BONE MINERAL DENSITY IN FEMALE PATIENTS WITH SYSTEMIC SCLEROSIS AND DIFFERENT SEROLOGICAL STATUS OF DISEASE

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There are controversial opinions whether bone mineral density (BMD) is lower in patients with systemic sclerosis (SSc) than in age-matched population. The objective is to determine bone mineral density (BMD) in postmenopausal SSc patients, to investigate possible relationship between BMD and antibody status and to determine the association of dose and duration of glucocorticoid (GC) therapy and BMD in patients with SSc. Fifty-nine postmenopausal patients with SSc and 35 age-matched healthy controls were examined. BMD was measured at the lumbar spine (L1-L4) and proximal femur by DXA densitometer-Hologic at the Institute for Rheumatology "Niška Banja". The serological tests recorded the presence of patients’ antinuclear antibodies (ANA), antencentromere antibodies (ACA) and antitopoisomerase antibodies (ATA). Valentinie’s disease activity score was identified in all the patients with SSc. We found significantly lower average BMD and T score in postmenopausal SSc patients compared to the control groups (lumbar spine: p <0.0001; femoral neck, p <0.0001). No difference was found in BMD and T score in SSc patients with ACA versus ATA. Increasing age correlated with significantly lower BMD (r = -0.714, p = 0.001) and T score (r = -0.705, p = 0.001) at femoral neck. There was a negative correlation between disease duration and lower BMD (r = -0.467, p = 0.038) and T score (r = -0.455, p = 0.04) at the femoral neck. Scleroderma patients have significantly lower BMD at the hip and lumbar spine than healthy control subjects. No statistical difference in BMD was found between ACA and ATA in SSc patients. Aging and longer duration of the disease are associated with a greater loss of bone on the hip, while the long-term use of GC is associated with a decrease in BMD on the spine. There was no significant difference in the correlation between disease activity and bone density in examined patients with SSc.


Key words: bone mineral density, systemic sclerosis, antinuclear antibodies

Introduction

There are controversial opinions whether the frequency of osteoporosis (OP) is lower in patients with systemic sclerosis (SSc) or this possible affiliation, which has been recorded in few published studies, is the result of accompanying risk factors for the occurrence of osteoporosis in systemic sclerosis (1). Clinical heterogeneity of groups and small number of SSc patients in the studies have affected the evaluation of the results of research which focused on the risk of OP occurrence in scleroderma (2). There are only a few studies which analyze the markers of bone resorption in systemic sclerosis (3, 4).

Aims

1. To determine bone mineral density in postmenopausal female patients with systemic sclerosis and compare it with bone density of age-matched healthy controls.
2. To investigate the relation between BMD and antinuclear antibodies and indicator of disease activity in SSc patients.

Material and methods

A total of 59 postmenopausal patients (average age 60.26 ± 6.86, average disease duration 9.5 ± 6.4 years) who met ACR (American College
Bone mineral density in female patients with systemic sclerosis

Bone mineral density (BMD) was measured on the lumbar spine (L1-L4) and hip (proximal femur) by DXA densitometer-Hologic at the Institute for Rheumatology Niška Banja. The values were recorded as absolute, in g/cm, and as T-score (standard deviation as compared to young and healthy population).

The patients were subjected to clinical, laboratory examination and additional serological tests which recorded the presence of total anti-nuclear antibodies (ANA), anticientromere antibodies (ACA) by immunofluorescence on HEP2 cells, and antitopoisomerase antibodies (ATA) by counter immunoelectrophoresis.

In 2002, European Scleroderma Study Group and Scleroderma Clinical Trials Consortium determined that Valentini Disease Activity Index was a good indicator of SSc activity assessment SSc (5).

**Table 1. Overview of Valentini Disease Activity Index in SSc patients**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Rodnan skin score &gt; 14</td>
<td>1.0</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>0.5</td>
</tr>
<tr>
<td>Changes in skin stiffness during one month*</td>
<td>2.0</td>
</tr>
<tr>
<td>Digital necrosis</td>
<td>0.5</td>
</tr>
<tr>
<td>Changes which refer to vascular symptoms during one month*</td>
<td>0.5</td>
</tr>
<tr>
<td>Arthritis</td>
<td>0.5</td>
</tr>
<tr>
<td>Diffusion lung capacity &lt; 80%</td>
<td>0.5</td>
</tr>
<tr>
<td>Changes which refer to cardiopulmonary symptoms*</td>
<td>2.0</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate &gt;30mm/1. hour</td>
<td>1.5</td>
</tr>
<tr>
<td>Hypocomplementemia</td>
<td>1.0</td>
</tr>
<tr>
<td>Total Disease Activity Index</td>
<td>10.0</td>
</tr>
</tbody>
</table>

*The changes are evaluated by the patient

The abovementioned was done by means of a questionnaire which consisted of 10 selected clinical and laboratory characteristics of SSc. Each characteristic had constant numerical value (score) from 0.5 - 2.0. The total score was defined for each patient by summing up numerical values for each characteristic. The total sum could range from 0 to 10. Maximum value of the score (maximum disease activity) was 10. Table 1 shows the overview of Valentini Disease Activity Index in SSc patients. The score for each patient was defined based on the stated parameters.

**Results**

After comparing BMD of patients with systemic sclerosis and healthy controls, we found a significantly lower value of BMD (in g/cm² and T-score) in SSc patients, at both spine and hip (lumbar spine: 0.900 ± 0.16 g/cm² vs. 1.024±0.09 g/cm², p <0.0001; T-score -1.47 ± 1.49 vs -0.37 ± 0.75, p < 0.0001; hip: 0.749±0.17 g/cm² vs. 0.963 ± 0.10 g/cm², p <0.0001; T-score -1.30 ± 1.38 vs. 0.04 ± 0.70, p <0.0001). The results are shown in Figures 1, 2 and 3.

No statistically significant difference was found after investigating the relation between BMD and the presence of specific antibodies. SSc patients with positive ACA had no significantly different BMD as compared to patients with positive ATA at both hip and spine (ACA+BMD at lumbar spine 0.881 ± 0.14 g/cm² vs. ATA+ 0.911 ± 0.13 g/cm², p = 0.618; ACA+T-score -1.7 ± 1.45 vs. ATA+: -1.50 ± 1.34, p = 0.830. ACA+ BMD hip: 0.837 ± 0.18 g/cm² vs. ATA+ 0.719 ± 0.07 g/cm², p = 0.524. ACA+ T-score -0.85 ± 1.48 vs. ATA+ T-score -1.52 ± 0.44, p = 0.643 (Figure 4). There was no statistically significant difference in disease duration between ACA + and ATA+ SSc patients (Figure 5).

![Figure 1. Values of bone mineral density (BMD) in g/cm² at spine and hip in SSc patients](image1)

![Figure 2. Values of bone mineral density (T-score) at spine and hip in SSc patients](image2)
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Nineteen patients with higher Valentini Disease Activity Index (≥6) had lower BMD as compared to 40 patients with Disease Activity Index ≤6, but without significant difference (p = 0.07). Ageing correlated with significantly lower hip BMD (expressed in g/cm² and T-score). There was a negative correlation between these two entities (BMD hip, r = -0.714, p = 0.001 and T-score, r = -0.705, p=0.001), which was shown in Figure 6.

Investigation confirmed negative correlation between disease duration and hip BMD; longer disease duration was accompanied by lower hip BMD in SSc patients (BMD hip, r = -0.467, p = 0.038 and T-score hip, r = -0.455, p = 0.04). The results were shown in Figures 7 and 8.

Discussion

Premature menopause, the use of corticosteroids, and other factors conditioned by the presence of SSc (malabsorption, inflammation) are present in numerous studies on osteoporosis in systemic sclerosis (6).

The mechanisms that cause the loss of bone density in autoimmune diseases are very complex: from direct effect of immune cells on cartilage and bone to indirect consequences of the disturbance of systemic control of bone remodeling. Therefore, there are two new areas of research: osteoimmunology which analyses the direct impact of im-
immune cells on the bone, and integrated approach which implies the presence of neuroendocrine loop which regulates bone remodeling (7, 8).

Generalized osteopenia was recorded in significant percentage of patients with SSc (9). Additionally, Di Munno et al. (1995) and Ferri et al. (1991) found lower distal radius, lumbar spine and whole body BMD (10, 11). Our research has proved that postmenopausal patients with SSc have lower bone mineral density as compared to age-matched healthy controls.

A few papers analyzed the presence of reduced BMD in systemic sclerosis and showed that there was no significant difference in BMD between patients with normal inflammation markers and patients with changed inflammation markers in SSc, i.e., the presence or absence of total antinuclear antibodies (12, 13). However, the analysis of BMD in SSc patients with a specter of specific antibodies, both ACA and ATA which are related with different forms of the disease, has not been carried out yet. It is well known that ACA is frequently present in limited form of SSc, while ATA is present in diffuse form of SSc. This research has not confirmed a significant difference in BMD between the two tested groups with the same disease duration.

Frediani et al. (2004), as well as Omar et al., (2014) pointed to the reduced bone density in SSc patients with diffuse form of the disease, diffuse skin lesions, i.e., in patients whose visceral organs, one or more, were affected by the disease (14-16). Other studies concluded that bone density correlated with the degree of skin changes. However, the evaluation of the correlation between BMD and the degree to which visceral organs were affected was not done. Atteritano et al. (2013) proved that patients with systemic sclerosis had a high degree of vitamin D deficiency, which was associated with bone density (17). Many authors suggested that the degree of skin changes directly correlated with the degree of internal organ deterioration and severity of SSc (17-19).

Ageing is related to lower BMD in SSc and longer disease duration, which is in accordance with the results of the research which has been published worldwide.

**Conclusion**

Patients with systemic sclerosis have significantly lower spine and hip bone mineral density than age-matched healthy controls. There is no significant difference in BMD between patients with anticientromere and antitopoisomerase antibodies. Longer disease duration is connected with significantly lower bone mineral density. Indicators of systemic sclerosis activity, expressed in EUSTAR score of activities, do not correlate with osteopenia and osteoporosis in SSc patients.
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References

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MINERALNA GUSTINA KOSTI KOD BOLESNICA SA RAZLIČITIM SEROLOŠKIM STATUSOM U SISTEMSKOJ SKLEROZI

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Postoje kontroverzna mišljenja o tome da li je koštana gustina (KG, BMD - Bone Mineral Density) kod bolesnika sa sistemskom sklerozom (SSc) niža u poredenju sa zdravom populacijom. Cilj našeg istraživanja bio je da uporedimo KG sa onom u kontrolnoj grupi zdravih žena istih godina starosti, da utvrdimo povezanost KG i subseta specifičnih antitela, kao i da utvrdimo povezanost doze i dužine trajanja terapije glukokortikoidima i KG kod bolesnika sa SSc.

Istraživanjem je obuhvaćeno 59 žena u postmenopauzi sa SSc i 25 zdravih žena u postmenopauzi kontrolne grupe. KG je merena na lumbalnoj kičmi (L1-L4) i kuku (vratu femura) na aparatu Hologic u Institutu Niška Banja. Vrednosti su izražene u g/cm² i prema Tscore-u. Serološki testovi podrazumevali su određivanje ANA, ACA i ATA. Kod svih bolesnika odreen je Valentinijev skor aktivnosti bolesti.

Nađena je statistički značajno niža KG kod postmenopauzalnih SSc bolesnica u poredenju sa kontrolnom grupom zdravih žena na kičmi i kuku (lumbalna kičma: p<0,0001; vrat femura, p < 0,0001). Nije nađena razlika u BMD i Tscore-u na kičmi i kuku kod bolesnika sa SSc i +ACA, odnosno +ATA. Starenje je povezano sa padom koštane gustine na kuku (BMD: r = -0,714, p = 0,001; Tscore: r = -0,705, p = 0,001). Nađena je negativna korelacija između trajanja bolesti i KG na kuku, BMD: r = -0,467, p = 0,038: Tscore: r = -0,455, p = 0,04. Nađena je statistički značajna negativna korelacija srednjeg intenziteta između trajanja terapije GK i BMD na kičmi (r = -0,350, p = 0,042).

Bolesnice sa SSc imaju manju KG na kičmi i kuku u odnosu na zdrave žene. Nije bilo značajne razlike u koštanoj gustini kod SSc bolesnica sa različitim spektrom antitela. Starenje i duže trajanje bolesti su povezani sa većim gubitkom kosti na kuku, dok je dugotrajna upotreba GK povezana sa smanjenjem KG na kičmi. Nije nađena značajna razlika u povezanosti aktivnosti bolesti i koštane gustine kod ispitivanih bolesnica sa SSc.

Ključne reči: mineralna gustina kosti, sistemska skleroza, antinukleusna antitela