Original article

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

Bojana Stamenković[1,2], Mila Bojanović[2,3], Sonja Stojanović[1,2], Valentina Živković[1,2], Jovan Nedović[1], Jelena Jovanović[1], Dragan Đorđević[1,2]

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), anticentromere 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 ne-gative 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.

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

[1]Institute for Treatment and Rehabilitation of Rheumatic and Cardiovascular Diseases "Niška Banja", Serbia
[2]University of Niš, Faculty of Medicine, Niš, Serbia
[3]Clinic for ENT Diseases, Clinical Center, Niš, Serbia

Contact: Bojana Stamenković
Jug Bogdanova 26a, 18000 Niš, Serbia
E-mail: bojana.stamenkovic.70@gmail.com

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 heterogenecity 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

of Rheumatology) criteria for SSc and 35 age-matched healthy controls (58.80 ± 5.94) were examined.

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 antinuclear antibodies (ANA), anticentromere 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

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

*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/cm^2 and T-score) in SSc patients, at both spine and hip (lumbar spine: 0.900 ± 0.16 g/cm^2 vs. 1.024±0.09 g/cm^2, p <0.0001; T-score -1.47 ± 1.49 vs -0.37 ± 0.75, p < 0.0001; hip: 0.749±0.17 g/cm^2 vs. 0.963 ± 0.10 g/cm^2, 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 pati-ents with positive ACA had no significantly dif-ferent BMD as compared to patients with positive ATA at both hip and spine (ACA+BMD at lumbar spine 0.881 ± 0.14 g/cm^2 vs. ATA+ 0.911 ± 0.13 g/cm^2, 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/ cm^2 vs. ATA+ 0.719 ± 0.07 g/cm^2, 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).

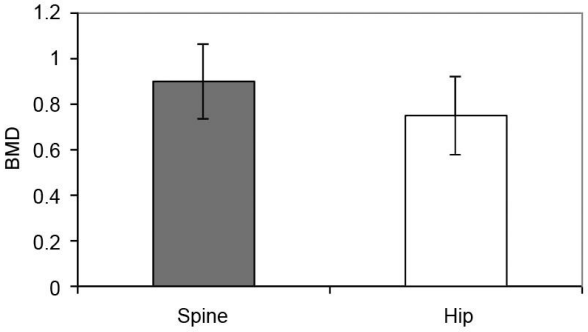


Figure 1. Values of bone mineral density (BMD) in g/cm^2 at spine and hip in SSc patients

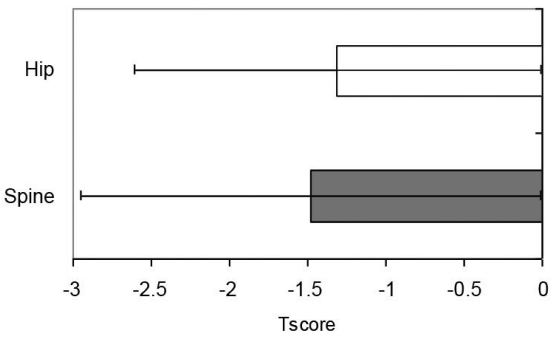


Figure 2. Values of bone mineral density (T-score) at spine and hip in SSc patients

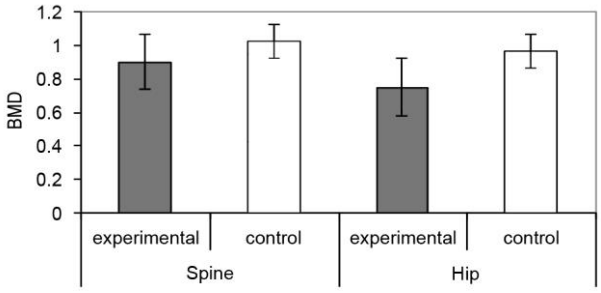


Figure 3. Difference in bone mineral density (BMD) between experimental group of SSc patients and healthy controls

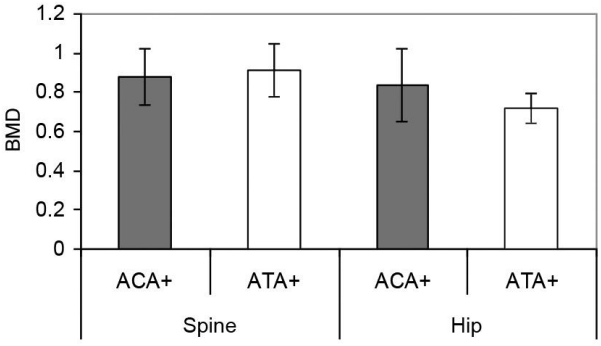


Figure 4. Correlation between bone mineral density (BMD) at spine and hip with the presence of antibodies in SSc patients

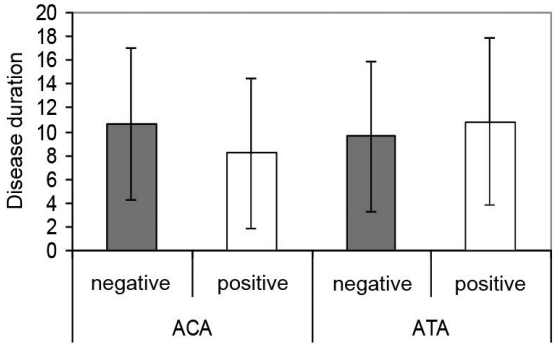


Figure 5. Disease duration in ACA+ and ATA+ SSc patients

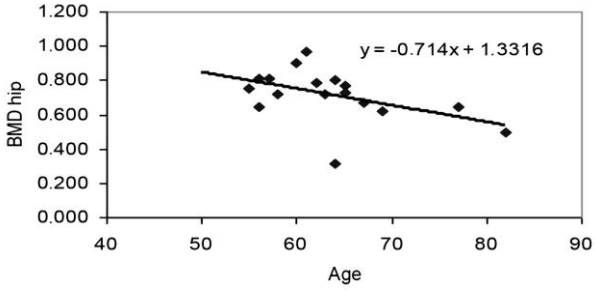
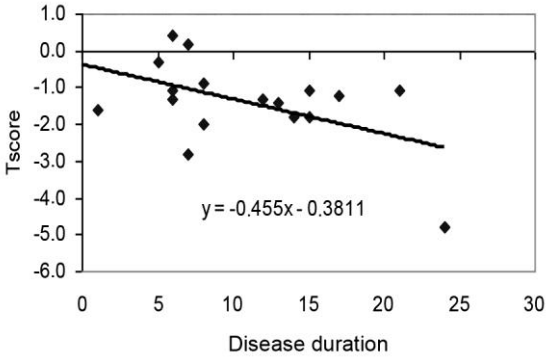
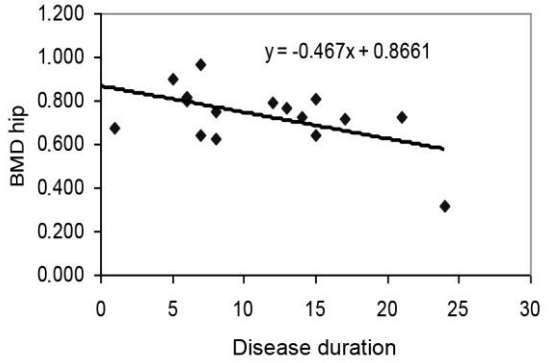


Figure 6. Correlation between aging and BMD (g/cm2) at proximal femur

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/cm^2 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.





Figures 7 and 8. Correlation between bone mineral density at spine and hip (BMD and T-score) and duration disease in patients with systemic sclerosis

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-

mune 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 ana-lysis of BMD in SSc patients with a specter of spe-cific antibodies, both ACA and ATA which are re-lated 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 re-search has not confirmed a significant difference in BMD between the two tested groups with the sa-me 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 or-gans, one or more, were affected by the disease (14-16). Other studies concluded that bone den-sity correlated with the degree of skin changes.

However, the evaluation of the correlation be-tween BMD and the degree to which visceral or-gans 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 pub-lished worldwide.

Conclusion

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

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

Bojana Stamenković[1,2], Mila Bojanović[2,3], Sonja Stojanović[1,2], Valentina Živković[1,2], Jovan Nedović[1], Jelena Jovanović[1], Dragan Đorđević[1,2]

[1]Institut za lečenje i rehabilitaciju Niška Banja, Niška Banja, Srbija
[2]Univerzitet u Nišu, Medicinski fakultet, Niš, Srbija
[3]Klinika za uvo, nos i grlo, Klinički centar Niš, Niš, Srbija

Kontakt: Bojana Stamenković
Jug Bogdanova 26a, 18000 Niš, Srbija
E-mail: bojana.stamenkovic.70@gmail.com

Postoje kontroverzna mišljenja o tome da li je koštana gustina (KG, BMD - one Mineral Density) kod bolesnica sa sistemskom sklerozom (SSc) niža u poređenju sa zdravom populacijom. Cilj našeg istraživanja bio je da uporedimo KG u SSc 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 bolesnica 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/cm^2 i prema Tscor-u. Serološki testovi podrazumevali su određivanje ANA, ACA i ATA. Kod svih bolesnika određen je Valentinijev skor aktivnosti bolesti.

Nađena je statistički značajno niža KG kod postmenopauzalnih SSc bolesnica u poređenju 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 Tscor-u na kičmi i kuku kod bolesnica 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.

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