than in such women with high levels of estradiol. In the postmenopausal period, there was a similar tendency towards lower *T*-score and BMD. Thus, women with the estradiol level lower than 20 pg/mL had 17.3% and 51.1% lower *T*-score in the lumbar spine and hip, respectively, comparing to women with the estradiol level above 20 pg/mL. In women of pre- and postmenopausal age with the low estradiol level, the growth of the proportion of individuals with decreased BMD was detected. In women of premenopausal age, a clear association between the decreased level of estradiol and the presence of fragility fractures was detected.

The analysis of the association between BMD and the level of IL-6 showed that increased serum IL-6 in SLE patients was associated with the bone tissue loss (Table 3). This is evidenced by the progressive decrease in BMD of the lumbar spine from 0.98 ± 0.03 g/cm^2 at optimal IL-6 level (<12.5 ng/L) to 0.81 ± 0.02 g/cm^2 at its high levels (>20.0 ng/L). In the hip, the changes of BMD were similar: 1.01 ± 0.03 g/cm^2 vs. 0.82 ± 0.03 g/cm^2, respectively. Simultaneously with the increase in serum IL-6, the proportion of individuals with reduced BMD and fractures increased.

Table 1. The association of BTMs with BMD and the course of the disease in SLE patients ($n = 58$).

Indices	Patients with normal BTMs $n = 15$	Patients with decreased bone formation markers and increased bone resorption markers $n = 15$
OC level, ng/mL	15.8 ± 0.52	11.4 ± 0.55*
PICP level, ng/mL	110.3 ± 9.18	71.3 ± 8.12*
CTX level, ng/mL	1.1 ± 0.04	1.4 ± 0.07*
PYD level, ng/mL	11.1 ± 0.26	15.6 ± 0.79*
Lumbar *T*-score	–0.48 ± 0.35	–2.08 ± 0.23*
Hip *T*-score	–0.48 ± 0.32	–1.54 ± 0.36*
Lumbar Z-score	0.09 ± 0.34	–1.7 ± 0.17*
Hip *Z*-score	–0.14 ± 0.22	–1.03 ± 0.31*
Lumbar BMD, g/cm^2	0.98 ± 0.04	0.79 ± 0.03*
Hip BMD, g/cm^2	1.01 ± 0.05	0.87 ± 0.03*
Patients with decreased BMD, *n*(%)	4 (26.7%)	11 (73.3%)*
Presence of fractures, *n*(%)	0 (0%)	3 (20.0%)*
DI, points	2.07 ± 0.57	4.40 ± 0.62*
SLEDAI, points	13.0 ± 2.05	18.3 ± 1.51*
Exposure dose of GCs, g	25.09 ± 5.02	69.02 ± 12.28*

Comments: * reliable differences ($P < 0.05$) for patients with normal BTMs.

Table 2. BMD of pre- and postmenopausal women with SLE depending on the estradiol level.

Indices	Premenopausal period		Postmenopausal period	
	Above 50 pg/mL	Below 50 pg/mL	Above 20 pg/mL	Below 20 pg/mL
Lumbar spine (n = 81)				
N	30	16	21	14
T-score	–0.50 ± 0.22	–1.43 ± 0.27*	–1.27 ± 0.25	–1.49 ± 0.31
BMD, g/cm^2	0.97 ± 0.03	0.86 ± 0.03*	0.87 ± 0.02	0.86 ± 0.03
Z-score	–0.23 ± 0.21	–1.17 ± 0.23*	–0.52 ± 0.27	–0.95 ± 0.33
Patients with decreased BMD, *n*(%)	1(3.3%)	4(25%)*	15(71.4%)	9(64.3%)
Hip (n = 49)				
N	18	10	12	9
T-score	–0.52 ± 0.24	–1.23 ± 0.23	–0.88 ± 0.26	–1.33 ± 0.21
BMD, g/cm^2	0.98 ± 0.03	0.84 ± 0.06*	0.95 ± 0.04	0.84 ± 0.05
Z-score	–0.38 ± 0.20	–1.03 ± 0.34	–0.78 ± 0.28	–1.10 ± 0.40
Patients with decreased BMD, *n*(%)	1(3.3%)	2(12.5%)	6(28.6%)	8(88.9%)*
Individuals with the history of fractures, *n*(%)	3(10.0%)	5(31.3%)*	2(9.5%)	3(21.4%)

Comments: * reliable differences ($P < 0.05$) concerning the compared group.

Table 3. BMD of the lumbar spine and hip in SLE patients depending on the IL-6 level.

Variables	Optimal IL-6 level <12.5 ng/L	Critically high IL-6 level 12.5–20.0 ng/L	High IL-6 level >20.0 ng/L
Examined individuals in the group, *n*	24	39	21
Patients with decreased BMD, *n*(%)	5(20.8%)	15(38.5%)	11(52.3%)*
Individuals with fractures, *n*(%)	2(8.3%)	5(12.8%)	6(28.6%)*
Lumbar spine			
T-score	–0.42 ± 0.26	–1.16 ± 0.12*	–1.97 ± 0.19*
BMD, g/cm^2	0.98 ± 0.03	0.90 ± 0.01*	0.81 ± 0.02*
Z-score	0.13 ± 0.30	–0.61 ± 0.11*	–1.38 ± 0.20*
Examined individuals in the group, *n*	16	25	13
Hip			
T-score	0.17 ± 0.31	–1.0 ± 0.18*	–0.96 ± 0.25*
BMD, g/cm^2	1.01 ± 0.03	0.93 ± 0.03*	0.82 ± 0.03*
Z-score	–0.09 ± 0.17	–0.70 ± 0.17*	–1.36 ± 0.19*

Comments: * reliable differences ($P < 0.05$) concerning patients with the optimal IL-6 level.

To identify the factors most involved in the development of osteoporosis in SLE women, and to determine their most prognostically unfavorable combination, we used multiple linear regression. As possible predictors of osteoporosis, we chose the following indicators: age of patients, exposure dose of GCs, damage index (DI, points), serum estradiol level, levels of IL-6 and BTMs (CTX, P1CP, OC). The forward selection of stepwise regression was used because it provides for the introduction into the linear regression equation of the most informative indicators, which had the largest partial correlation coefficient and increased the coefficient of determination.

First, the mathematical model that is most informative for predicting the development of osteoporosis in patients with SLE was selected. We performed stepwise incorporation of the selected regressors into a linear regression equation in which the *T*-score of the lumbar spine (Y) was a criterion variable. Four models were created that described the linear dependence of Y (X_i). Statistical analysis of these models showed (Table 4) that mathematical model no. 4 is the most beneficial for predicting osteoporosis under these conditions, since it best describes the variance in the criterion variable Y (adjusted R^2 for model no. 4 is significantly higher than for other mathematical models) and has the least standard error of the estimate. Therefore, later we used this model of osteoporosis prediction for this category of patients.

The mathematical model no. 4 proves that the most significant and independent predictors of osteoporosis are the following: X_1 – IL-6 levels; X_2 – OC levels; X_3 – level of CTX; X_4 – level of estradiol.

The selected predictors have different contributions to the prediction of osteoporosis, because the indices of their

Table 4. Statistical characteristics of forecasting models for osteoporosis.

Model	R	R^2	Adjusted R^2	Standard error of the estimate
1	0.898[a]	0.806	0.799	0.442
2	0.928[b]	0.861	0.850	0.382
3	0.949[c]	0.901	0.890	0.327
4	0.959[d]	0.920	0.907	0.301

Comments: predictors are constant; [a] X_1 (IL-6); [b] X_1 and X_2 (OC); [c] X_1, X_2 and X_3 (CTX); [d] X_1, X_2, X_3 and X_4 (estradiol).

β-coefficients are different (the higher the β-coefficient is, the greater the contribution of this predictor to the development of osteoporosis). Thus, in SLE women, the development of osteoporosis is most closely associated with bone metabolism imbalance (for OC $\beta = 0.359$; for CTX $\beta = -0.321$), slightly less with systemic inflammation (for IL-6 $\beta = -0.281$) and the least with decreased serum estradiol content ($\beta = 0.167$).

5. DISCUSSION

Therefore, our study has shown that in SLE postmenopausal women, osteopenia and osteoporosis are found in 50.0% and 18.4%, respectively. In 11.3% of women of reproductive age *Z*-score was below the expected range of age. In total, decreased BMD was detected in 35.2% of women with SLE and in 17.2% of individuals from the control group.

Numerous studies also indicate a high frequency of osteoporosis in patients with SLE. Thus, according to Gu et al. (2019), osteoporosis is found in 16% of patients with SLE.[7] Cramarossa et al. (2017) stated that 17.3% of premenopausal women had decreased BMD. In postmenopausal women, osteopenia was detected in 43.2% of cases, and osteoporosis in 12.3%.[8]

In our study, the frequency of osteoporosis in the control group was 6.3% in both study areas. According to Povoroznyuk et al. (2007), the frequency of osteoporosis in Ukrainian women was 20% in the spine and 11% in the femoral neck.[9] In our opinion, this difference can be explained by fewer study participants (29 in our study and 353 in the study of Povoroznyuk et al.). In addition, the average age of the examined women was almost 10 years younger, and was equal to 46.79 ± 2.30 vs. 55.2 ± 12.5 years, respectively.

According to the study, 30 (51.7%) patients with SLE had increased bone resorption and 28 (48.3%) had decreased bone formation processes, while 15 (25.9%) individuals suffered of these both processes. The results obtained are consistent with the data of a number of papers, which indicate that bone resorption processes, rather than decreased bone formation, are dominant in the development of osteoporosis in patients with SLE.[10,11] According to Teichmann (1999), the increase in bone resorption in patients with SLE was not accompanied by the expected compensatory increase in bone formation markers.[10] However, there are reports that do not note the differences between the metabolic state of bone tissue in patients with SLE and individuals from the control group.[12]

Increased bone resorption and slowing of the bone formation processes was closely associated with changes in BMD and fractures. According to literature data, regardless of a woman's reproductive age, BMD is more closely associated with bone resorption markers than bone formation markers.[13–15] However, there is evidence that patients with SLE who have low PINP suffer from faster bone tissue loss.[16] Thus, low levels of bone formation markers may predict bone tissue loss in patients taking GCs.

Our findings show that the content of bone tissue metabolism markers reveals a close correlation with the course and severity of SLE. Our findings correspond to the research results of Yao et al. (2018) and Sarkissian et al. (2019), that also confirmed an adverse effect of the course of the disease SLEDAI on the processes of bone formation and resorption in patients with SLE.[17,18] However, some findings do not confirm the involvement of the severity of SLE to changes in the metabolic state of bone.[19]

Our analysis of the correlation between the content of bone remodeling markers with GCs treatment indicates that suppression of the bone formation process and activation of bone destruction is associated with an increase in the exposure dose of GCs. According to Dovio et al. (2004), straight after the start of treatment with GCs, persistent suppression of bone formation processes and rapid, but transient, enhancement of resorptive processes is noticed.[20]

In the next part of the study, it was found that in patients with SLE, estradiol content was almost twice lower than that in the control group and equals 59.9 ± 5.6 pg/mL vs. 110.2 ± 15.8 pg/mL. With some exceptions,[21–23] the literature data also indicate a decrease in estradiol content in patients with SLE compared to the control group.[24,25] The leading causes of hypoestrogenia (impaired gonadal activity) in patients with SLE are inflammatory activity, autoimmune oophoritis, hyperprolactinemia, impaired function of the hypothalamic-pituitary-ovarian axis, GC and cytostatic treatment.[25] At the same time, hyperestrogenia in patients with SLE is associated with the accumulation of the highly active 16α-Hydroxyestrone[26] and the decrease in the content of 2-Hydroxyestrone.[27] In such cases, the level of estradiol can be both increased[21–23] and decreased.[24,25]

Our findings show that BMD in SLE women has a specific association with the estradiol level. *T*-score and lumbar/hip BMD in premenopausal women were decreasing in proportion with the decreasing of estradiol. Hypoestrogenia was associated with a significant increase of fractures, indicating a likely increase in the number of fragility fractures

in patients with a relatively low estradiol age, compared to patients with normal levels. In postmenopausal women with low estradiol levels, only a tendency to the growth of the proportion of individuals with fractures can be observed.

To determine metabolic predictors that are largely integrated into the pathogenesis of bone tissue remodeling in SLE women, we used multiple linear regression. It is found that the most significant and independent predictors of osteoporosis are the following: X_1 – IL-6; X_2 – OC; X_3– CTX; X_4 – estradiol.

6. CONCLUSIONS

In women with SLE, decreased BMD (according to *Z*- or *T*-score depending on menopause) is found in 35.2% of the cases in comparison with 17.2% of the cases in the control group.

In total, 28 (48.3%) women with SLE have decreased bone formation markers (P1CP and OC), and 30 (51.7%) women have increased bone resorption markers (CTX and pyridinoline). The combination of decreased bone formation markers and increased bone resorption markers was found in 15 (25.9%) patients with SLE. Imbalance of bone metabolism is associated with the severity of the disease, inflammation activity, and exposure dose of GCs.

The level of estradiol in SLE women is 1.8 times lower than in individuals from the control group. The deterioration of BMD is closely related to the serum concentration of estrogens.

According to the data of multiple linear regression, independent predictors of BMD disorder in women with SLE are the levels of OC and CTX (regression coefficients $\beta = 0.359$ and $\beta = -0.321$, respectively), slightly less, levels of IL-6 (regression coefficients $\beta = -0.281$), and the least, decreased levels of estradiol (regression coefficient $\beta = 0.167$).

Conflict of interest

None declared.

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Ethics

All study participants signed an informed consent, and the investigation was carried out in compliance with the Declaration of Helsinki, and recommendations of the Committee on Bioethics of the Presidium of National Academy of Medical Sciences of Ukraine.

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