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Abstract

Aims: Although considered as a feature of inflammatory rheumatic diseases, there is a lot of controversy around low bone mass in patients with psoriatic arthritis. The aim of this cross-sectional study was to analyze bone mineral density in patients with psoriatic arthritis, as well as to investigate its possible association with some measures of disease activity and functional capacity.

Subjects and Methods: Sixty-nine patients with established psoriatic arthritis (mean age 56.20±12.23 years) and who has not been treated with specific antiosteoporotic drugs were recruited from the out-patient clinic database. Bone mineral density was measured by dual-energy X-ray absorptiometry at the lumbar spine and at the left hip. Disease activity measures included: duration of morning stiffness, tender and swollen joint count, patient's and physician's global assessment, presence of dactylitis and enthesitis, ESR, CRP and Disease Activity Score 28. Health Assessment Questionnaire was used to assess functional status.

Results: According to WHO definition, spinal osteoporosis was found in 7.2% of patients, total hip osteoporosis in 1.4% of patients and femoral neck osteoporosis in 2.9% of patients. There was no significant association of any of the measures of disease activity with BMD at any site. Higher HAQ scores were associated with lower total hip BMD.

Conclusions: In our sample of patients with psoriatic arthritis we did not find increased prevalence of osteoporosis. There was no association of BMD with indices of disease activity, while negative correlation was found between HAQ and total hip BMD.

Key words: Arthritis, Psoriatic, Osteoporosis, Prevalence, Disease activity

Zusammenfassung

Ziele: Obwohl es als ein Merkmal entzündlich-rheumatischer Erkrankungen angesehen wird, gibt es viel Kontroverse über die niedrige Knochenmasse bei Patienten mit psoriatischer Arthritis. Das Ziel dieser Querschnittsstudie war es, die Knochenmineraldichte bei Patienten mit psoriatischer Arthritis zu analysieren, sowie ihre mögliche Verbindung mit einigen Ausmaßen der Krankheitsaktivität und funktionaler Kapazität zu untersuchen.

Probanden und Methoden: Neunundsechzig Patienten, bei denen psoriatische Arthritis festgestellt wurde (Durchschnittsalter 56.20±12.23 Jahre), und die nicht mit gezielten antiosteoporotischen Medikamenten behandelt wurden, wurden aus der klinischen Datenbank ambulanter Patienten angeworben. Die Knochenmineraldichte wurde an der Lendenwirbelsäule und an der linken Hüfte mittels Dualröntgenabsorptiometrie gemessen. Die Ausmaße der Krankheitsaktivität umfassten: Dauer der Morgensteifheit, schmerzende Gelenkschwellung, allgemeine Einschätzung durch den Patienten selbst und durch den Arzt, Manifestation von Daktylitis und/oder Enthesitis, ESR und CRP, und Krankheits-Aktivitäts-Score (DAS 28). Ein Fragebogen zur Beurteilung der Gesundheit (HAQ) wurde verwendet, um den funktionalen Status der Patienten zu beurteilen.

Ergebnisse: Laut Definition der Weltgesundheitsorganisation wurde bei 7,2% der Patienten Wirbelsäulenosteoporose, bei 1,4% der Patienten Osteoporose des Hüftgelenks und bei 2,9% der Patienten Osteoporose des Schenkelhalses festgestellt. Es gab keine signifikante Verbindung von keinem der Ausmaße der Krankheitsaktivität mit der Knochenmineraldichte an keinem der

Messbereiche. Eine höhere HAQ Punktzahl wurde in Verbindung gebracht mit niedrigerer Knochenmineraldichte des Hüftgelenks.

Schlussfolgerung: Anhand unserer Stichprobe der Patienten mit Psoriasis-Arthritis haben wir keine erhöhte Prävalenz der Osteoporose gefunden. Es gab keine Verbindung von Knochenmineraldichte mit Hinweisen auf Krankheitsaktivität, während negative Korrelation festgestellt wurde zwischen dem HAQ und der Knochenmineraldichte des Hüftgelenks.

Schlüsselwörter: Arthritis, psoriatische, Osteoporose, Prävalenz, Krankheitsaktivität

Introduction

Osteoporosis is considered one of the common features in patients with inflammatory rheumatic diseases, contributing to a significant decrease in quality of life, predominantly due to fragility fractures [1-3]. Bone is affected negatively by the disease process and often by the therapy itself [4-6]. The clinical relevance of osteoporosis in these diseases is still underestimated.

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis of unknown aetiology associated with psoriasis [7,8]. It is classified in spondyloarthropathies, a group of rheumatic diseases that share similar clinical, genetic, histological, and immunohistochemical patterns. PsA itself is characterised by synovitis, enthesitis, dactylitis and spondylitis usually accompanied with skin and very often nail psoriasis [8]. Apart from chronic inflammation, medications such as methotrexate or steroids, and sometimes prolonged immobilization due to joint pain have been recognized as possible risk factors that contribute to bone loss in those patients [9].In spite of that in PsA there is a lot of controversy about it, as the results of bone status in these patients are still conflicting [10-13].

Also, there is a very limited number of studies which evaluated simultaneously a disease activity and/or functional capacity on one side and bone density on the other side in patients with PsA [14]. Therefore, the aim of this cross-sectional study was to add the evidence regarding bone mineral density (BMD) in PsA, as well as to investigate its association with some measures of disease activity and with measures of functional limitations.

Materials and Methods

Subjects

Sixty-nine ambulatory, community-dwelling patients (31 men and 38 women) with established PsA, recruited from the out-patient clinic database of the University Hospital, were asked to participate in the study. The only additional criterion was that none have been receiving (in the past or present) specific medications for treatment of osteoporosis. The diagnosis of PsA was reconfirmed by one rheumatologist experienced in PsA (SG). No patients previously diagnosed to have PsA were excluded due to having different rheumatic condition at the time of the study. According to medical record, no patient had other disease or condition that affect bone metabolism (i.e. hyperparathyreoidism, hyperthyreosis, hepatic or renal failure, alcoholism or malnutrition).

The study was approved by the Ethics Committee of the University Hospital Center "Sisters of Mercy" in Zagreb (Croatia). Prior to inclusion to the study, an informed consent was obtained from all participants.

Data collection

Data were collected using an interviewer-administered questionnaire. Besides demographics (age, gender), history data included duration of psoriasis and duration of symptoms and signs of arthritis, as well as previous or current treatment with disease-modifying antirheumatic drugs (DMARDs) and/or corticosteroids.

Measures of disease activity and severity

The morning stiffness duration was determined (in minutes). Physical examination included the number of tender joints and number of swollen joints, as well as presence of dactylitis and number of affected fingers (hands and feet) and presence of enthesitis along with number of affected entheses. For the count of tender and swollen joints the American College of Rheumatology (ACR) joint count (68 tender and 66 swollen joints; hips are not assessed for swelling) was obtained [15]. The presence or absence of enthesitis was based on the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), ranging from 0 to 13 and representing the number of entheses painful on palpation [16]. Patient's and physician's global assessment were estimated using a 100 mm horizontal visual analogue scale (VAS).

Inflammatory activity was measured by two standard laboratory parameters: erythrocyte sedimentation rate (ESR, Westergren's method, normal values in men <15mm/h and in women <20mm/h) and C-reactive protein (CRP, ELISA, normal values <5 mg/L) which were determined in fresh samples.

Disease Activity Score (DAS) 28 (range 0-10) was used as a composite indicator of disease activity. The score is calculated from the following variables: 28 tender joint count/ swollen joint count (knees, shoulders, elbows, wrists, metacarpophalangeal and proximal interphalangeal joints of the hand), erythrocyte sedimentation rate (ESR) and global health [17,18]. A score >5.1 indicates high disease activity, ≤5.1 and >3.2 moderate disease activity, ≤3.2 and ≥2.6 low disease activity, and <2.6 indicates remission. Cumulative steroid dose was calculated by multiplying prednisolone (or equivalent glucorticoid) daily dose with days of treatment.

Measures of functional status

Functional ability was assessed by Health Assessment Questionnaire (HAQ) for all patients Health Assessment Questionnaire (HAQ) (range 0-3) is a standard self-report functional status (disability)

measure. HAQ-DI (disability index) consists of 20 questions that cover 8 domains of daily living. The scores for all 8 domains are averaged to obtain an overall score on a 4-level response scale from 0 (no disability) to 3 (severe disability), with a notion that highest sub-category score determines the value of each category [19]. HAQ-DI was successfully used in clinical trials of PsA and hence was proposed as an useful tool for measuring functional ability in these patients [20].

Bone density measurement

BMD (g/cm^2) was measured by dual-energy X-ray absorptiometry at the lumbar spine (L2-L4) and at the left hip (total hip and femoral neck) in standard manner. Callibration with a lumbar spine phantom is performed weekly. The patients were categorized according to WHO definition: osteoporosis if T score was less than -2.5 SD, osteopenia if T score was between -1.0 to -2.5 SD and normal T score if values were better than -1.0 SD [21]. Given that there is no control group, in order to provide the information how patient population performs as compared to an age- and sex- matched controls the results were expressed as Z scores, too.

Statistics

Data were analyzed using the software SPSS, *ver* 14**.** The results were shown as mean ± standard deviation. Differences in means between men and women were tested using Student′s t-test. The relationship between two variables was tested with the linear correlation. The normality of distribution within variables was tested using the Kolmogorov-Smirnov test. Variables which were not distributed normally (morning stiffness, swollen joint count, CRP) were recalculated to the new variables, using the logarithmic function. Statistical significance was set up at $p< 0.01$.

Results

The mean age was 54.3±12.1 years for men and 57.7±12.2 for women (Table 1). There were 27 (39.1%) patients on steroid therapy. Eleven patients (15.9%) have been receiving methotrexate and 19 patients (27.4%) sulphasalazine.

Duration of the disease was longer, although not significantly, in women than in men. Women were also older than men. Dactylitis was observed in 45,2% patients, mostly affecting up to 3 finger (33,9% of the total sample), while clinical signs of enthesitis were observed in 78,1% of patients.

According to WHO classification of osteoporosis, most patients had an osteoporosis at the lumbar spine (7.2%), following with the femoral neck (2.9%).(Figure 1) Around 80% of patients had a normal BMD at the total hip. Women had lower BMD than men at each region, but the difference was not statistically significant.

Parameters of disease activity and functional disability were generally higher in women than in men (Table 2). Number of sites with clinical signs of enthesitis was significantly higher in women than in men ($p=0.009$).

There was no significant correlation of any of measures of disease activity with BMD at any site (Table 3). No significant difference in BMD at each measured region was found between patients with <5 and with ≥5 fingers/toes affected in a clinical form of dactylitis. Higher cumulative steroid dose was associated with lower lumbar spine BMD and Z score. There was a negative correlation between HAQ scores and total hip BMD i.e. higher the HAQ score lower was total hip BMD.

Discussion

In our sample of middle aged patients with PsA the prevalence of osteoporosis was approximately 7%. The comparison of prevalence of osteoporosis between our patients and other population depends on the source of data. As for Croatian population there are few data. According to the study of Cvijetić *et al.* the prevalence of osteoporosis in healthy people, aged 20 to 79 years is 6% in women and 4% in men [22]. Using morphometric vertebral measurement on lateral radiographs of thoracic and lumbar spine Grazio *et al.* found prevalence of vertebral fractures to be 11.8% (15.8% men, 9.7% women) in a population aged 50 and above [23]. Approximate prevalence of osteoporosis in United States is 10.3% [24]. In Germany 7.8 million persons (6.5 million women) were affected by osteoporosis, in 2003 [25], while prevalence of osteoporosis in women 45 years and older was 14.2% [26]**.** Based on reported data, we may conclude that the osteoporosis in our patients with PsA is not more prevalent than in general population. Results from other studies are different. Frediani and co-authors found significantly lower BMD in patients with PsA than in healthy subjects regardless of sex, menopausal status, or age [10]. Another study which included only patients with psoriasis and controls without psoriasis revealed that osteoporosis was significantly more frequent in men with psoriasis compared with the controls, but not in women [27]. In a small study of patients with plaque psoriasis those with associated psoriatic arthropathy had a significantly lower mean lumbar spine Z-score (- 1.16) than those without arthropathy (+1.38, P =0.015), while neither previous nor current treatment with systemic steroids, retinoids or methotrexate significantly affected BMD [28]. However, several other studies have determined normal total, peripherial or periarticular bone mass in patients with PsA, i.e it was not different from the control group [11-13]. In their study of comparing patients with psoriasis and patients who also had psoriatic arthritis Borman et al. did not find any significant difference in BMD [29]. In the most recent study Pedreira *et al* analyzed bone density separately in postmenopausal women with psoriasis, PsA and in controls and found no significant differences between those groups, too [30].

As it is well known that chronic inflammation is an important factor for bone loss the possible correlations were investigated in our sample of PsA patients. Inflammatory process may influence bone metabolism because of pro-inflammatory mediators interleukin-1, interleukin-6, and tumour necrosis factor (TNF)-alpha), which stimulate osteoclast activity and consequently a bone loss [8, 31,32]. As for the role of TNF- alpha it is also well known that anti-TNF alpha therapy has a beneficial effect on bone density and bone turnover markers. In a review by Barnabe and Hanley who summarized the results of 3 studies in patients with spondyloarthopathies, an increase in BMD at the lumbar spine (3.2-3.6%) and at the hip (1.8-2.2%) was demonstrated as a result of TNF-alpha antagonist therapy [33]. In those studies, changes in markers of bone remodelling showed a modest increase in formation and decline in resorption. It is of note that none of the patients in our group was treated with biologic therapy. It has been indicated existence of association between chronic inflammation and bone loss through the action of osteoprotegerin (OPG) and receptor activator of nuclear factor-κB ligand (RANKL). Since activated T-cells produce and secrete RANKL, the RANKL/OPG system may play an important role in the pathogenesis of inflammatory diseases, including arthritis [34]. On the other hand, OPG increases bone

density by acting as a decoy receptor for RANKL. This inverse effect of OPG on osteoporosis and arthritis may probably explain a relatively preserved bone mass in our patients. In various studies, alterations of OPG serum levels have been differently linked to inflammatory diseases, including not only PsA but the other most prevalent spondyloarthropathy, ankylosing spondylitis [8].

It is of note that ankylosing spondylitis and PsA share common genetic, clinical and radiological features. PsA radiological changes include both destructive changes (e.g. erosions) and new bone formation, the latter being the main radiological characteristic of ankylosing spondylitis [35,36]. In spite of bony growth in ankylosing spondylitis osteoporosis of the lumbar spine was found in up to 34.3% and osteoporosis of the hip in up to 29% patients [37-42]. Moreover, Capaci et al. found that even 61.6% of patients with mild AS had spinal osteoporosis and osteopenia, while 46.6% had osteoporosis and osteopenia at the total hip [43].

One must bear in mind that PsA arthritis is a heterogeneous disease. Although two main clinical patterns can be identified (peripheral disease and axial disease) PsA usually presents as oligoarticular and mild disease. But, in considerable proportion of patients with time PsA becomes polyarticular and in those patients poorer physical function and health related quality of life is observed [7]. Health outcomes and especially osteoporosis in the rheumatic diseases have been a very active area of research in the past years, with a significant number of published studies, although most of them have been in the area of rheumatoid arthritis or, in a lesser extent of ankylosing spondylits [44-49]. Although a joint damage is generally greater in RA than in PsA it has been shown that, after equivalent disease duration, function and quality of life scores are the similar for both groups [50].

Our results did not show significant correlations between BMD and measures of disease activity. Moreover, duration of disease was not a significant predictor of bone density. For these results we do not have a straight explanation. As according to the finding of moderately high DAS 28 and small elevation of ESR and CRP above normal values one can infer that high activity of the disease whose natural course is characterized by exacerbation and remission might not be long enough.

In our study negative correlations between cumulative steroid dose and lumbar spine BMD and Z score were observed. The role of low-dose corticosteroid treatment as an independent risk factor for osteoporosis in rheumatic diseases is still controversial. Most studies on that relationship have been focused on patients with rheumatoid arthritis [51]. Therefore, our results contribute to the knowledge that cumulative steroid dose might be linked with osteoporosis in patients with PsA.

As for functional ability score (HAQ) we found its negative correlation with total hip BMD. It could be explained with the fact that decreased mobility associated with lower functional capacity could contribute to osteoporosis. It is of note that in our study measures of disease activity and functional ability were obtained using established methods. However, although their use in PsA has become acceptable and for some even recommended, one must bear in mind that none of disease activity measurements and functional indices is specifically designed for psoriatic arthritis, as they are "borrowed" from RA and AS. It is also known that most of those scores are better suited for clinical trials [52]. In PsA, MID for HAQ-DI, pain is shown to be the best predictors for a patient's perception of overall changes in disease status [53]. It should be emphasized the limitation of DAS 28 in assessing

disease activity in PsA, because it does not include distal interphalangeal joints of the hands, as well as feet. Nevertheless, it is a measure with absolute value and could be interesting for assessing PsA arthritic activity in practice. Moreover, it has been proven that DAS28 might be a valuable tool to assess disease activity in PsA patients included in clinical trials [54]. It was found that indices of disease activity performed better than the single variables and the DAS28 low-disease activity criterion performed as well as the ACR20, PsARC (Psoriatic Arthritis Response Criteria) and OMERACT criteria. Therefore, we felt that keeping DAS28 is of more value that omitting it.

Frediani *et al* found that demineralization was not related to the indices of inflammation (ESR, CRP) or disease duration, but there was a significant correlation between BMD and HAQ score both in men and postmenopausal women [10]. Results from the study where BMD was measured using ultrasound showed that values were unrelated to disease duration or to ESR and C-reactive protein [55]. Also, in the sample of patients with PsA from India, no correlation was found between BMD and the duration of the disease [56].

It seems that in patients with RA, the indicators of disease activity are better correlated to bone mass. In cross sectional and prospective studies inflammatory disease activity may be the most important factor associated with bone loss and fractures in RA, compared with well known risk factors such as menopausal status, low BMI, reduced physical activity, and corticosteroids [57-59].

The main limitation of the study is the lack of control group, which may enable a direct comparison of osteoporosis prevalence and risk factors between patients and matched controls. However, due to the fact that finding of osteoporosis in our sample of patients was relatively low, we think that direct comparison of BMD with matching control group would not have added new information. The cross-sectional design is another limitation inherent in the study design. Diversity of types of PsA i.e. not having an uniform group in that respect might have somewhat influenced our results, too.

The group of patients in our study is likely to be subject to residual confounding by body mass index, calcium and vitamin D intake and other unmeasured risk factors. There could be misclassification with the diagnoses of PsA as we did not use any formal classification criteria, although it is not likely, because the diagnosis was established by experienced rheumatologist.

Conclusions

Patients in our sample with long-term PsA had low prevalence of osteoporosis. Indicators of disease activity did not correlate significantly with measures of bone mass. Higher HAQ scores correlated with lower total hip BMD while higher cumulative steroid dose was associated with lower lumbar spine BMD and Z score.

The authors declare that no one of them have conflict of interest regarding this paper.

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Table 1. Age, medical history data, bone mineral density and Z-score in men and women.

Parameter	*Men (N 31) mean±SD*	*Women (N 38) mean±SD*
Age (yrs.)	54.3±12.1	57.7±12.2
Duration of Ps (mo.)	208.3±101.7	239.2±162.2
Duration of PsA (mo.)	161.2±101.2	158.6±119.9
Cumulative prednisolone (or equivalent) dose (mg/yrs.)	59.4±45.9	41.8±24.6
Lumbar spine BMD (g/cm^2)	1.025±0.164	0.988±0.157
Total hip BMD (g/cm^2)	1.034±0.157	0.942±0.144
Femoral neck BMD (g/cm^2)	0.823±0.125	0.750±0.232
Lumbar spine Z score	-0.058±1.583	0.716±1.623
Total hip Z score	0.413±1.059	0.876±1.246
Femoral neck Z score	0.045±0.929	0.549±1.229

For all variables $p>0.01$

Figure 1 - in a separate file

Figure 1. Distribution of patients according to WHO classification of osteoporosis in lumbar spine, hip and femoral neck. (N=69)

Table 2. Measures of disease activity and functional status in men and women.

Variable	*Mean*	*Standard deviation*	*Minimum*	*Maximum*
Morning stiffness (min)				
-men	43.3	50.8	0	180
-women	62.9	118.3	0	720
Tender joint count (0-68)				
-men	15.8	14.6	0	47
-women	24.5	17.9	2	60
Swollen joint count (0-66)				
-men	8.8	11.1	0	47
-women	7.1	6.9	0	27
Dactylitis – number of fingers (0-20)				
-men	2.5	4.2	0	18
-women	1.7	2.1	0	8
Enthesitis – number of sites (0- 13)				
-men	2.9[1]	3.5	0	11
-women	5.6	4.0	0	13
Patient's global assessment (VAS/0-100)				
-men	50.5	25.4	0	100
-women	44.3	20.5	1	81
Physician's global assessment (VAS/0-100)				
-men	65.4	18.5	25	97
-women	55.0	21.8	16	95
Health Assessment Questionnaire - HAQ (0-3)				
-men	0.86[2]	0.79	0	2.6
-women	1.55	0.77	0.1	3.0
ESR (mm/h)				
-men	20.1	15.5	2.0	63.0
-women	28.9	17.6	3.0	84.0
CRP (mg/L)				
-men	13.1	16.4	0.9	59.0
-women	8.1	7.5	0.4	24.0
Disease Activity Score 28 – DAS 28 (0-10)				
-men	3.7	1.4	1.2	6.1
-women	4.5	1.2	1.8	7.3

[1]p=0.009; [2]p=0.000 (t-test; men:women)

Table 3. Correlation matrix between variables of interest.

	Lumbar spine BMD (g/cm^2)	*Total hip BMD (g/cm^2)*	*Femoral neck BMD (g/cm^2)*	*Lumbar spine Z score*	*Total hip Z score*	*Femoral neck Z score*
Age (yrs.)	0.063	-0.097	-0.110	0.241	0.213	0.208
	(0.611)	(0.429)	(0.366)	(0.046)	(0.079)	(0.085)
PsA duration(mo)	0.012	-0.022	-0.054	0.225	0.220	0.219
	(0.923)	(0.859)	(0.660)	(0.067)	(0.073)	(0.074)
Patient's global assessment	0.197	0.094	0.011	-0.165	-0.176	-0.170
	(0.106)	(0.442)	(0.927)	(0.174)	(0.148)	(0.162)
Physician's global assessment	0.259	0.200	0.226	-0.163	-0.174	-0.171
	(0.034)	(0.104)	(0.063)	(0.183)	(0.154)	(0.162)
Morning stiffness (min)	0.040	-0.013	-0.070	0.005	0.000	-0.002
	(0.753)	(0.914)	(0.583)	(0.964)	(1.000)	(0.987)
Tender joint count (0-68)	-0.070	0.015	-0.063	0.064	0.078	0.076
	(0.568)	(0.898)	(0.607)	(0.599)	(0.524)	(0.534)
Swollen joint count (0-66)	0.097	-0.002	0.007	0.003	-0.006	-0.005
	(0.470)	(0.988)	(0.958)	(0.978)	(0.966)	(0.970)
ESR (mm/h)	0.127	-0.044	0.064	0.306	0.161	0.214

	(0.314)	(0.724)	(0.609)	(0.013)	(0.198)	(0.086)
CRP (mg/L)	0.186	0.153	0.174	-0.020	-0.025	-0.024
	(0.195)	(0.286)	(0.225)	(0.889)	(0.859)	(0.865)
HAQ	-0.140	*-0.315*	-0.206	0.197	0.181	0.179
	(0.252)	*(0.009)*	(0.088)	(0.104)	(0.136)	(0.140)
DAS	0.105	0.003	-0.027	0.163	0.129	0.111
	(0.408)	(0.977)	(0.827)	(0.192)	(0.304)	(0.379)
Enthesitis (No.)	-0.131	-0.133	-0.085	0.201	0.207	0.209
	(0.315)	(0.309)	(0.515)	(0.122)	(0.111)	(0.109)
Dactilitis (No.)	-0.057	-0.048	-0.112	-0.178	-0.149	-0.115
	(0.658)	(0.709)	(0.384)	(0.166)	(0.247)	(0.373)
Cumulative dose of steroid therapy	*-0.783*	-0.306	0.003	*-0.683*	-0.376	-0.322
	(0.000)	(0.146)	(0.988)	*(0.000)*	(0.063)	(0.116)

Results are presented as Pearson's coefficient of correlation and p value in brackets