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Features of Bone Mineral Density, Calcium-Phosphorus Metabolism and Bone Remodeling in Patients with Systemic Lupus Erythematosus

Introduction. Systemic lupus erythematosus (SLE) is a complex autoimmune disease with variable clinical manifestations associated with multiple autoantibodies, formation and deposition of immune complexes, and other immune processes [6, 7, 11]. Despite significant advances in treatment, the disease remains disabling, in particular, due to increased bone fragility and low-energy fractures [8]. The prevalence of osteopenia in patients with SLE ranges from 25.0 % to 75.0 %, and osteoporosis (OP) from 1.4 % to 68.0 % [5]. The incidence of symptomatic fractures in patients with SLE is 1.2-4.7 times higher than in the general population and ranges from 6.0-42.0 % [4].

The main regulators of calcium-phosphorus metabolism (CPM) are parathyroid hormone (PTH) and vitamin D, which, together with calcitonin, ensure a stable concentration of Ca and phosphorus (P) in the blood [1]. The interest of scientists in elucidating the relationship between the activity of SLE and vitamin D is reflected in numerous studies with different designs and rather contradictory results [2, 3]. Instead, the relationship between bone mineral density (BMD) and SLE activity has been insufficiently studied and reported in the scientific literature. In 29.0-35.0 % of patients with SLE with vertebral fractures, unchanged BMD is observed [11].

Bone metabolism is ensured by multidirectional but associated processes: bone formation by osteoblasts and bone resorption by osteoclasts. However, the mechanism of impaired bone remodeling in patients with SLE so far is not fully understood. Among the key pathogenetic factor of OP in patients with SLE is enhanced osteoclastogenesis induced by proinflammatory cytokines [4]. At the same time, some scientific publications report that the cause of osteopenia in such patients is slowed bone biosynthesis due to decreased osteoblast function [8, 9], and some researchers have not found any significant changes in bone metabolism in SLE affected patients with reduced BMD [9]. The study of bone remodeling in patients with SLE will help to improve the therapy and quality of their treatment.

The aim of the study. To invstigate features of bone mineral density, calcium-phosphorus metabolism and bone remodeling in patients with systemic lupus erythematosus.

Materials and methods. After obtaining written consent for the examination by the principles of the Helsinki Declaration of Human Rights, the Council of Europe Convention on Human Rights and Biomedicine, and relevant laws of Ukraine, patients were randomly enrolled in the clinical trial with preliminary stratification by the presence of SLE disease (according to the criteria of the American College of Rheumatology (ACR; 1997) and the order of the Ministry of Health of Ukraine N 676 of 12.10.2006 "On Approval of Protocols for the Provision of Medical Care in the Specialty of Rheumatology"), female gender and premenopausal status aged 21 to 51 years (mean age 38.95 ± 0.79). The cohort under investigation included 123 patients who were examined and treated during 2012-2018 in the Rheumatology Department of the Municipal Non-Profit Enterprise of the Lviv Regional Council "Lviv Regional Clinical Hospital" (study group (SG)). The comparison group (CG) consisted of 25 women without SLE in premenopausal status of the appropriate age. The control group included 25 practically healthy women.

In order to study BMD, dual-energy X-ray densitometry (DXA) of the lumbar spine was performed using a dual-energy X-ray absorptiometer (Stratos, France). To assess bone mass, the T-criterion was used, which is calculated automatically and corresponds to the number of standard

deviations (SD) in the difference between the average value of the study area for people aged 20 to 45 years and the result obtained in the subjects.

According to the recommendations of the World Health Organization, the T-criterion distinguishes four categories of bone tissue status:

1. Normal: T-score ≥ -1.00.

2. Reduced bone mass (osteopenia), preclinical osteoporosis:

T-criterion < -1.0 but > -2.50.

Degrees of osteopenia: osteopenia I: T-criterion < -1.00 but > -1.40; osteopenia II: T-criterion < -1.50 but > -1.90; osteopenia III: T-criterion < -2.00 but > -2.40.

3. Osteoporosis: T-score ≥ -2.5 without a history of fractures.

For the study of CPM, total Ca, ionized Ca, P in blood and Ca, P, creatinine in daily urine, as well as PTH and 25-hydroxyvitamin D in serum were determined using a commercial test kit on an automatic biochemical analyzer COBAS INTEGRA 400 plus (Roche, Switzerland) according to standard methods.

To assess the rate of bone remodeling, markers of bone formation were studied as follows: osteocalcin, a bone glutamine protein synthesized by osteoblasts during bone formation, procollagen type 1 amino-terminal propeptide (P_1NP) specific for the formation of type I collagen, and a biochemical marker of bone resorption, isomerized C-terminal telopeptide (β-crosslaps), specific for the degradation of type I collagen in bone. Markers of bone remodeling (osteocalcin, P_1NP and β-crosslaps) in serum were detected by immunochemical analysis using an automatic immunochemical analyzer COBAS INTEGRA (Roche, Switzerland) supplemented using a test kit from the same company, according to the attached instructions.

To achieve the goal, the first step included the evaluation of bone damage prevalence in patients with SLE; the second step was directed towards the characterizatione the bone condition in patients with SLE by summarizing the results of BMD assessment, CPM indices and markers of bone remodeling.

The material was processed in Excel (Microsoft) on a personal computer using descriptive statistics and Student's t-test.

Results and discussion. The results of the first step, evaluating the prevalence of bone damage in patients with SLE, are presented in table 1 and fig. 1.

Table 1

The state of bone mineral density according to the results of dual-energy X-ray absorptiometry of the lumbar spine in women of the study and comparison groups (n; %)

BMD	SG, n	CC, n	SG, %	CG, %
Osteoporosis	21	0	17.07	0.00
Grade III osteopenia	18	1	14.63	4.00
Grade II osteopenia	26	3	21.14	12.00
Grade I osteopenia	23	4	18.70	16.00
Total	88	8	71.54	32.00
Normal	35	17	28.46	68.00

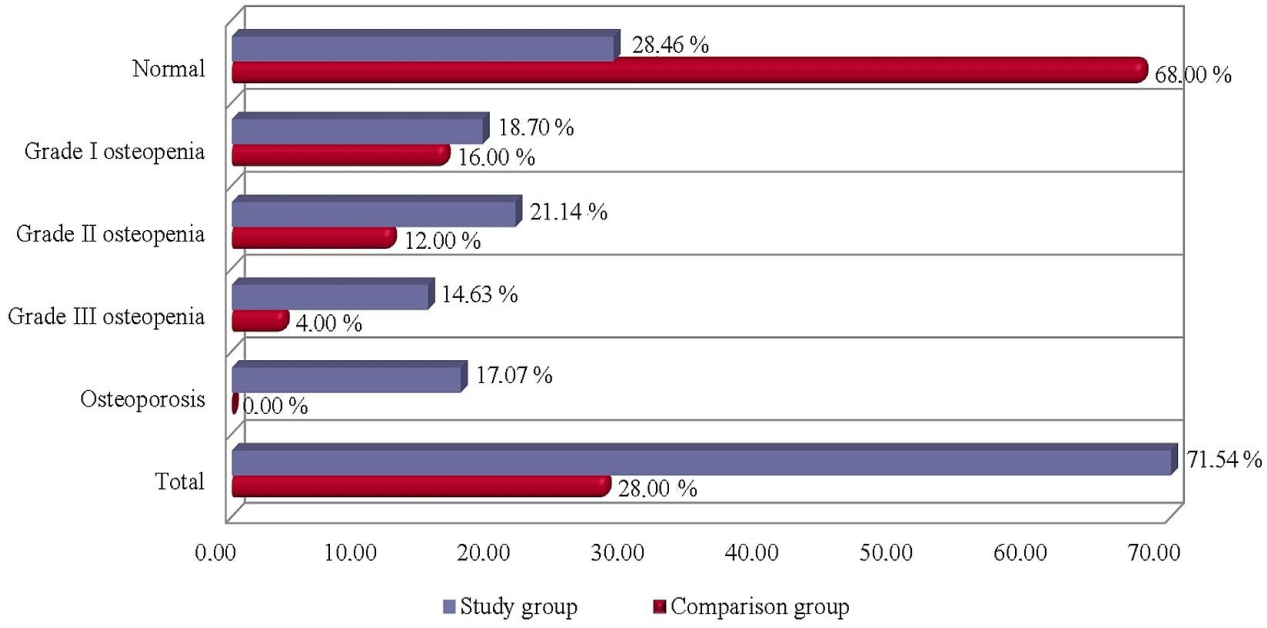

Fig. 1. The state of bone mineral density according to the results of dual-energy X-ray absorptiometry of the lumbar spine in patients of the study and the comparison groups women.

According to the results of lumbar spine DXA scans, 88 (71.54 %) women of the SG and only 8 (32.00 %) women of the CG had a decrease in BMD ($p < 0.001$). OP was detected in 21 patients of the SG (17.07 %), and no cases of OP were found in the CG. Grade III osteopenia was detected in 18 patients with SLE (14.63 %) and in one woman of the CG (4.00 %) ($p > 0.05$). Grade II osteopenia was detected in 26 patients with SLE (21.14 %) and 3 women of the CG (12.00 %) ($p > 0.05$). Grade I osteopenia was recorded in 23 women with SLE (18.70 %)

and 4 of the CG (16.00 %) ($p > 0.05$). Normal BMD was detected in 35 women of the SG (28.46 %) and 17 women of the CG (68.00 %) ($p < 0.001$).

The results of achieving the study goal by performing the second step, which was directed on the characterization of bone status in women with SLE based on the results of BMD assessment, CPM indices, and markers of bone remodeling, are presented in table 2 and fig. 2-5.

According to the results of lumbar spine DXA scans in the patients with SLE, the mean value of the T-criterion (-1.29) ± 0.10 was significantly lower than in women of the CG (-0.76) ± 0.23 ($p < 0.05$) and control (-0.50) ± 0.10 ($p < 0.05$).

According to the mean values, no significant differences were found in between the SG, CG and control: total blood Ca 2.34 ± 0.03 mmol/l versus 2.43 ± 0.04 ($p > 0.05$) and 2.39 ± 0.03 ($p > 0.05$) mmol/l; ionized blood Ca 1.27 ± 0.02 mmol/l versus 23 ± 0.06 mmol/l ($p > 0.05$) and 1.24 ± 0.01 ($p > 0.05$) mmol/l; blood P 1.15 ± 0.10 mmol/L versus 1.22 ± 0.08 ($p > 0.05$) and 1.16 ± 0.06 ($p > 0.05$) mmol/l. Also no significant difference were found in between the mean urinary P values in SG, CG, and control (12.68 ± 0.69 mmol/24 h versus 11.38 ± 0.87 mmol/24 h and 11.35 ± 1.32 mmol/24 h, $p > 0.05$). However, the Ca level in the urine was higher in patients with SLE (5.25 ± 0.28 mmol/24 h) than in CG (3.76 ± 0.46 mmol/24 h) and control (3.58 ± 0.76 mmol/24 h), $p < 0.05$. The mean values of the markers of bone mineral metabolism regulation, unlike PTH, did not differ significantly between the SG, CG, and control (49.78 ± 3.37 pg/ml versus 46.89 ± 0.90 pg/ml and 43.42 ± 3.30 pg/ml), the level of 25-hydroxyvitamin D was significantly lower in SG (15.14 ± 0.80 ng/ml) than in CG (19.62 ± 0.46 ng/ml) and control (22.38 ± 1.34) $p < 0.05$.

Table 2

Mean values of bone mineral density, calcium-phosphorus metabolism and markers of bone remodeling of the study group, comparison group and control

Parameters	SG	CG	Control
BMD			
Lumbar spine	-1.40 ± 0.10*#	-0.76 ± 0.23	-0.50 ± 0.10
CPM			
Total Ca (serum), mmol/l	2.34 ± 0.03	2.43 ± 0.04	2.39 ± 0.03
Ionized Ca (serum), mmol/l	1.27 ± 0.02	1.23 ± 0.06	1.24 ± 0.01
P (serum), mmol/l	1.15 ± 0.10	1.22 ± 0.08	0.16 ± 0.06
Ca (urine), mmol/24 h	5.50 ± 0.29*#	3.76 ± 0.46	3.58 ± 0.67
P (urine), mmol/24 h	12.68 ± 0.69	11.38 ± 0.87	11.35 ± 1.32
PTH (serum), pg/mL	49.78 ± 3.37	46.89 ± 4.50	43.42 ± 3.30
25-hydroxy-vitamin D, ng/ml	15.53 ± 0.73*#	19.62 ± 0.46	22.38 ± 1.34
Bone remodeling			
Osteocalcin	11.88 ± 0.48*#	18.61 ± 0.75	19.28 ± 1.88
P_1NP	41.67 ± 2.13	39.67 ± 2.34	41.59 ± 3.94
β-crosslaps	0.51± 0.02*#	0.26 ± 0.02	0.28 ± 0.02

Notes: * - $p < 0.05$ by Student's t-test compared to the comparison group; # - $p < 0.05$ by Student's t-test compared to the comparison group and control.

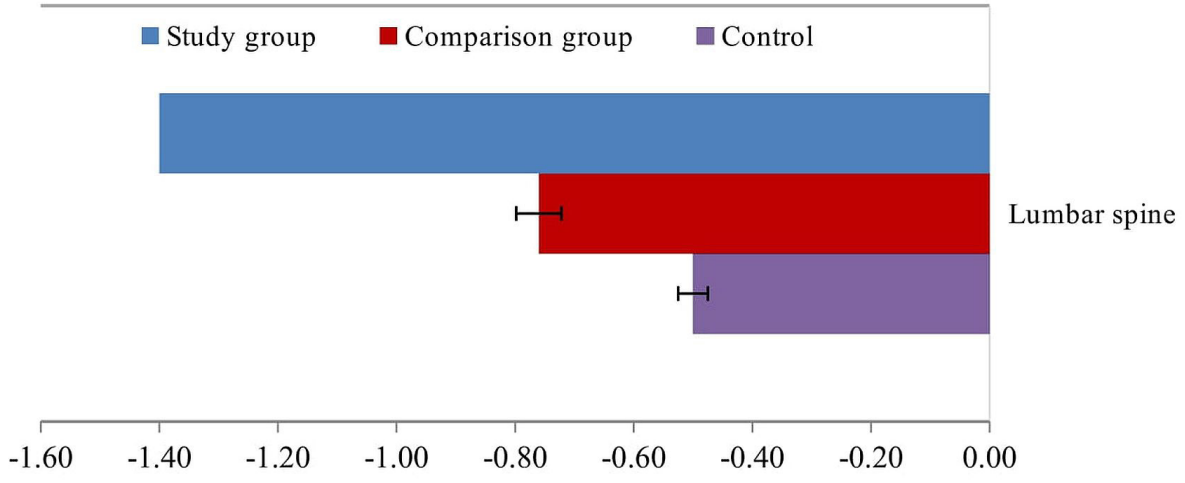

Fig. 2. The mean value of bone mineral density according to the results of dual-energy X-ray absorptiometry in women of the study group, comparison group, and control.

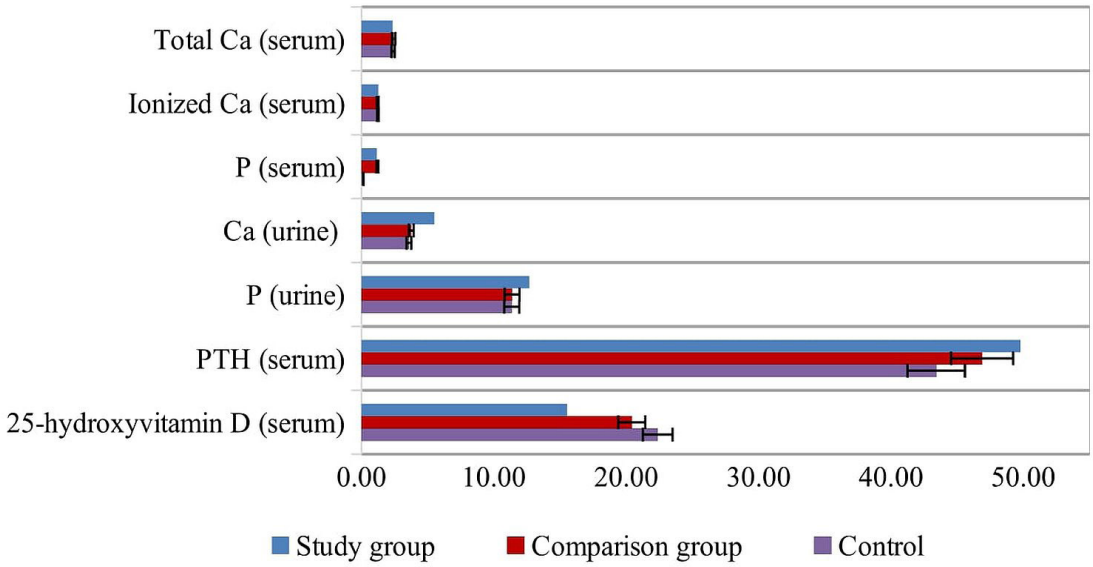

Fig. 3. Mean values of calcium-phosphorus metabolism and markers of its regulation in women of the study group, comparison group, and control.

The evaluation of osteoblastic function markers revealed significant differences between the SG, CP, and control, in particular, osteocalcin level in woman with SLE was significantly lower than in CG and control (11.81 ± 0.49 ng/ml versus 18.61 ± 0.75 ng/ml and 19.28 ± 1.88, $p < 0.001$). No significant differences were detected between the mean values of P_1NP in SG and CG (41.67 ± 2.13 ng/ml versus 39.67 ± 2.34 ng/ml), as well as SG and control (41.67 ± 2.13 ng/ml versus. 41.59 ± 3.94 ng/ml, $p > 0.05$).

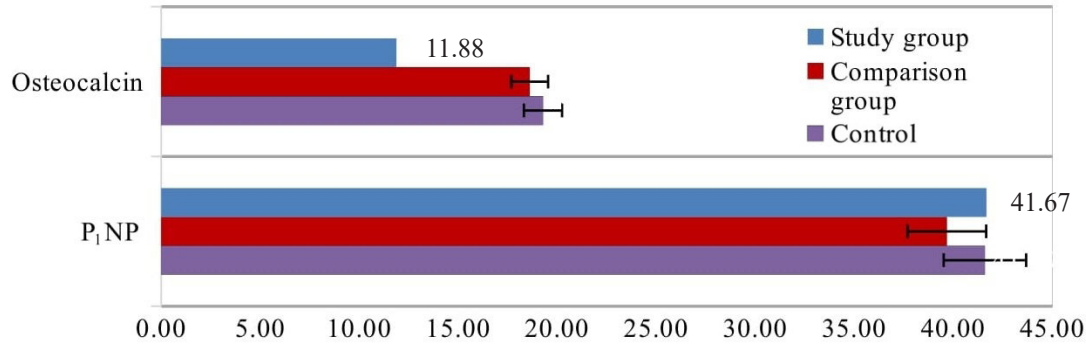

Fig. 4. Mean values of the markers of the osteoblastic function in women of the study group, comparison group, and control.

The assessment of osteoclastic function revealed a significantly higher levels of β-cross laps in patients with SLE (0.51 ± 0.02 ng/ml) compared to CG (0.26 ± 0.02 ng/ml) and control (0.28 ± 0.02 ng/ml), $p < 0.001$.

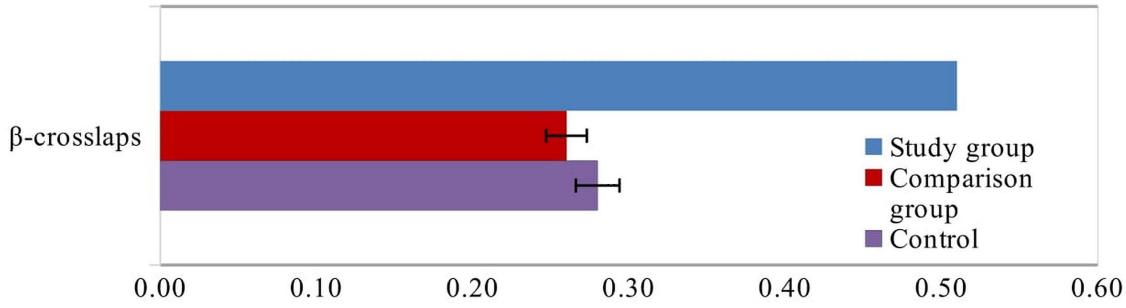

Fig. 5. Mean values of the osteoclastic function markers in women of the study group, comparison group, and control.

Conclusions. Bone mineral density, calcium-phosphorus metabolism and bone remodeling in patients with systemic lupus erythematosus have peculiarities as follows: a significant decrease in bone mass in 71.54 % of patients, namely 18.70 % - grade I osteopenia, 21.14 % - grade II osteopenia, 14.63 % - grade III osteopenia; 17.07 % - osteoporosis, increased calcium excretion, vitamin D deficiency, decreased osteoblastic and enhansed osteoclastic functions.

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Conflict of interests

TThe authors declare no conflicts of interest.

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Introduction. Systemic lupus erythematosus (SLE) is a complex autoimmune disease with variable clinical manifestations associated with multiple autoantibodies formation and deposition of immune complexes, and other immune processes. Despite significant advances in treatment, the disease remains disabling, in particular, due to increased bone fragility and low-energy fractures. The study of bone remodeling in patients with SLE should help to improve the therapy and quality of their treatment.

The aim of the study. To investigate the features of bone mineral density, calcium-phosphorus metabolism and bone remodeling in patients with systemic lupus erythematosus.

Materials and methods. The study involved 123 women with SLE aged 21-51 years. The comparison group (CG) consisted of 25 women without SLE in premenopausal status of the appropriate age. The control group included 25 practically healthy women.

In order to study bone mineral density (BMD), dual-energy X-ray densitometry (DXA) of the lumbar spine was performed using a dual-energy X-ray absorptiometer. For the study of calcium-phosphorus metabolism (CPM), total calcium (Ca), ionized Ca, phosphorus (P) in blood and Ca, P, creatinine in daily urine, as well as parathyroid hormone (PTH) and 25-hydroxyvitamin D in serum were determined. Markers of bone remodeling (osteocalcin, procollagen type 1 amino-terminal propeptide (P_1NP) and isomerized C-terminal telopeptide (β-crosslaps) in serum were measured.

To achieve the stated goal, the first step included the determination of bone damage prevalence in patients with the diagnosed SLE; the second step was directed towards the characterization the particular bone condition in patients with SLE based on the results of BMD, CPM indices and markers of bone remodeling assessment.

Results. According to the results of DXA of the lumbar spine, 88 (71.54 %) women of the SG and only 8 (32.00 %) women of the CG had a decrease in BMD ($p < 0.001$). According to the mean values, the studied CPM indices of the SG patients, CG and control group wemen exposed no significant differences. Similarly, no significant differences were detected in the mean values of urinary phosphorus and in between blood PTH values in SG, CG, and control. The level of 25-hydroxyvitamin D was significantly lower in SG (15.14 ± 0.80 ng/ml) than in CG (19.62 ± 0.46 ng/ml) and control (22.38 ± 1.34 ng/ml) $p < 0.05$. The mean value of osteocalcin in woman with SLE was significantly lower than in CG and control (11.81 ± 0.49 ng/ml versus 18.61 ± 0.75 ng/ml and 19.28 ± 1.88, $p < 0.001$). No significant difference were detected in between the mean values of P1NP in SG, CG and control. The mean values of β-cross laps were significantly higher in patients with SLE (0.51 ± 0.02 ng/ml) compared to GC (0.26 ± 0.02 ng/ml) and control (0.28 ± 0.02 ng/ml), $p < 0.001$.

Conclusions. Bone mineral density, calcium-phosphorus metabolism and bone remodeling in patients with systemic lupus erythematosus have peculiarities as follows: a significant decrease in bone mass in 71.54 % of patients, namely 18, 70 % - grade I osteopenia, 21.14 % - grade II osteopenia, 14.63 % - grade III osteopenia; 17.07 % - osteoporosis, increased calcium excretion, vitamin D deficiency, decreased osteoblastic and enhansed osteoclastic functions.

Keywords: systemic lupus erythematosus, osteoporosis, bone mineral density, calcium-phosphorus metabolism, P_1NP, β-crosslaps.

Особливости мінеральної щільности кісток, кальцієво-фосфорного обміну та кісткового ремоделювання у хворих на системний червоний вовчак

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Вступ. Системний червоний вовчак (СЧВ) – системна хвороба сполучної тканини, що виникає внаслідок генетично зумовленої недосконалости імунорегуляторних процесів, що призводить до утворення безлічі антитіл до власних клітин і їхніх компонентів та виникнення імунокомплексного запалення, наслідком якого є ураження багатьох органів і систем.

Попри значні досягнення у лікуванні, хвороба призводить до інвалідизації, зокрема через збільшення крихкости кісток і виникнення низькоенергетичних переломів. З'ясування особливостей ремолелювання кісток у хворих на СЧВ уможливить удосконалити діягностику й підвищити якість лікування.

Мета. Дослідити особливости мінеральної щільности кісток, кальцієво-фосфорного обміну та кісткового ремоделювання у хворих на системний червоний вовчак.

Матеріяли й методи. До клінічного дослідження у рандомізований спосіб із попередньою стратифікацією за наявності діягнозу СЧВ, жіночої статі й пременопаузального статусу віком від 21 до 51 року (середній вік 38,95 ± 0,79) залучили 123 хворих, які впродовж 2012–2018 рр. перебували на обстеженні та лікуванні у ревматологічному відділі Комунального неприбуткового підприємства Львівської обласної ради «Львівська обласна клінічна лікарня» (дослідна група (ДГ). Групу порівняння (ГП) склали 25 жінок без СЧВ у пременопаузальному статусі відповідного віку. До контрольної групи (КГ) увійшли 25 практично здорових жінок.

З метою дослідити мінеральну щільність кісткової тканини (МЩКТ) проведено двоенергетичну рентгенівську денситометрію (ДРА) поперекового відділу хребта. Досліджували кальцієво-фосфорний обмін (КФО), визначали показники загального кальцію (Са), йонізованого Са, фосфору (Р) у крови та Са, Р, креатиніну в добовій сечі, а також паратгормону (ПТГ) і 25-гідроксивітаміну D в сироватці крови. Щоб оцінити швидкість ремоделювання кісткової тканини, досліджували маркери формування кісткової тканини (остеокальцин, амінотермінальний пропептид проколагену I типу (procollagen type 1 amino-terminal propeptide – P_1NP) та ізомеризований С-кінцевий телопептид (Carboxyterminal Cross-linking Telopeptide of Bone Collagen – (β-crosslaps) в сироватці крови.

Для досягнення зазначеної мети з'ясовували поширеність ушкодження кісток у хворих на СЧВ, визначали стан кісток у хворих на СЧВ за результатами оцінювання МЩКТ, показниками КФО, маркерів кісткового ремоделювання.

Результати. За результатами ДРА поперекового відділу хребта, у 88 (71,54 %) жінок ДГ і лише у 8 (32,00 %) жінок КГ є зниження МЩКТ ($p < 0,001$). За результатами ДРА, у поперековому відділі хребта у хворих на

СЧВ жінок ДГ отримали середнє значення Т-критерію (-1,29) ± 0,10, що достовірно менше, ніж у жінок ГП (-0,76) ± 0,23 ($p < 0,05$) і КГ (-0,5) ± 0,1 ($p < 0,05$). За середніми значеннями досліджувані показники КФО крови хворих ДГ, жінок ГП і КГ достовірно не відрізнялися. Також не було достовірної відмінности за середніми значеннями Р сечі у ДГ, ГП і КГ. Проте вміст Са у сечі був більшим у хворих на СЧВ (5,25 ± 0,28 ммоль/24 год), ніж у ГП (3,76 ± 0,46 ммоль/24 год) і КГ (3,58 ± 0,76 ммоль/24 год), $p < 0,05$. Щодо маркерів регуляції мінерального обміну кісткової тканини, то на відміну від ПТГ, середні значення якого достовірно не відрізнялися між показниками у хворих жінок ДГ, ГП і здорових жінок КГ, вміст 25-гідроксивітаміну D був достовірно меншим у жінок, хворих на СЧВ (15,14 ± 0,80 нг/мл), ніж у ГП (19,62 ± 0,46 нг/мл) і КГ (22,38 ± 1,34), $p < 0,05$. Середнє значення остеокальцину у жінок було достовірно меншим, ніж у здорових (11,81 ± 0,49 нг/мл проти 18,61 ± 0,75 нг/мл і 19,28 ± 1,88, $p < 0,001$). Достовірної різниці між середніми значеннями P_1NP у хворих жінок із ДГ і здорових із КГ не виявлено. Середнє значення β-crosslaps достовірно більше у хворих на СЧВ жінок (0,51 ± 0,02 нг/мл), ніж у ГП (0,26 ± 0,02 нг/мл) та КГ (0,28 ± 0,02 нг/мл), $p < 0,001$.

Висновки. Мінеральна щільність кісток, кальцієво-фосфорний обмін і кісткове ремоделювання у хворих на системний червоний вовчак мають певні особливости: достовірне зменшення маси кістки у 71,54 % хворих, а саме – у 18,70 % – остеопенія I, у 21,14 % – остеопенія II, у 14,63 % – остеопенія III, у 17,07 % – остеопороз, збільшення екскреції кальцію, недостатности вітаміну D, послаблення остеобластної і посилення остеокластної функцій.

Ключові слова: системний червоний вовчак, остеопороз, мінеральна щільність кісткової тканини, кальцієво-фосфорний обмін, P_1NP, β-crosslaps.

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