Characteristics and features of bone turnover in rheumatoid arthritis patients with osteoporosis

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Abstract.
Rheumatoid arthritis (RA) is a systemic autoimmune disease with a chronic inflammatory process that negatively affects bone metabolism, leading to a violation of bone mineral density (BMD). Bone remodeling markers are important indicators of the state of bone tissue that can provide additional important information for the clinician about BMD disorders. The patients were randomly enrolled in the study with preliminary stratification by the presence of RA as well as the criteria of the American College of Rheumatology and the European League Against Rheumatism in 2010, also normal bone mineral density (BMD) and osteoporosis (OP) were diagnosed by ultrasound bone densitometry. The study included 42 patients (33 women (78.57 %) and 9 men (21.43 %)) aged 38 to 60 years. The control group consisted of 22 healthy individuals of (18 women (81.81 %) and 4 men (18.19 %) with no BMD disorders. Markers of bone formation, osteocalcin (OC), P1NP and bone resorption β-CrossLaps were studied. Based on the results, it can be concluded that the serum content of both OC and P1NP is significantly lower, while β-CrossLaps is slightly higher in RA patients with OP compared to healthy individuals. Also, OC and P1NP in the blood serum is significantly lower in RA patients with OP compared with RA patients with normal BMD, and the content of β-CrossLaps did not have a significant difference in RA patients with OP compared with RA patients with normal BMD. In rheumatoid arthritis patients with OP, bone mineral density disorder is marked by a decrease in bone formation and an increase in resorption processes.

Keywords: rheumatoid arthritis osteoporosis bone mineral density osteocalcin P1NP β-CrossLaps
**Introduction.** Rheumatoid arthritis (RA) is a systemic autoimmune disease with an unknown etiology that causes a chronic inflammatory process affecting joints, often leading to extra-articular lesions [1]. It also negatively affects bone turnover and leads to bone mineral density (BMD) disorders [2], which is concomitant with continuous remodeling. Osteocalcin (OC), which is a vitamin K-dependent bone non-collagenous protein, amino-terminal propeptide of type I procollagen (P1NP) and alkaline phosphatase (ALP), especially its bone-specific fraction, are responsible for osteoblastic bone function. An isomerized C-terminal telopeptide specific for the degradation of type I collagen in the cross-linked tissue (β-CrossLaps) is a marker of osteoclast function.

Laboratory tests of bone metabolism markers in RA patients contribute to a better understanding of the disease's pathogenesis, providing additional essential diagnostic information about BMD disorders beyond instrumental methods. They can also be useful in selecting the appropriate treatment tactics and evaluating their effectiveness [3].

**The aim of the study.** To characterize bone metabolism in patients with rheumatoid arthritis and osteoporosis and determine their features.

**Materials and methods.** After signing a voluntary consent to participate in the study, as required by the Helsinki Declaration of Human Rights, the Council of Europe Convention on Human Rights and Biomedicine, patients were randomly enrolled in the study with preliminary stratification by the presence of RA (seropositive (rheumatoid factor, cyclic citrullinated peptide antibodies) polyarthritis (affecting small joints of the hands, radiocarpal, shoulder, knee joints; X-ray stage II-III; functional joint impairment II); active phase, Disease Activity Score II) diagnosed in accordance with the Order of the Ministry of Health of Ukraine No. 676 of 12. 10.2006 "On approval of protocols for the provision of medical care in the specialty "Rheumatology" [4], as well as the criteria of the American College of Rheumatology and the European League Against Rheumatism in 2010 [5], normal BMD and osteoporosis diagnosed by ultrasound bone densitometry (UBD) of the calcaneus with the device SONOST - 2000.
(OsteoSysCo, Ltd, Seoul, Korea), which, as proved by Abragamovich U. O. et al. [6], the diagnostic value is not inferior to the "gold standard" of dual-energy X-ray densitometry.

The study included 42 patients (33 women (78.57 %) and 9 men (21.43 %)) aged 38 to 60 years (the average age at the time of the study for women was 48.33±0.68 years, for men - 45.89±2.04 years). All patients received treatment at the Rheumatology Department of the Municipal Non-Profit Enterprise of the Lviv Regional Council "Lviv Regional Clinical Hospital" from 2013 to 2019. Treatment included a short course of methylprednisolone at a dose of 4.0 to 24.0 mg/day during an exacerbation in a treatment complex (average course 7600.0 ± 260.0 mg) and not receiving medications for the treatment of BMD disorders.

BMD was measured according to the recommendations of the World Health Organization [7], and the T-score was determined. Patients were classified into the comparison group (CG) if the T-score was greater than -1.0 standard deviation (SD), indicating normal BMD, or the experimental group (EG) if the T-score was less than -2.5 SD, indicating osteoporosis (OP). The control group (CnG) consisted of 22 healthy individuals (18 women (81.81 %) and 4 men (18.19 %) with no BMD disorders. The average age of women at the time of examination was 42.95±2.14 years, men - 38.69±2.11 years), in whom no BMD disorders were detected by the results of UBD and the value of the T-score was greater than - 1.0 SD. Markers of bone formation (OC (2.0-22.0 ng/ml), P1NP (premenopausal women - 15.13-58.59 ng/ml; men - 15.00-80.00 ng/ml)) and bone resorption (β-CrossLaps (premenopausal women premenopause - <0.573 ng/ml; men: 30-50 years - <0.584 ng/ml, 50-70 years - <0.704 ng/ml)) were studied in serum using immunochemical analysis with electrochemiluminescence detection. The reference values were based on the reference values provided by the test system manufacturer in the instructions.

The study was performed in two stages: first, the markers of bone formation (OC and P1NP) and bone resorption (β-CrossLaps), were evaluated in RA patients with osteoporosis compared to healthy individuals of the control group; second, the markers were compared between RA patients with
osteoporosis (EG) and RA patients without BMD disorders (CG).

The data were processed using MS Excel and SPSS software. The point-biserial correlation was used to determine the strength and direction of the association between two criteria, and the p-value was determined to establish the reliability of the difference. A difference was considered statistically significant if \( p < 0.05 \).

**Results.** Table 1 displays the results of bone remodeling marker content determination in RA patients from EG, CG as well as from CnG.

<table>
<thead>
<tr>
<th>Groups of patients (CG, EG) and CnG (n)</th>
<th>Bone formation markers (M ± m in ng/ml; n; p)</th>
<th>Bone resorption markers (M ± m; p)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OC</td>
<td>P1NP</td>
</tr>
<tr>
<td>CG (18 patients)</td>
<td>24.91±2.75</td>
<td>40.34±4.58</td>
</tr>
<tr>
<td>EG (24 patients)</td>
<td>15.38±2.60</td>
<td>26.58±2.03</td>
</tr>
<tr>
<td>CnG (22 people)</td>
<td>20.37±0.76</td>
<td>37.40±2.37</td>
</tr>
<tr>
<td>p-value</td>
<td>p1&lt;0.005</td>
<td>p1&lt;0.001</td>
</tr>
</tbody>
</table>

Notes: p1 - significance of differences between the values of EG and CnG; p2 - significance of differences between the values of EG and CG, p3 - significance of differences between CG and CnG.

By analyzing the markers of bone formation OC and P1NP, as well as bone resorption β-CrossLaps at the first stage of the study, we found that the serum OC level was significantly lower in RA patients with OP of the DG (15.38±2.60 ng/ml) compared to its level in healthy CnG patients (20.37±0.76 ng/ml; \( p < 0.005 \)). Serum P1NP was significantly lower in RA patients with OP of the EG (26.58±2.03 ng/ml) compared to its level in CnG patients (37.40±2.37 ng/ml; \( p < 0.001 \)), and the serum β-CrossLaps level was slightly higher in RA patients with OP of the EG (0.36±0.03 ng/ml) compared to its level in healthy CnG people (0.31±0.01 ng/ml; \( p > 0.050 \)).
Based on these results, it can be concluded that the serum content of both OC and P1NP is significantly lower, while β-CrossLaps is slightly higher in RA patients with OP compared to healthy individuals of the CnG.

During the second stage of the study, we determined the markers of bone formation OC and P1NP, as well as bone resorption β-CrossLaps and we found that the OC index was significantly lower (EG) (15.38±2,60 ng/ml) compared to RA patients with normal BMD of the EG (24.91±2.75 ng/ml; p>0.002). P1NP was significantly lower in RA patients with OP (EG) (26.58±2.0 ng/ml) compared to RA patients with normal BMD (CG) (40.34±4.58 ng/ml; p>0.005), and the content of β-CrossLaps in RA patients with OP of the EG (0,36±0,003 ng/ml) and in RA patients with normal BMD of the CG (0.35±0.01ng/ml; p>0.050) did not show significant difference.

From these results, we can argue that the content of OC and P1NP in the blood serum is significantly lower in RA patients with OP of the EG compared with RA patients with normal BMD of the CG, and the content of β-CrossLaps did not have a significant difference in RA patients with OP of the EG compared with RA patients with normal BMD of the CG.

Conclusions.
1. In rheumatoid arthritis patients with OP, bone mineral density (BMD) disorder is marked by a decrease in bone formation and an increase in resorption processes.
2. The impaired BMD remodeling process in these patients has distinct features, which are significantly more pronounced weakening of bone formation.

References: