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FREQUENCY OF OSTEOPOROSIS AND THE RELEVANT RISK FACTORS IN FEMALE PATIENTS WITH RHEUMATOID ARTHRITIS

ROMATOİD ARTRİTLİ BAYAN HASTALARDA OSTEOPOROZ SIKLIĞI VE RİSK FAKTÖRLERİ

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SUMMARY

Our aim was to investigate frequency of osteoporosis and the relevant risk factors in female patients with rheumatoid arthritis.

This study included 77 female patients with rheumatoid arthritis. A thorough history was taken and physical examination and laboratory investigations were carried out in all patients. Bone mineral density of both the lumbar vertebra and the hip was measured with dual energy x-ray absorptiometer.

It can be concluded that one of every three women with rheumatoid arthritis suffer from osteoporosis of the lumbar vertebra and/or the femur. Duration of the disease, rheumatoid factor titer, erythrocyte sedimentation rate, modified health assessment questionnaire scores, Steinbroker's functional stage, presence of subchondral erosion, duration of steroid treatment and dose of steroids and postmenopausal osteoporosis are the risk factors for osteoporosis in patients with rheumatoid arthritis.

Key Words: *Rheumatoid arthritis, Osteoporosis, Female patients.*

ÖZET

Amacımız, romatoid artritli bayan hastalarda osteoporoz sıklığını ve ilişkili risk faktörlerini araştırmaktı. Çalışmaya romatoid artrit tanısı alan 77 bayan hasta dahil edildi. Hastaların ayrıntılı hikayesi alınarak, klinik muayene ve laboratuvar bulguları kaydedildi.Kemik mineral yoğunluğu dual enerji x-ışını absorbsiyometre ile hem lumbal vertebra hem de kalçadan ölçüldü.

Çalışmamız, romatoid artritli her üç kadından birinde lumbal vertebra ve/veya femurda osteoporoz olduğunu ve postmenaposal osteoporoz ile ilişkili risk faktörleri yanında hastalık süresi, romatoid faktör titresi, eritrosit sedimentaston hızı, modifiye sağlık değerlendirme anketi skoru, Steinbroker fonksiyonel evresi, subkondral erozyon varlığı, steroid tedavi süresi ve dozunun romatoid artritli kadınlarda osteoporoz için risk faktörü olduğunu göstermiştir.

Anahtar Kelimeler: *Romatoid artrit, osteoporoz, bayan hasta.*

INTRODUCTION

Generalized osteoporosis is one of the most common extra-articular manifestations of rheumatoid arthritis (RA) and appear on both axial and appendicular skeleton (1-3). The mechanisms of bone loss in RA has not been understood well; however, increased pro-inflammatory cytokines which play a major role in the pathogenesis of the disease and increased bone resorption have been implicated (4,6). Recent studies have shown that osteoclast differentiating factor is released from many cells between the bone and the pannus in patients with RA, which supports the theory that both local and systemic bone destruction is largely regulated by osteoclast activation (7,8). The most important factors effective on osteoporosis in RA are the disease activity, decreased mobility caused by functional impairment and steroid treatment (1,9-11). In addition, there have been studies reporting that low dose of steroids (11-14), sex and menopause affect bone mass (15). It has also been reported that effects of RA on axial bone mass are different from those on appendicular bone mass (16). The aim of this study was to investigate the frequency of osteoporosis in female patients with RA and the relevant risk factors for osteoporosis.

MATERIALS AND METHODS

This study included 77 female patients with RA based on ACR (American Collage of Rheumatology) criteria (1987). Patients

with bilateral hip prosthesis, those who underwent bilateral oopherectomy, those who can not walk functionally, those with systemic and/or metabolic disorders affecting bone metabolism and those with a history of a drug treatment effective on bone density were not included in the study. All patients were asked about their demographic and physical characteristics, their disease and the treatments they received before. To evaluate disease activity, the number of swollen joints and sensitive joints, duration of morning stiffness and pain severity were recorded. We used 100 mm visual analogue scale (VAS) to determine the pain severity. Also, involvement of weight bearing joints, extraarticular involvements and types of joint involvements (poly/oligoarticular) were recorded. Steinbroker's functional staging (SFS) and modified health assessment questionnaire (MHAQ) were used to determine functional status and disability respectively. Serum C-reactive protein (CRP) levels, erythrocyte sedimentation rate (ESR) and rheumatoid factor (RF) titer were investigated. Hand-wrist x-rays were taken to assess subchondral erosion of the hand joints and toracho-lumbar x-rays were obtained to assess fractures of the vertebra. BMD of both lumbar vertebra and the hip was measured with dual energy x-ray absorpsiometer. Patients with T scores of ≤ -2.5 were accepted as osteoporosis.

Variance analysis was used to analyze effects of constant variables with a normal distribution on the frequency of osteoporosis and Kruskall Wallis and Mann Whitney U tests were used to analyze effects of constant variables (table III) without a normal distribution on the frequency of osteoporosis. Kolmogorov Smirnov test was used to determine whether the variables showed a normal distribution. The variables with a normal distribution were expressed as mean values and standard deviations and the variables without a normal distribution were expressed as median values and quarterly deviations. Chi-square test and odds ratios were used to determine the relation between categorical variables (table IV) and osteoporosis. Pearson correlation coefficient was used to analyze the linear relation between BMD and the constant variables.

RESULTS

The mean age of the patients was 52 years (range: 21-73 years) and the mean duration of the disease was 10 years (range: 1-25 years). Forty-two patients (54.5%) were in the postmenopausal period and duration of menopause was 13 years (range: 1-35 years). Sixty-five patients were currently using one or more DMARDs, 4 patients quitted using the drugs and 8 patients never used the drugs. Thirteen patients were taking (16.9%) a high dose of steroids (>10mg/day prednisolon), 32 patients (41.6%) a low dose of steroids (<10mg/day prednisolon) for a mean 53.6 months. Forty-six patients (59.7%) were taking methotrexate (7.5-15mg/week). Sixty patients (78%) had morning stiffness lasting for a mean of 90 minutes. Twelve patients (15.6%) had a history of extravertebral fractures (colles, femur neck, ankle), 57 patients (74%) had subchondral erosion on their hand x-rays and 19 patients had(24.7%) at least one vertebral fracture on their thoraco-lumbar x-rays. The results of physical examinations and laboratory investigations are shown in tables I and II.

Table I: General Characteristics of Patients

General Characteristics of Patients	
Age* (year)	52 ±11.5 (21-73)
Height* (cm)	156± 5.5 (141-170)
Weight* (kg)	65±12.9 (36-97)
Duration of Disease* (years)	10 ±6.7 (1-25)
Duration of Menopause*(year)	13 ±8.5 (1-35)
The Number of Swollen Joints*	5 ±3.7 (1-13)
The Number of Sensitive Joints*	12 ±7.9 (0-26)
Duration of Morning Stiffness*(Min)	90± 79.7 (10-480)
Pain Severity* (VAS 0-100)	43 ±30.2 (0-98)
MHAQ score*	1.2 ±0.7 (0-2.7)
ESR* (mm/h)	45 ±23.3 (10-90)
CRP+ (mg/l)	12 (4-24)
RF+ titer	1/64 (1/32-1/128)

* mean ± standard deviation (minimum-maximum)
+ Median (%25-%75 deviation)

Table II: Physical Characteristics of Patients

	n	%
Smoking	5	% 6.5
Menopause	42	% 54.5
Polyarticular Involvement	73	% 94.8
Extraarticular involvement	13	% 16.9
Involvement of Weight Bearing Joints	71	% 92.2
Morning Stiffness	60	% 78
Subcondral Erosion	57	% 74
Vertebral Fracture	19	% 24.7
Extra-vertebral Fracture	12	% 15.6
Swollen Joint	51	% 66.2
Steinbroker's Stage		
Stage 1	19	% 24.7
Stage 2	43	% 55.8
Stage 3	15	% 19.5
Steroid Therapy	45	% 58.5
High Dose of steroids	13	% 16.9
Low Dose of Steroids	32	% 41.6
Methotrexate Therapy	46	% 59.7

Examination of BMD revealed that 25 patients (32.5%) had osteoporosis of the lumbar vertebra, 25 patients (32.5%) had osteoporosis of the femoral neck and 14 patients (18.2%) had osteoporosis of the total hip. There was a significant negative

correlation between age, duration of postmenopausal period, RF titer and BMD of lumbar vertebra, the femoral neck and the total hip. We found negative corelation between duration of steroid therapy and BMD of the femoral neck and the total hip. MHAQ scores and ESR were negatively correlated with BMD of the lumbar vertebra. Disease duration was negatively correlated only with BMD of the total hip (p<0.05, Table III).

Table III: Correlation Coefficients between BMD and Risk Factors

		BMD of Lumbar Vertebra	BMD of Femoral Neck	BMD of Total Hip
Age	r	-,327	-,361	-,270
	p	0.004	0.002	0.020
Weight	r	,212	,225	,277
	p	0.065	0.054	0.017
Height	r	,319	,289	,282
	p	0.005	0.012	0.015
Duration of Disease	r	-,092	-,147	-,238
	p	0.432	0.212	0.041
The Number of Swollen Joints	r	-,113	-,042	-,082
	p	0.330	0.724	0.488
The Number of Sensitive Joints	r	-,004	-,013	,043
	p	0.976	0.914	0.719
Duration of Morning Stiffness	r	,020	,106	,160
	p	0.866	0.369	0.173
MHAQ scores	r	-,238	-,175	-198
	p	0.038	0.136	0.091
Pain Severity	r	,071	-,017	-,007
	p	0.542	0.885	0.954
ESR	r	-,274	-,077	-,103
	p	0.017	0.513	0,381
CRP	r	-,205	-,047	-,032
	p	0.076	0.691	0.789
RF titer	r	-,236	-,250	-,250
	p	0.040	0.032	0.032
Duration of Menopause	r	-,445	-,480	-,348
	p	0.0001	0.0001	0.002
Duration of Steroid Therapy	r	-,175	-,238	-,307
	p	0.131	0.041	0.008

There was a significant positive correlation between height and BMD of the lumbar vertebra, the femoral neck and the total hip. Weight was positively correlated with BMD of the total hip (p<0.05, Table III). There was no relationship between osteoporosis and the number of swollen joints, the number of sensitive joints, duration of morning stiffness, pain severity, CRP levels which are indicators of disease activity, polyarticular involvement, extraarticular involvement and involvement of weight bearing joints which are indicators of disease severity. (p>0.05, Tables III and IV). Smoking was a risk factor for osteoporosis of the femoral neck and the total hip. Subchondral erosion was detected as a risk factor for osteoporosis of the lumbar vertebra and the femoral neck. Menopause was a risk factor for osteoporosis of the lumbar vertebrae, the femoral neck and the total hip (p<0.05, Table IV). Methotrexate and low doses of steroids were not risk factors for osteoporosis (p>0.05, Table IV), but high doses of steroids were risk factors for osteoporosis of the lumbar vertebra and the total hip (p=0.05, p=0.02 respectively, Table IV). SFS was directly related to the frequency of osteoporosis in the lumbar vertebra (p=0.002) and the total hip (p=0.04). BMDs of the lumbar vertebra, the femoral neck and the total hip were significantly lower in patients with vertebral fractures than those without vertebral fractures, and BMDs of the femoral neck was significantly lower in patients with extravertebral fractures than those without extravertebral fractures (p<0.05, Table V).

Table IV: P Values and Significant Odds Ratios to Show the Relationship between Osteoporosis and the Relevant Risk Factors

	BMD of Lumbar Vertebra*	BMD of Femoral Neck*	BMD of Total Hip*	Odds Ratios+
Polyarticular Involvement	0.853	0.677	0.478	-
Involvement of Weight Bearing Joints	0.892	0.920	0.901	-
Extraarticular Involvement	0.146	0.451	0.168	-
Methotrexate	0.421	0.324	0.629	-
Low Dose of Steroids	0.074	0.928	0.417	-
High Dose of Steroids	0.050	0.305	0.020	10 (1.26 -76.9)
Menopause	0.001	0.001	0.012	7 (2.5-19.6)
Smoking	0.243	0.016	0.012	2.2 (1.7-2.8)
Subchondral Erosion	0.046	0.018	0.124	3.8 (1.2-12.2)

* Results of Chi-square test

\+ Amount of risk for osteoporosis of the lumbar vertebrae, the femoral neck of the total hip (95% Confidence Interval)

Table V: BMDs of the Lumbar Vertebra, Femoral Neck and Total Hip in the Presence and Absence of Vertebral and Extra-vertebral Fractures.

		BMD of Lumbar Vertebra	P	BMD of Femoral Neck	P	BMD of Total Hip	P
Vertebral fracture	+	-2.87±1.29	0.0001	-2.74±1.27	0.0001	-2.38±1.18	0.0001
	-	-1.31±1.23		-1.55±1.12		-1.13±0.98	
Extra-vertebral fracture	+	-2.05±1.34	0.322	-2.60±1.27	0.023	-1.95±1.57	0.091
	-	-1.61±1.41		-1.70±1.21		-1.34±1.04	

DISCUSSION

The main finding of this study was that 32.5%, 32.5% and 18.2% of the patients had osteoporosis in the lumbar vertebra, the femoral neck and the total hip respectively. Sinigaglia et al found that 28.8% and 36.2% of the patients had osteoporosis on the lumbar vertebra and the femoral neck respectively (17). Kvien et al reported that osteoporosis more frequently appeared in female RA patients aged between 50 and 70 years than those aged with 17 and 70 years. In fact, 16.8%, 14,7% and 14.7% of the females aged between 17 and 70 years had osteoporosis of the lumbar vertebra, the femoral neck and the

total hip respectively, while 23.3%, 20.7% and 21.1% of the females aged between 50 and 70 years had osteoporosis of the lumbar vertebra, the femoral neck and the total hip respectively (18). Cortet et al performed their study with a follow-up period of 18 months on 45 females and 6 males with RA and found a bone loss of 2.1% in the lumbar vertebra and a bone loss of 3.1% in the femoral neck. They also showed that the loss increased to 5.3% in the femoral neck in postmenopausal women (19). Haugeberg et al in their study on female patients with RA reported that 31.5%, 28.6% and 29.9% of the patients had osteoporosis of the lumbar vertebra, the femoral neck and the total hip respectively (3). Nolla et al measured BMDs of the lumbar vertebra and the femoral neck and reported that osteoporosis was present on at least one area of examination in 44% of the patients (20).

Another important finding of this study was that there was a significant relationship between BMD and age, height, weight, duration of the disease, menopause and its duration, RF titer, ESR, subchondral erosion, SFS and MHAQ scores, but that there was no significant relationship between BMD and the number of swollen joints, the number of sensitive joints, duration of morning stiffness, pain severity, CRP levels, involvement of weight bearing joints, extraarticular joint involvement and polyarticular involvement. In addition, BMDs of the hip and the lumbar vertebra significantly decreased in patients with vertebral fracture and BMDs of the hip significantly decreased in patients with extravertebral fracture. Consistent with our findings, Sinigaglia et al showed that the duration of the disease was longer, MHAQ scores were poorer and the frequency of osteoporosis increased as the functional impairment increased in patients with RA and accompanying osteoporosis and that these patients were older than those with RA only (17). Kvien et al found a relationship between osteoporosis and age, body mass index (BMI), duration of the disease, current use of steroids, presence of a deformed joint, presence of extravertebral fracture and MHAQ scores (18). Haugeberg et al noted that advanced age, low BMI, current use of steroids and high scores of MHAQ are indicators of a decrease in BMD (3). Kröger et al woked on perimenopausal RA patients and demonstrated that there was a relationship between BMD of lumbar vertebra and age, weight and functional stage and between BMD of the femoral neck and weight, functional stage and cumulative use of steroids (21). Uçkan et al also found a correlation between BMD and age, duration of the disease, menopause and RF positivity. However, they found no correlation between BMD and MHAQ scores and steroid therapy. It may be due to sample size of their study was small and they did not classify the patients according to the cumulative dose of steroids (22). Gürsoy et al reported a significant negative correlation between BMD of the lumbar vertebra and age, height and the duration of postmenopause period (23).

Finally, we found that high doses of steroids were risk factors for osteoporosis and that there was a significant negative correlation between BMD of the femoral neck and the total hip and duration of steroid treatment. Nevertheless, there was no significant difference in BMD between patients on low doses of steroids and those not taking steroids. We also found that methotrexate treatment was not a risk factor for osteoporosis. Both Sambrook and Martin et al noted that bone densities were lower in patients on a low dose of steroids than control patients with no significant difference (24,25). Hall et al revealed that BMD of the femoral neck was significantly low and that BMD of the lumbar vertebra was low but not significant in patients taking a high cumulative dose of steroids. They also noted that BMD of the lumbar vertebra and the femoral neck were lower but not significant in patients taking a low cumulative dose of steroids than those not taking steroids. They added that BMD of the lumbar vertebra and the femoral neck were significantly lower in patients currently on steroids than those not on steroids (12). Haugeberg et al reported no significant difference in BMD between patients with a history of steroid treatment and those who never took steroids. However, they showed a significant decrease in BMD of the lumbar vertebra, the femoral neck and the total hip in patients currently on steroids (3). As a result, a short term treatment with low doses of steroids is not a risk factor for osteoporosis, but a long term treatment with high doses of steroids increases the risk considerably for osteoporosis of the hip due to cumulative effects of steroids in RA patients. In addition, consistent with the results of the present study, many other studies reported no negative effect of a low dose methotrexate on bone mineral densities (26-28).

In conclusion, one of every three women with RA has osteoporosis and the relevant risk factors are duration of the disease, RF titer, ESR, MHAQ scores, SFS, presence of subchondral erosion, duration of steroid therapy and doses of steroids as well as the factors effective on postmenopausal osteoporo-

sis, i.e. age, height, weight, smoking, menopause and its duration. However, the number of swollen joints, the number of sensitive joints, duration of morning stiffness, pain severity and CRP levels which are indicators of the disease activity, extraarticular involvement, polyarticular involvement and involvement of weight bearing joints are not risk factors for osteoporosis.

REFERENCES

1. Gough AKS, Lilley J, Eyre S et al. Generalised bone loss in patients with early rheumatoid arthritis. Lancet 1994; 344: 23-27.
2. Lane NE, Pressmann AR, Star VL et al. Rheumatoid arthritis and bone mineral density in elderly woman. J Bone Min Res1995; 10:257-263.
3. Haugeberg G, Uhlig T, Faleh JA et al. Bone mineral density and frequency of osteoporosis in female patients with rheumatoid arthritis. Arthritis Rheum 2000; 43: 522-530.
4. Eggelmeijer F, Papapoulos SE, Westedt ML et al. Bone metabolism in rheumatoid arthritis; relation to disease activity. Br j Rheumatol 1993; 32: 387-391.
5. Gough AKS, Peel NFA, Eastell R et al. Excretion of pyridinium crosslinks correlates with disease activity and appendicular bone loss in early rheumatoid arthritis. Ann Rheum Dis 1994; 53: 14-17.
6. Hakala M, Aman S, Laukkainen R et al. Application of markers of collagen metabolism in serum and synovial fluid for assessment of disease process in patients with rheumatoid arthritis. Ann Rheum Dis 1995; 54: 886-890.
7. Takayanagi H, Lizuka H, Juji T et al. Involvement of receptor activator of nuclear factor kB ligand/osteoclast differentiation factor in osteoclastogenesis from synoviocytes in rheumatoid arthritis. Arthritis Rheum 2000; 43: 259-269.
8. Gravallese EM, Manning C, Tsay A et al. Synovial tissue in rheumatoid arthritis is a source of osteoclast differentiation factor. Arthritis Rheum 2000; 43: 250-258.
9. Sambrook PN, Eisman JA, Champion DG et al. Determinants of axial bone loss in rheumatoid arthritis. Arthritis Rheum 1987; 30: 721-728.
10. Peel NFA, Moore DJ, Barnington NA etal. Risk of vertebral fracture and relationship to bone mineral density in steroid treated rheumatoid arthritis. Ann Rheum Dis 1995; 54:801-816.
11. Lems WF, Jahangier ZN, Jacobs JWG et al. Vertebral fractures in patients with rheumatoid arthritis treated with corticosteroids. Clin Exp Rheum 1995; 13:293-2977.
12. Hall GM, Spector TD, Griffin AJ et al. The effect of rheumatoid arthritis and steroid therapy on bone density in postmenopausal women. Arthritis Rheum 1993; 36: 1510-1516.
13. Butter RC, Davie MVJ, Worsfold M et al. Bone mineral content in patients with rheumatoid arthritis: relationship to low- dose steroid therapy. Br J Rheum 1991; 30: 86-90.
14. Buckley LM, Leib ES, Cartularo KS et al. The effect of low-dose corticosteroids on the bone mineral density of patients with rheumatoid arthritis. J Rheumatol 1995; 22: 1055-1059.
15. Als OS, Gotfredsen A, Riis BJ et al. Are disease duration and degree of functional impairment determinants of bone loss in rheumatoid arthritis? Ann Rheum Dis 1985; 44: 406-411.
16. Compston JE, Crawley EO, Evans C et al. Spinal trabecular bone mineral content in patients with non-steroid treated rheumatoid arthritis. Ann Rheum Dis 1986; 47: 660-664.
17. Sinigaglia L, Nervetti A, Mela Q et al. A multicenter cross sectional study on bone mineral density in rheumatoid arthritis. J Rheumatol 2000; 27: 2582-2589.
18. Kvein TK, Haugeberg G, Uhlig T et al. Data driven attempt to create a clinical algorithm for identification of women with rheumatoid arthritis at high risk of osteoporosis. Ann Rheum Dis 2000; 59: 805-811.
19. Cortet B, Guyot MH, Solau E, Pigny P et al. Factors influencing bone loss in rheumatoid arthritis: A longitudinal study. Clin Exp Rheum 2000; 18: 683-690.
20. Nolla JM, Fiter J, Gomez-Vaquero C et al. Value of clinical factors in selecting postmenopausal women with rheuma-

toid arthritis for bone densitometry. Ann Rheum Dis 2001; 60: 799-801.

21. Kröger H, Honkanen R, Saarikoski S et al. Decreased axial bone mineral density in perimenopausal women with rheumatoid arthritis – a population based study. Ann Rheum Dis 1994; 53: 18-23.

22. Uçkan F, Dursun E, Dursun N et al. Osteoporosis in patients with rheumatoid arthritis. J Rheum Med Rehab 2002; 13: 212-218.

23. Gürsoy S, Adam M. Romatoid artritli olguların fonksiyonel durumu, hastalık süresi, ESH, KMY değeri, osteokalsin ve CRP düzeyi arasında korelasyonların varlığının araştırılması. Romatizma 2000; 15: 167-171.

24. Sambrook PN, Eisman JA, Yeates MG et al. Osteoporosis in rheumatoid arthritis: safety of low dose corticosteroids. Ann Rheum Dis 1986; 45: 950-953.

25. Martin JC, Munro R, Campbell MK et al. Effects of disease and corticosteroids on apendicular bone mass in postmenopausal women with rheumatoid arthritis: comparison with axial measurements. Br J Rheumatol 1997; 36: 43-49.

26. Mazzantini M, Di Munno O, Incerti-Vecchi L et al. Vertebral bone mineral density changes in female rheumatoid arthritis patients treated with low-dose methotrexate. Clin Exp Rheumatol 2000; 18: 327-331.

27. Cranney B, Mckendry RJ, Wells GA et al. The effect of low dose methotrexate on bone density. J Rheumatol 2001; 28: 2395-2399.

28. Minaur NJ, KounaliD, Vedi S et al. Methotrexate in the treatment of rheumatoid arthritis. II. In vivo effects on bone mineral density. Rheumatology 2002; 41: 741-749.

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