

Bone Mineral Density and Trabecular Bone Score Indices in Women with Rheumatoid Arthritis according to the Age and use of Glucocorticoids

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Keywords Rheumatoid Arthritis; Glucocorticoids; Bone Mineral Density; Trabecular Bone Score; Women; Age

Abstract

Objectives: The present study was aimed to establish the influence of age and use of glucocorticoids on the Bone Mineral Density (BMD), Trabecular Bone Score (TBS) indices and their dynamics during one year in women with RA.

Material and Methods: We included 134 women with RA aged 31 to 78 years (mean age – 52.4 years; height – 1.64 m; weight – 68.5 kg; duration of RA – 9.1 years). While studying the effect of age on BMD and TBS indices the patients were divided into five groups by decades and compared indices with reference data for Ukrainian population. In order to evaluate the effect of GC on the studied parameters women were divided into three groups: 1st group comprised of 37 patients who did not take GC, 2nd group – 47 patients who have been prescribed with GC only at exacerbation, of the short, less than 6 months term, 3rd group – 50 patients who continuously received GC at a dose of ≥ 5 mg by prednisone for over 3 years. We used dual energy X-ray absorptiometry (Prodigy, GE Lunar, Madison, 2005, USA), measured BMD at the lumbar spine, femoral neck and ultradistal radius. Trabecular bone tissue score (TBS) of the lumbar spine was determined by TBS iNsight® (Med-Imaps, Pessac, France).

Results: Starting from the age of 50 years, the indices of TBS L_1-L_4 (1.156 ± 0.140 vs. 1.318 ± 0.155 in women aged 30–39 years; $t=3.5$; $p=0.001$) and BMD of different parts of the skeleton in women with RA are significantly decreasing. BMD indices of femoral neck and ultra distal radius in patients with RA aged 40-49, 50-59, 60-69 and 70-79 are lower than according parameters in healthy women. In addition, it was revealed that at the continuous administration of GC (in the 3rd group compared to the 1st group), TBS L_1-L_4 (1.147 ± 0.168 Vs 1.250 ± 0.135 ; $t=3.07$; $p=0.003$) was significantly lower, while significant changes in BMD parameters of the lumbar spine and femur have not been detected. Over the year of follow-up, the index TBS L_1-L_4 in 1st group decreased by 1.4%, in 3rd group – by 5.8%. Thus, the definition of TBS L_1-L_4 is a technique that can assess the impact of GC on bone tissue and dynamics of its loss as a result of treatment.

Conclusion: The indices of TBS and BMD in women with RA aged 50 years and older are significantly lower than parameters in healthy women. Patients who receive GC continuously have significantly lower TBS L_1-L_4 , in contrast of no significant changes in BMD. Consequently, the assessment of TBS L_1-L_4 is a technique that can assess the impact of GC on bone tissue and dynamics of its loss as a result of treatment.

Introduction

Rheumatoid Arthritis (RA) is a chronic inflammatory rheumatic disease and a frequent cause of secondary osteoporosis induced by the chronic inflammatory conditions and a long-term glucocorticoid therapy (GC). Patients with RA have a greater risk of osteoporosis and low-energy fractures than a general population [1]. Bone disorders are main extra-articular complications of rheumatoid arthritis [2]. According to our previous data, osteoporosis in women with RA aged 50-59 years was observed in 25.6% patients at lumbar spine; in 30.8% cases at the femoral neck and 33.4% – at total radius [3].

Glucocorticoid therapy is usually associated with increased fracture risk that cannot be fully explained by decreased Bone Mineral Density (BMD); this may be a consequence of alterations in the micro-architectural properties of bone. Other well known risk factors of systemic osteoporosis at RA are age, duration of postmenopausal period in women, low body mass index, reduced physical activity and duration of disease [4-6]. The TBS L_1-L_4 is a new method which can be measured by DXA, and correlates with parameters of bone micro architecture [7,8]. According some literature data the combining TBS index with BMD is important in complex assessment of bone status. However, there are insufficient data about combination of BMD and TBS in bone assessment in women with RA.

Table 1: Clinical characteristic of patients with RA depending on age (ANOVA analysis).

Parameters / Group	Age, years					F	p
	30-39 (n=14)	40-49 (n=45)	50-59 (n=37)	60-69 (n=26)	70-79 (n=12)		
Height, m	1.66±0.07	1.64±0.05	1.61±0.07*	1.63±0.06	1.58±0.05*	3.1	0.007
Weight, kg	66.7±8.6	69.9±13.7	67.9±17.2	68.0±11.2	67.8±13.1	0.3	0.94
Duration of RA, years	7.7±4.9	8.9±7.1	12.0±9.5	8.9±7.4	5.8±5.1	1.9	0.08
DAS28, score	4.6±0.9	5.1±1.1	5.0±1.1	5.3±0.9*	5.1±0.7	2.8	0.005
HAQ, score	1.4±0.6	1.6±0.8	1.5±0.7	1.5±0.9	1.9±0.6	0.5	0.89

Data presented as mean ± SD; * – significant differences compared to women 30-39 years, p<0.05.

Purpose

The aim of this study was to evaluate the influence of age and use of glucocorticoids on the bone mineral density, trabecular bone score indices and their dynamics during one year in women with rheumatoid arthritis.

Materials and Methods

The study was conducted at the D. F. Chebotarev Institute of Gerontology NAMS Ukraine (Kyiv) and approved by Ethics Committee of the Institute. All patients signed informed consent for participation in the study and conservative treatment of osteoporosis in the institute clinic. 134 women with RA aged from 31 to 78 years were examined (mean (M±SD) age – 52.4±12.7 years; height 1.63±0.06 m; weight 68.5±13.8 kg; average duration of disease is 9.1±7.6 years). 112 (83.6%) patient had positive rheumatoid factor. All the patients have been taking methotrexate as a basic treatment (from 7.5 to 20 mg/week, average duration of treatment was 8.2±6.1 years). The clinical activity of RA was quantified by the Disease Activity Score (DAS) 28, and the functional activity was determined by the Health Assessment Questionnaire (HAQ).

In order to study the influence of age on bone mineral density and trabecular bone score indices, women were divided into 5 groups by decade. Their main characteristics are summarized in (Table 1).

With the purpose to estimate the influence of GCs on BMD and trabecular bone score (TBS) indices, all patients were divided into the three groups: first group (G1) includes 37 patients who did not use of GCs previously (mean age 53.8±13.0 years; height 1.63±0.07 m, weight 68.5±15.3 kg, duration of RA 8.7±7.1 years, duration of postmenopausal period 8.7±7.4 years), second group (G2) – 47 patients who took GC only at the exacerbated stage for less than 6 month

(mean age 50.9±10.6 years; height 1.63±0.07 m, weight 68.6±12.4 kg, duration of disease 9.9±8.8 years; duration of postmenopausal period 5.7±6.3 years), third one (G3) – 50 patients who used GC in a dose of more than 5 mg of prednisolone for more than 3 years (mean age 53.1±14.7 years; height 1.62±0.06 m; weight 67.6±13.7 kg; duration of RA 8.6±6.7 years; duration of postmenopausal period 8.6±8.1 years). Patients did not differ as to age, basic anthropometric parameters, duration of disease and duration of postmenopausal period in these groups (Table 2).

Bone mineral density of lumbar spine, femoral neck and total radius were measured using the Dual-Energy X-Ray Absorptiometry (DXA) method (Prodigy, GEHC Lunar, Madison, WI, USA) and TBS L₁-L₄ was assessed in posterior-anterior spine by TBS iNspire[®] software package installed on our DXA machine (Med-Imaps, Pessac, France).

We compared BMD and TBS in patients with RA indices with the reference data for Ukrainian population which we have got in Ukrainian Medical Center of Osteoporosis in earlier studies [9-11].

Evaluation of TBS dynamics in the patients of the first (G1) and third (G3) groups during the year was conducted on the background of ongoing therapy which included doses of GCs (for the patients of second group) and/or without any osteoporotic treatment. TBS (%) calculated the dynamics of index by formula: $\Delta TBS (\%) = (\Delta TBS / TBS) \times 100\%$, where Δ is difference of absolute indices.

The statistical analysis was conducted using the methods of descriptive statistics, t – Students coefficient for independent and dependent variables and one-way analysis of variance (ANOVA). All parameters are represented at Mean (M) ±Standard Deviation (SD). At the analysis used the software's packages of "Statistica 6.0" Copyright © StatSoft, Inc. 1984-2001.

Table 2: Clinical characteristic of patients with RA depending on GC-taking (ANOVA analysis).

Parameters / Group	G1	G2	G3	F	p
Age, years	53.8±13.0	50.9±10.6	53.1±14.7	1.51	0.22
Height, m	1.63±0.07	1.63±0.07	1.62±0.06	0.67	0.51
Weight, kg	68.5±15.3	68.6±12.4	67.6±13.7	0.47	0.63
Duration of postmenopausal period, years	8.7±9.8	5.7±6.4	8.6±10.1	2.13	0.12
Duration of RA, years	8.0±7.1	9.9±8.8	9.1±6.7	0.67	0.51
DAS28, score	4.9±1.3	5.2±1.1	5.1±0.9	0.27	0.76
HAQ2, score	1.4±0.8	1.6±0.9	1.6±0.6	0.42	0.66

Data presented as mean ± SD.

Table 3: Age-dependent features of the Bone Mineral Density in healthy Ukrainian women and patients with RA.

Age group / Indices	(L ₁ -L ₄)		Femoral neck		Ultradistal radius	
	Healthy control	Women with RA	Healthy control	Women with RA	Healthy control	Women with RA
30-39 years	1,19±0,13	1,16±0,15	0,95±0,13	0,94±0,23	0,68±0,07	0,44±0,07#
40-49 years	1,18±0,19	1,11±0,18	0,96±0,13	0,85±0,22#	0,68±0,09	0,45±0,10 #
50-59 years	1,05±0,17*	1,01±0,23*	0,90±0,12*	0,72±0,25*#	0,65±0,08	0,41±0,15 #
60-69 years	1,01±0,18*	0,98±0,20*	0,82±0,12*	0,69±0,23*#	0,58±0,09*	0,36±0,09 *#
70-79 years	0,98±0,24*	0,98±0,18*	0,76±0,13*	0,65±0,20*#	0,53±0,11*	0,37±0,11*#

Data presented as mean ± SD; * – significant difference compared to group 30-39 years (p<0.05); # – significant difference compared to healthy control of same age group (p<0.05).

Table 4: Trabecular bone score (TBS L₁-L₄) at women with RA and healthy control depending on age (mm⁻¹).

Age group / Indices	Healthy control	Women with RA
30-39 years	1.416±0.078	1,318±0,155 #
40-49 years	1.344±0.121	1.302±0.142
50-59 years	1.248±0.142 *	1,156±0,140 *#
60-69 years	1.191±0.138 *	1.153±0.137 *
70-79 years	1.138±0.136 *	1.103±0.185 *

Data presented as mean ± SD; * – significant difference comparatively with group 30-39 years (p<0.05); # – significant difference compared to healthy control of same age group (p<0.05).

However, there was no significant difference between groups in BMD of lumbar spine and femur neck. Only BMD of total radius in G3 group was significantly lower comparing to the second G2 group (0.583±0.176 g/cm² Vs 0.631±0.118 g/cm²; t=-2.18; p=0.032) and to the first one (Table 5).

Continuous administration of GC was associated with the violation of the quality of the bone tissue. Women who receive GC continuously have significantly lower TBS L₁-L₄, while significant changes in BMD parameters of the lumbar spine and femur have not been detected.

After the year of observation, the TBS L₁-L₄ at patients of the G1 group was 1.232±0.128 mm⁻¹ (decreased by 1.4%), while in patients of the G3 group - 1.08±0.114 mm⁻¹ (lowering by 5.8%) (Figure 1). There

Table 5: Bone parameters' characteristic (Bone Mineral Density and TBS L₁-L₄) at women with RA depending on GC-taking.

Parameters / Group	G1	G2	G3	F	p
BMD of lumbar spine, g/cm ²	1.066±0.191	1.089±0.211	1.034±0.216	0.98	0.38
BMD of neck mean, g/cm ²	0.721±0.266	0.800±0.251	0.805±0.220	0.76	0.47
BMD of radius total, g/cm ²	0.675±0.229	0.631±0.188	0.583±0.176*	3.7	0.05
TBS L ₁ -L ₄ , mm ⁻¹	1.250±0.135	1.274±0.138	1.147±0.168*	10.67	<0.0001

Data presented as mean ± SD; G1 group – patients with RA, who did not take GCs; G2 – women patients who took GC only at the exacerbated stage for less than 6 months; G3 groups – patients with RA, whose used of GCs continuously; * – significant difference, compared to the G1 group, p<0.05.

Results

We found a significant effect of age on the BMD indices of different parts of the skeleton in women with RA (lumbar spine: F=3.4, p<0.001, femoral neck: F=4.9, p=0.004, total radius: F=4.1, p<0.001). In all these sites a significant decline of BMD indices in patients with RA starts from 50 years in healthy control and patients with RA (Table 3).

In addition, BMD indices of femoral neck and ultradistal radius in patients with RA aged 40-49, 50-59, 60-69 and 70-79 were lower than parameters in healthy women.

A decline of index of TBS L₁-L₄ in patients with RA also begins from 50 years and makes 1,156±0,140 mm⁻¹ Vs 1,318±0,155 mm⁻¹ at the women of age group 30-39 years (t=3.5; p=0.001). With age the decrease of this parameter progresses and in age of 60-69 years is 1.153±0.137 mm⁻¹ (t=3.3; p=0.002, compared to a group of 30-39 years), and in 70-79 years - 1.103±0.185 mm⁻¹ (t=2.9; p=0.007, in comparison with a group of 30-39 years) (Table 4). The results of the analysis of Anova also showed a significant effect of age on the TBS L₁-L₄ in patients with RA (F=7.3, p<0.001).

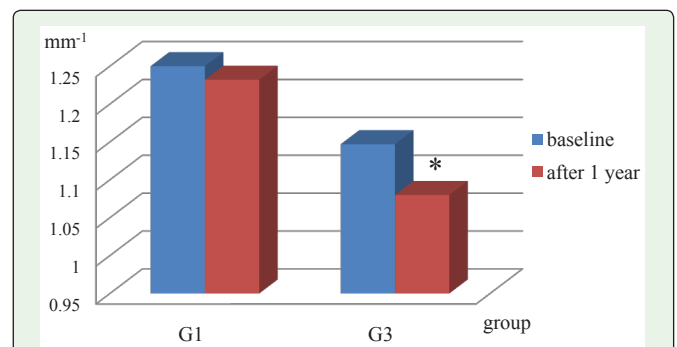


Figure 1: Trabecular Bone Score (TBS L₁-L₄) at women with RA depending on GC-taken.

Patients, who continuously used GCs, had significant lower indexes of TBS L₁-L₄ comparatively with the patients who did not take GCs or used it only at exacerbation by a short course. Thus, the TBS L₁-L₄ of patients from the G3 group was significantly lower comparing to the G1 (1.147±0.168 Vs 1.250±0.135; t=-3.07; p=0.003), and comparing to the G2 group (1.274±0.138; t=3.95; p=0.0002).

was no significant difference in BMD parameters among groups during the year. These findings indicate that TBS L_1-L_4 measurement, not BMD, reflects quality changes of bone tissue which occur under GCs taken.

Discussion

Rheumatoid Arthritis (RA) is a chronic inflammatory rheumatic disease and a frequent cause of secondary osteoporosis. The frequency of osteoporosis at these cohort patients is higher compared to a population level. Moreover patients with RA in comparison with postmenopausal women more frequently have fragility fracture in particular vertebral deformations [1,5,12].

Glucocorticoid therapy is associated with increased vertebral and non-vertebral fracture risk. Some studies show that it cannot be fully explained by decrease of BMD, however it may be a consequence of alterations of micro-architectural properties of bone [13,14]. Also various other risk factors of osteoporosis (age, low of body mass index, duration of disease and postmenopausal period, low physical activity and) can increase osteoporotic fracture risk in women [4-6].

Nowadays, measurement of BMD by Dual-Energy X-Ray Absorptiometry (DXA) is a golden standard for diagnosing osteoporosis. However, it does not directly reflect deterioration in bone microarchitecture. TBS is a new parameter that is determined from gray-level analysis of dual-energy X-ray absorptiometry images [1,14, 15]. The TBS L_1-L_4 is a novel gray-level texture measurement that can be extracted from DXA images, correlates with 3D parameters of bone microarchitecture [7,8]. Combining TBS trabecular texture index with BMD incrementally improves fracture prediction in women and men. Recent literature data shows that reduced lumbar spine TBS was associated with recent use of glucocorticoids, prior major fracture, rheumatoid arthritis, chronic obstructive pulmonary disease, high alcohol intake, and higher body mass index [16]. In contrast, recent osteoporosis therapy was associated with a significantly lower likelihood for reduced TBS. Similar findings were seen after adjustment for lumbar spine or femoral neck BMD. So, lumbar spine TBS is strongly associated with many risk factors that are predictive of osteoporotic fractures [16].

The first study assessing value of TBS and vertebral fracture in patients with RA was conducted by Bréban S, et al. [17] one hundred eighty-five women aged 56.0 ± 13.5 yr, with the duration of RA 15.5 ± 9.9 yr were studied. Lumbar spine, total hip, and femoral neck BMD were assessed by DXA. TBS was calculated from anteroposterior image of lumbar spine BMD. Vertebral fractures from T4 to L4 were evaluated using Vertebral Fracture Assessment software on DXA device. The proportions of patients with vertebral fractures and T-score ≤ -2.5 were only 24.2%, 21.2%, and 33.3% at lumbar spine, total hip, and femoral neck, respectively. T-scores were significantly lower in patients with vertebral fractures than in patients without, the largest difference being observed at femoral neck ($p=0.0001$). Moreover, TBS was significantly lower in patients with vertebral fractures Vs without ($p=0.0001$). Upon the opinion of scientists, TBS measured at the lumbar spine has better discrimination value than lumbar spine BMD, and similar to femoral neck BMD, for prediction of presence of vertebral fractures in patients with RA. In this population, at low risk according to BMD, TBS could help to detect patients with vertebral fractures [17].

Colson F, et al. [18] have determined that that GCs-treated women have a significant deterioration of bone microarchitecture as assessed by TBS which worsen with the presence, the type and number of fracture, even from 5 mg daily while no difference of lumbar spine BMD was observed in the study population. The results show that TBS, as a parameter of microarchitecture, is a good tool in the awareness of glucocorticoid-induced osteoporosis. 71% of the patients had TBS while 51% of the study population showed the decrease of lumbar spine BMD. This study supports observations that GC therapy influences fractures incidence by a mechanism independent of BMD, TBS of which could explain it [18].

Among well-known risk factors of bone loss in patients with RA, main factors are age and taking GC. The present study was aimed to establish the influence of age and use of glucocorticoids on the bone mineral density, trabecular bone score indices and their dynamics during one year in women with rheumatoid arthritis.

There was no difference in weight, duration of RA, index of functional activity by the HAQ between the groups. Height was significantly lower at patients of age groups 50-59 and 70-79 years, comparatively with group 30-39 years, which, possibly, related to the presence of spine osteoporosis and deformations of vertebrae in these patients.

We have observed the significant decrease of TBS and BMD of lumbar spine, proximal femur and forearm with age in healthy women and patients with RA. In addition, BMD indices of femoral neck and ultra distal radius in patients with RA aged 40-49, 50-59, 60-69 and 70-79 were lower than parameters in healthy women. The maximal decrease of TBS L_1-L_4 was determined in women aged from 40-49 years to 50-59 years that we can explain by increasing deficit of estrogen in perimenopausal period. Further decrease of TBS L_1-L_4 with age gradually progresses.

The continuous use of GC leads to a significant decrease of TBS, and hence, according to the literature data, an increased risk of vertebral fractures. For patients who are GC-users, TBS, but not BMD, reflects bone microarchitecture deterioration which is an indicator for those patients of a higher vertebrae and non-vertebral risk of fracture. TBS is a determinant of bone state and must be monitored during the long-term treatment with GC.

Our results are similar to the world literature data regarding clinical value of TBS L_1-L_4 in patients with RA. Thus, we must observe BMD in different parts of skeleton and TBS L_1-L_4 in GC-users. TBS index is important in complement to BMD for secondary GC osteoporosis assessment and management. Assessing both bone mineral density and microarchitecture (TBS L_1-L_4) enables clinicians to get a more precise profile of risk of fractures for their patients and improve their management of osteoporosis.

Conclusion

Parameters of bone mineral density of different parts of skeleton and TBS L_1-L_4 significantly decreased with age in women with RA. BMD indices of femoral neck and ultradistal radius in patients with RA aged 40-49, 50-59, 60-69 and 70-79 are lower than related parameters in healthy women. Age influences both on BMD and TBS to the same extent, these indices significantly decrease beginning from 50 years.

The admission of GC is associated with decrease of TBS. We have found the significantly lower TBS L₁-L₄ in patients, who are used of GCs continuously, while significant changes of BMD of the lumbar spine and femur have not been observed. Spine TBS L₁-L₄ decreased by 1.4% after one year for G1 and by 5.8% for G3. Thus, TBS L₁-L₄ is a determinant of bone state and must be monitored to assess the effect of GC on bone and dynamics of bone loss as consequences of its consumption.

Limitations

The limitation of this study is that only women, not both sexes, were included in analysis and small groups with RA aged 30-39 and 70-79 years. The another limitation was short (one year) period of follow-up.

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