

Bone mineral density changes in patients with rheumatoid arthritis

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Abstract

Background and objective: Bone loss regarded as a major health concern which is thought to be associated with a number of chronic illnesses including rheumatoid arthritis. This study was designed to determine the frequency of low bone mass as well as the influence of disease duration on bone mass in the patients with rheumatoid arthritis.

Methods: Sixty patients with rheumatoid arthritis who were visiting Rizgary Teaching Hospital in Erbil from April 2015 to March 2016 were included in a cross-sectional study. Bone mineral density was measured using dual energy X-ray absorptiometry.

Results: There was increased frequency of bone loss in patients with rheumatoid arthritis. There was a positive association between bone mineral density of the spine and femoral neck with disease activity measured by disease activity score and disease activity index ($P < 0.05$). There was a significant association between bone mineral density and disease duration.

Conclusion: Significant proportions of patients with rheumatoid arthritis have osteoporosis at the femoral neck and lumbar spine, and disease duration longer than five years is associated with a significant increase in bone loss.

Keywords: Rheumatoid arthritis; Bone loss; Bone densitometry

Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory disease that affects all ethnic groups throughout the world¹ characterized by symmetric erosive synovitis.² Female are 2.5 times more likely to be affected than male.³ Rheumatoid arthritis is associated with periarticular bone loss adjacent to inflamed joints and generalized osteoporosis, leading to increased risk of fractures in both the appendicular and axial skeleton.⁴ The chronic synovial inflammation in RA can promote osteoclast genesis, leading directly to both focal and generalized bone loss and increased risk of fractures. In addition, many indirect factors associated with inflammatory arthritis contribute to risk of osteoporosis including immobility, weight loss, and use of medications known to promote bone loss such as glucocorticoids and disease

modifying agents.⁵ Bone mass in RA appears to be adversely affected by functional impairment and active inflammation, especially in early course of disease.⁵ Osteoporosis is a disease defined by low bone density and deterioration of micro architectures, which reduces bone strength and increase fracture risk. The prevalence of osteoporosis increase markedly with increasing age, fractures related to osteoporosis are a major public health problem in all developed countries, affection up to 30% of women and 12% of men at some time of their life.¹ The threshold for establishing a diagnosis of osteoporosis will be based on the world health organization (WHO) definition; bone mineral density (BMD) is measured by using dual energy X-ray absorptiometry (DEXA) at proximal femur and lumbar spine.⁶ Osteoporosis is an extra-articular

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complication of rheumatoid arthritis. Decrease bone mineral density (BMD) plus an Increase of both hip and vertebral fractures in patients with RA compared with patients without RA has been demonstrated in several studies.^{7,8} The Disease Activity Score 28 (DAS28) is a major scoring system for evaluating disease activity of RA. The initial development of DAS was reported by van der Heijde et al. in 1990 and 1992, and then DAS was modified by a group of investigators from the Netherlands.⁹ The use of DAS28 is officially recommended by the European League against Rheumatism (EULAR) for evaluating disease activity and the improvement in disease activity in clinical trials and also in daily clinical practice. DAS28 is calculated according to the formula that is composed of the number of tender joints and swollen joints, patient's global assessment of disease activity on a visual analogue scale (VAS), and erythrocyte sedimentation rate (ESR), or C-reactive protein (CRP).⁹ In clinical practice, CRP and ESR are used in monitoring disease activity and response to the treatment. CRP is one of the best indicators of the acute phase response to inflammation, because it may increase to 1,000 fold during an acute phase reaction. Increased values are found in chronic and acute inflammation.¹⁰ This study was designed to assess the frequency of bone loss with RA in patients living in Erbil city as no similar studies has been conducted before in Kurdistan region.

Methods

This cross-sectional study was carried out in the Rheumatology and Medical Rehabilitation Department of Rizgary Teaching Hospital in Erbil City from April 2015 to March 2016. Sixty patients who fulfilled EULAR-ACR-2010 and ACR 1987 criteria for RA were chosen by convenience method of sampling. The exclusion criteria included those patients who had metabolic and endocrine disease (hypothyroidism and hyperthyroidism), other inflammatory

diseases like systemic lupus erythematosus, inflammatory bowel diseases, patients who had BMI less than 19, patients less than 16 years and above 55 years of age, patients with chronic alcoholism, who were pregnant and those who were on certain drugs such as cyclosporine, prednisolone >5 mg, thyroxin, heparin, and anticonvulsants. Data were collected and recorded on a specially designed questionnaire after getting verbal consent from the patients. Laboratory investigations were done to estimate ESR, latex test. Bone mineral density was measured for all patients using DEXA at proximal femur and lumbar spine to diagnose osteoporosis according to world health organization definition. T-score = 1 standard deviation (SD) consider normal, T-score between- 1 to > -2.5 consider osteopenia T-score \leq -2.5 consider osteoporosis. The activity of disease was assessed by DAS28 and CDAI parameters. Based on DAS28 patients were graded as in remission <2.6, low active <3.2, moderate 3.2-5.1 and highly active >5.1 and for CDAI were entitled into in remission <2.8, low active <10, moderate 10-22 and highly active >22. The influence of disease duration on BMD was assessed by comparison of the BMD values between patients with disease duration of less than two years with those with disease duration of 2-5 years as well as with patients with a disease duration longer than five years. Drug therapy was noted. The data were managed by Excel using Chi-square test. A *P* value less than 0.05 was considered statistically significant. The study protocols of the original research projects and the current study were approved by the Research Ethics Committee at the College of Medicine of Hawler Medical University.

Results

A total of 60 participants joined the study; 93.3% of them were female and 6.7% were male. The female to male ratio was 14:1. The mean age \pm SD were 42.2 ± 9.3 years, the age of participants was ranging from 24

to 55 years. Most of the study participants were female, non-smoker, having RA for less than two years, with sun-exposure of less than 20 minutes and walking for less than half an hour per day. Most of the participants had negative rheumatoid factor and family history of RA;

they were receiving DEMARD and steroids as the first treatment option, with regular compliance, morning stiffness of less than one hour associated with high DAS 28 levels and remission CDAI results (Table 1).

Table 1: Descriptive data of participants.

Variables	Categories	No.	%
Gender	Male	4	6.7
	Female	56	93.3
Disease duration	< 2 years	27	45
	2 – 5 years	12	20
	> 5 years	21	35
Smoking	Yes	7	11.7
	No	53	88.3
Sun exposure	≥ 20 min	20	33.3
	< 20min	40	66.7
Walking	≥ 30 min	14	23.3
	< 30 min	46	76.7
Current medications	Steroids	4	6.7
	DEMARD	13	21.7
	DEMARD + Biologics	19	31.7
	DEMARD + Steroids	23	38.3
	None	1	1.7
Compliance	Regular	41	68.3
	Irregular	19	31.7
Family history	Positive	26	43.3
	Negative	34	56.7
Morning stiffness	< 1 hour	46	76.7
	≥1 hour	14	23.3
Rheumatoid factor	Positive	28	46.7
	Negative	32	53.3
DAS-28	Remission	12	20
	Low	5	8.3
	Moderate	12	20
	High	31	51.7
CDAI	Remission	28	46.7
	Low	10	16.7
	Moderate	6	10
	High	16	26.7

There was a significant statistical association between BMD spine and duration of disease, CDAI and DAS28. Totally 8 cases (13.3%) had osteoporosis in lumbar spine, while 13 cases (21.6) had osteopenia. Most of the patients with normal BMD spine had the disease for less than two years in contrast to patients with osteopenia and osteoporosis who had the disease for more than five years. The large

percentage of participants with normal BMD spine were in remission phase according to CDAI and DAS 28 results while most of osteopenia and osteoporosis cases had moderate or high CDAI and DAS levels. There was a non-significant statistical relationship between BMD spine and gender and smoking. The majority of participants were non-smoker and female (Table 2).

Table 2: Association between BMD Spine and different measures.

Measure	Category	BMD Spine			P value
		Normal No. (%)	Osteopenia No. (%)	Osteoporosis No. (%)	
Gender	Male	2 (50%)	1 (25%)	1 (25%)	0.73
	Female	37 (66.1%)	12 (21.4%)	7 (12.5%)	
Smoking	Yes	4 (57.1%)	0 (28.6%)	3 (14.3%)	0.88
	No	35 (66%)	11 (20.8%)	7 (13.2%)	
CDAI	Remission	22 (78.6%)	3 (10.7%)	3 (10.7%)	0.01
	Low	7 (70%)	2 (20%)	1 (10%)	
	Moderate	4 (66.7%)	0 (0%)	2 (33.3%)	
	High	6 (37.5%)	8 (50%)	2 (12.5%)	
DAS 28	Remission	12 (100%)	0 (0%)	0 (0%)	0.01
	Low	1 (20%)	2 (40%)	2 (40%)	
	Moderate	10 (83.3%)	2 (16.7%)	0 (0%)	
	High	16 (51.6%)	9 (29%)	6 (19.4%)	
Duration	< 2 years	26 (96.3%)	0 (0%)	1 (3.7%)	0.001
	2-5 years	6 (50%)	4 (33.3%)	2 (16.7%)	
	> 5 years	7 (33.3%)	9 (42.9%)	5 (23.8%)	

Except for smoking, there was a significant statistical association between BMD of the femoral neck and all associated features. The frequency of OP and osteopenia in FN (femoral neck) were 23.3% (14 cases), 28.3% (17cases) respectively. Most of the patients with normal BMD the disease for less than two years in reverse to patients with osteoporosis who had the disease for

more than five years. The largest proportion of participants with normal BMD spine were in remission phase according to CDAI results while most of osteopenia and osteoporosis cases had moderate or high CDAI levels. Approximately 70% of osteopenia and osteoporosis conditions had high DAS readings in contrast to only 30% of normal BMD participants (Table 3).

Table 3: Association between BMD Femoral neck and different measures.

Measure	Category	BMD Femoral Neck			P value
		Normal No.(%)	Osteopenia No. (%)	Osteoporosis No. (%)	
Gender	Male	0 (0%)	1 (25%)	3 (75%)	0.03
	Female	29(51.8)	16 (28.6%)	11 (19.6%)	
Smoking	Yes	4(57.1%)	0 (0%)	3 (42.9%)	0.16
	No	25 (47.2%)	17(32.1%)	11(20.8%)	
CDAI	Remission	20 (71.4%)	3(10.7%)	5(17.9%)	0.03
	Low	4 (40%)	4 (40%)	2 (20%)	
	Moderate	1 (16.7%)	3 (50%)	2 (33.3%)	
	High	4 (25%)	7 (43.8%)	5 (31.3%)	
DAS 28	Remission	8 (66.7%)	3 (25%)	1 (8.3%)	0.03
	Low	2 (40%)	1 (20%)	2 (40%)	
	Moderate	10 (83.3%)	1 (8.3%)	1 (8.3%)	
	High	9 (29%)	12 (38.7%)	10 (32.3%)	
Duration	< 2 years	19 (70.4%)	7 (25.9%)	1 (3.7%)	0.001
	2-5 years	5 (41.7%)	5 (41.7%)	2 (16.7%)	
	> 5 years	5 (23.8%)	5 (23.8%)	11 (52.4%)	
BMD Spine	Normal	26 (66.7%)	10 (25.6%)	3 (7.7%)	0.001
	Osteopenia	2 (15.4%)	5 (38.4%)	6 (46.2%)	
	Osteoporosis	1 (12.5%)	2 (25%)	5 (62.5%)	

Discussion

Osteoporosis (OP) has frequently been described in patients with RA and longitudinal studies have documented increased rate of bone loss in RA patients.^{12,13} Hence we investigated prospectively the occurrence of osteoporosis and bone loss in RA patients and its association with disease activity. Furthermore, we estimated BMD in relation to disease duration. Our results show that osteoporosis occurred in 23.3% and 13.3% in the femoral neck and spine, respectively. This finding is more than Haungeberg *et al.*, in a study of RA patient aged 20-70 years with a mean disease duration of 13 years, found OP at FN and LS in 14.7% and 16.8% of cases, respectively.¹⁴ Our finding is less than that found in the study done in Iran in which 40.4% of cases had OP.¹⁵ In that study, the frequency of OP at the FN and LS were 34.9% and 25%, respectively. This difference could be due to life-style, treatment option, lack of regular exercise and sun exposure. Additionally, in most other similar studies the prevalence of OP in RA has been higher than expected. A study in a cohort of general Chinese men has shown a significant association between RA and OP: the men with RA had a significant higher prevalence of OP (21.62% in RA group vs 8.36% in the non-RA group, $P = 0.005$).¹⁶ Our findings were consistent with other studies reported that RA was associated with OP, a previous study has shown that there is a higher prevalence of OP in a group of Korean female RA patients (22.1%) compared with the healthy control group (11.4%).¹⁷ Similarly, cohort study of 394 female patients with RA compared to control also revealed doubled prevalence of OP.¹⁸ A study focusing on young patients with RA.^{19,20} In our study, we found that patients diagnosed with RA had significantly reduced bone mass (osteopenia) in spine and FN 21.6%, 28.3% respectively, this is close to Haungeberg *et al.*, In a study of RA patient aged 20-70 years with a mean disease

duration of 13 years, found the prevalence of reduced bone mass was 27.6% at FN, and 31.6% at LS.¹⁴ The etiology of reduced bone mass in RA is multifactorial, including lifestyle risk factors and disease-related determinants. Persistently high levels of inflammation, low levels of physical activity and use of corticosteroids are associated with increased risk of bone loss.^{12, 13, 21-26}

Our study also shows a positive association between BMD changes in RA patients and disease activity indicating higher DAS28 and CDAI in osteopenia and osteoporosis cases. This is in agreement with another study that has evaluated BMD and disease activity in RA patients as done in Birmingham 1996. Our finding did not match with the study done in Cairo, Egypt 2011²⁷ which state that BMD changes do occur in patients with early RA, and are not necessarily correlated with disease activity (DAS-28). It is important to mention that disease duration of more than five years is associated with bone loss in particular at FN regardless of treatment. Most of the patients with normal BMD of spine and FN had disease duration for less than two years in reverse to patients with osteoporosis who had the disease for more than five years. This was matched with other study done in Iran 2005.²⁸ Finally, we found that there was statistically significant difference between BMD FN and spine, OP were more frequent in FN it could be ascribed to osteoarthritis of the spine (osteoarthritis affect spine earlier than FN, in turn, lead to false increase of BMD), atherosclerosis of the aorta, and vertebral deformities, which increase the measured BMD and thus obscure a possible relation between potential predictors and 'true' BMD.²⁹ The same mechanism might explain the lower percentage of variance explained by the final model of spine BMD compared with hip BMD. Because of the difficult interpretation of a spine BMD measurement, recent recommendations prefer the measurement of BMD in the hip to other sites.³⁰ There were some weak points in our study, it was a prospective

cross-sectional study, and the sample size was relatively small. Furthermore, the selection of cases was not through random sampling, and certainly, there was selection bias. Thus more study is required to know the exact pathophysiology of bone loss in RA patient.

Conclusion

The results of this study indicate that a significant proportion of patients with RA have OP at the FN and LS, and disease duration longer than five years is associated with a significant increase in bone loss. Further longitudinal studies are required to know the exact pathophysiology of bone loss in RA patients. More interventional studies are required to investigate treatment option to prevent OP in RA patients.

Conflicts of interest

The authors report no conflicts of interest.

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