Measurement of Foot Bone Mineral Density in Rheumatoid Arthritis: Its Application and Clinical Relevance

Romatoid Artritli Hastalarda Ayak Kemik Mineral Yoğunluğunun Ölçülmesi: Yöntemin Uygulanması ve Klinik Önemi

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Abstract

Objective: Hand and foot joints are the primary targets in rheumatoid arthritis (RA) and decrease in the periarticular bone mineral density (BMD) is one of the earliest and considerable change in the affected joint. This study aimed to assess the relationship between foot bone mineral density (fBMD) measured by Dual Energy X-ray absorptiometry (DEXA) and BMD at axial sites, disease activity, functional status and quality of life in patients with RA

Materials and Methods: 50 patients with RA, 40 age- and sex-matched patients with osteoarthritis (OA) and 14 voluntary healthy individuals were included in the study. C-reactive protein, erythrocyte sedimentation rate (ESR), Ritchie Articular Index (RAI), Health Assesment Questionnare (HAQ), and Foot Function Index (FFI) were measured. X-ray of the feet was scored by Larsen and Sharp/van der Heijde methods. Axial and fBMD were measured by DXA.

Results: The results of the present study revealed that Turkish patients with RA carrying SE with HLA-DRB1 genes is significantly related with the production of anti-CCP. The diagnostic sensitivity and specificity of anti-CCP for RA is determined as 73,3% and 100% respectively.

Conclusion: These results suggest for the first time that foot BMD measurement by DEXA is a useful and precise method. Foot BMD may reflect both localized and generalized bone loss and may be a potential outcome measure particularly in patients with marked foot involvement. *(Turk J Rheumatol 2010; 25: 56-62)*

Key words: Foot, bone mineral density, DEXA, rheumatoid arthritis

Received: 11.09.2008 **Accepted:** 29.01.2009

Özet

Amaç: Romatoid artritte (RA) el ve ayak eklemleri genellikle öncelikli olarak etkilenmektedir. Periartiküler kemik mineral yoğunluğundaki (KMY) değişiklikler ise bu hastalığın en erken ve dikkati çeken radyolojik bulgularındandır. Bu kontrollü çalışmada RA'lı hastalarda geliştirdiğimiz bir yöntemle DEXA ile ayak KMY'si, aksiyel iskelet KMY'si, hastalık aktivitesi, fonksiyonel durumu ve yaşam kalitesi ile ilişkileri değerlendirilmiştir.

Yöntem ve Gereçler: Çalışmaya 50 RA'lı hasta ile yaş ve cins olarak eşleştirilmiş 40 OA'lı hasta ve 14 gönüllü sağlıklı birey alındı. Hastaların C-reaktif protein düzeyi, eritrosit sedimantasyon hızı, Ritchie artiküler indeksi (RAİ), sağlık sorgulama anketi (HAQ), ayak fonksiyon indeksi (FFİ) ölçüldü. Ayak grafileri Larsen and Sharp/van der Heijde yöntemi ile skorlandı. Aksiyel ve ayak KMY'leri Lunar dansitometre cihazında DEXA yöntemi ile ölçüldü.

Bulgular: Ayak KMY'leri kısa dönem tutarlılığı 14 sağlıklı bireyden 3 kez tekrarlanan ölçümle hesaplandı, yüzde değişim katsayısı % 2.18 olarak oldukça uygun bulundu. Her iki ayak ve aksiyel (spinal ve kalça) KMY kontrollere göre anlamlı bir şekilde düşüktü. Sağ ayak KMY ile aksiyel KMY anlamlı şekilde ilişkiliydi. Ancak hastalık süresi ile aktivite indeksleri (RAİ ve FFİ) arasında ilişki yoktu. Her iki ayak total KMY ile Sharp eklem mesafe ve erozyon skoru (SEMS ve SES) arasında negatif bir ilişki varken Larsen skoru ile ilişki bulunamadı. Ayak KMY ile el SEMS, SES ve Larsen skoru arasında anlamlı düzeyde negatif bir ilişki bulundu.

Sonuç: Bu sonuçlar DEXA ile ilk kez yapılan ayak KMY ölçümünün kullanışlı ve geçerli bir yöntem olduğunu göstermiştir. RA'li hastalarda, ayak KMY ölçümü hem bölgesel hemde yaygın kemik kaybını yansıtabilir ve özellikle ayak tutulumu olan hastalarda potansiyel bir sonuç ölçümü olarak kullanılabilir.

(Turk J Rheumatol 2010; 25: 56-62)

Anahtar sözcükler: Ayak, kemik mineral yoğunluğu, DEXA, romatoid artrit

Alındığı Tarih: 11.09.2008 **Kabul Tarihi:** 29.01.2009

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doi: 10.5152/tjr.2010.02

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory auto-immune disease characterized by persistent joint inflammation resulting in joint damage and loss of function. Numerous studies have shown that substantial irreversible damage occurs within the first 2 years, as evidenced by the maximal rate of erosive joint disease during this period (1-3).

Radiological osteopenia of the hands is one of the requirements of American College of Rheumatology (ACR) classification criteria for RA (4). However, X-ray examination is unable to detect bone loss when it is less than 30%. Dual energy X-ray absorptiometry (DEXA) appears to be a more sensitive method in detecting early bone loss in patients with RA. The relationship between BMD, disease duration and bone damage indicates that the DEXA method may be useful in the evaluation of disease activity and progression (5, 6).

Rheumatoid arthritis has a significant effect on foot structure (7) with an estimated prevalence of structural and related problems of up to 50%. Bukhari et al. (8) reported 38% foot involvement in early and/or late stages of the disease. Priola et al. (9) reported that early forefoot involvement is an indication of aggressive disease.

Periarticular osteoporosis is demonstrated on hands by DEXA at an early stage of the disease. Previous studies reported that DEXA method was a useful and precise method and the DEXA results correlated with radiographic damage in the rheumatoid hands (10, 11).

The aim of this study was to investigate the relationship between BMD of the foot, axial BMD, quality of life, functional status and disease activity. We also aimed to better understand the importance of foot involvement in RA and to assess the validity of foot BMD measurement.

Material and Methods

Fifty RA patients who met 1987 ACR criteria for the classification of RA and 48 age- and sex-matched patients with osteoarthritis (OA) were included in the study. In order to detect the short-term precision for DEXA of the foot, 14 healthy volunteers were participated in the validation study.

Patients were under treatment with corticosteroids, disease modifying anti-rheumatic drugs (i.e. methotrexate, sulphasalazine, etc. or combination) or non-steroid anti-inflammatory drugs. Disease activity, disease duration, morning stiffness, and other concomitant disorders were recorded. Routine laboratory studies (complete blood count, C-reactive protein, erythrocyte sedimentation rate, rheumatoid factor etc.) were done. Ritchie Articular Index (RAI), Foot Function Index (FFI) (12), Stoke index, Health Assessment Questionnaire (HAQ), visual analog scale (VAS) of pain were assessed in all patients by the same clinician. Bilateral anteroposterior (AP) radiographs of the hands, posteroanterior (PA) and lateral radiographs of the feet were taken in patients with RA and OA using standard protocols and scored with modified Larsen and Sharp/van der Heijde methods (13, 14).

The study was approved by the Local Ethical Committee of our Institution and written informed consent was obtained from all participants.

Foot Function Index

Foot Function Index (FFI) is an index developed by Budiman-Mak and colleagues to evaluate foot functions in RA patients. It is successfully used in osteoarthritis and plantar fasciitis patients as well. The FFI includes a total of 23 questions and has subscales of pain, disability, and activity limitation. The total score was 10 (12).

Foot BMD by Dual Energy X-ray Absorptiometry Method

DEXA scans were all performed on a Lunar DPX densitometer. We used the same DEXA methodology for the measurement of hand BMD with an analysis package that was originally developed for the measurement of bone mass of small animals and modified for hand BMD measurements. This method did not require a phantom like the aluminum alloy and Perspex plates preferred in previous studies because the current we used was too low (150 μA). We used a collimator of 0.86 mm and detail mode that had pixels of 1.2 × 2.4 mm.

Participants sit on a stiff seat placed on the measurement table with hips at 90 degrees of flexion and knees at 120 degrees of semi-flexion. The foot was placed flat (sole facing down and ankle semi-flexed) on the measurement plate along the longitudinal center line of the scan field. The subtalar bones were palpated and defined the starting position of the laser pointer. Scanning began from subtalar bones through the distal parts of the metatarsal bones and proximal phalanges and required approximately 10 min depending on foot size. The same procedure was repeated for the other foot (Figure 1). The region of interest was subtalar, metatarsal, and phalangeal bones, and it was possible to exclude distal parts of the talar bones during the analysis. The measurements were in grams/cm^2.

Axial BMD Measurements

Axial (spine and hip) BMD measurements were done on L2-L4, femur neck, Ward's triangle, trochanteric area and total femur using the same machine.

Short-term precision of BMD was detected by repeated measurements of right foot, 1-5. metotarsophalangeal (MTP) region, 2. distal metatars and total foot areas of healthy volunteers (15). The coefficient of variation for total foot areas was 2.18%. After showing that the method is sufficient and safe, similar measurements were done in all patients and the control group. Measurement of each foot lasted approximately for 6 minutes.

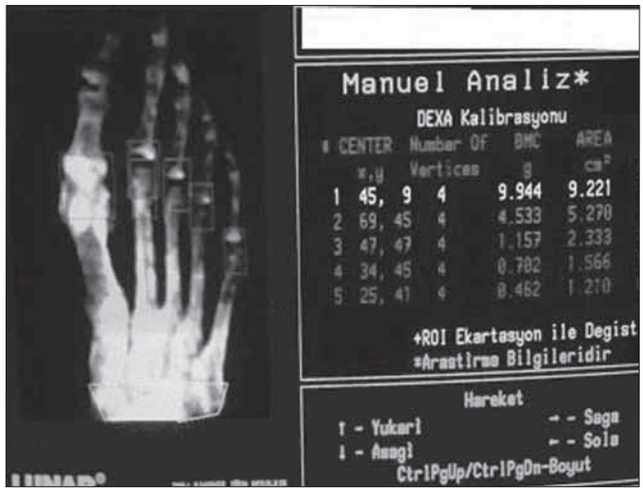

Figure 1. Foot BMD analysis by DEXA

Table 1. Clinical characteristics of the patients with rheumatoid arthritis (RA)

Parameter	Patients with RA (n=50)
Disease duration (year)	9.3±5.8 (1-25)
Morning stiffness (hour)	1.3±1.6 (0-5.6)
VAS (cm) (median, range)	51 (12-100)
HAQ (median, range)	0.925 (0-2.45)
FFI (median, range)	
Pain	4.52 (0-8.94)
Disability	4.04 (0-8.70)
Limitation	2.95 (0-8.70)
Total	3.68 (0-8.57)
RAI	21.0±13.8 (0-61)
Stoke index	6.6±4.3 (1-17)

VAS: Visual Analog Scale; HAQ: Health Assessment Questionnaire; RAI: Ritchie Articular Index, FFI: Foot Function Index

Table 2. Radiographic scoring (mean±SD and range)

	Larsen		Sharp joint narrowing score		Sharp erosion score	
	Hand	Foot	Hand	Foot	Hand	Foot
Rheumatoid arthritis	49.5±.0.1	15.6±8.3	49.7±16.8	17.3±7.0	64.7±20.9	42.4±18.6
(n=50)	(17-111)	(3-36)	(27-109)	(5-38)	(32-131)	(13-98)
Osteoarthritic controls	0.9±1.09	0.5±0.7	1.2±1.1	0.9±0.9	0	0
(n =40)	(0-3)	(0-2)	(0-4)	(0-3)		
p	<0.001	<0.001	<0.001	<0.001	NA	NA

NA: Not available SD: standart deviation

Statistics

Statistical evaluations were done by using SPSS for Windows 10.0 package statistics program (SPSS Inc. Chicago IL USA). For group comparisons *t* test, Mann Whitney U test and chi-square test were used. The Pearson and Spearman correlation coefficients were used to assess relationship between parameters. Percent coefficient of variation was calculated for short-term precision. All data are presented as mean ± SD and $p<0.05$ was considered significant.

Results

All patients with RA were scored according to Stoke index; 8 and above were included in group 1A (20 female, 0 male); and the others in group 1B (25 female, 5 male). In RA group, patients with disease duration ≤ 3 years were labeled as early RA (5 female, 1 male), and the rest were labeled as late RA (40 female, 4 male). In 16% of patients, disease first manifested with foot complaints. Clinical data of the patients are shown in Table 1.

Foot function index (FFI) was correlated with disease duration ($r= 0.32$, $p= 0.024$), VAS-pain ($r =0.71$, $p<0.001$), morning stiffness ($r= 0.58$, $p <0.001$), RAI ($r= 0.64$, $p<0.001$), Stoke index ($r= 0.70$, $p<0.001$) and HAQ score ($r =0.87$, $p<0.001$). There was a negative correlation between age and BMD (Table 5) at all sites however only femur total BMD correlated significantly with FFI ($r= -0.293$, $p <0.05$).

Demographic characteristics, BMD values and radiographic scores of the study group are shown in Table 2 and 3. Foot BMD is positively related to L2-L4 spine, femur trochanter, Ward's, neck BMD and age ($p<0.001$) (Table 4) (Figure 2 and 3)

There was a significant difference between Group1A, Group1B patients regarding FFI, HAQ, RAI ($p<0.001$) whereas no difference in BMD of axial, total foot and talar and first to fifth MTP regions and 2. MTP distal region. However, a significant difference was confirmed statistically between control group and Group1A patients. There was a negative relation between erythrocyte sedimentation rate (ESR) and first MTF joint BMD ($p<0.05$). A negative relation between right foot total BMD and RAI was found ($r= 0.30$, $p= 0.032$). A negative relation was present between both feet total BMD and feet SJNS and SES ($p<0.05$); and no relation with Larsen score. A negative relation was present between total BMD of the foot and hand SJNS and hand SES and hand Larsen ($p<0.001$) (Table 6).

Discussion

Osteoporosis may develop in three distinct patterns as periarticular, marginal erosions and widespread in patients with RA. Generalized bone loss is an early feature of RA and its prevalence is estimated approximately two fold higher than the healthy population (11, 16). This early bone loss is more pronounced in hands than in hip and lumbar spine (17-19).

Table 3. Demographic characteristics and BMD values of the patients

		Rheumatoid arthritis (n=50)	Osteoarthritis (n=40)	P
	Age	52±10.9 (31-81)	52.4±11.1 (33-77)	>0.05
	Sex (male/female)	5/45	3/37	>0.05
	Weight (kg)	67.7±11,0 (43-94)	71.6±9.0 (53-93)	>0.05
	Height (m)	1.58 (1.36-1.75)	1.57 (1.41-1.80)	>0.05
	BMI (kg/m^2)	26.9±3.9 (18.8-36.3)	29.0±4.3(21.2-40.5)	<0.05
	Pre/post-menopausal	20/25	12/25	>0.05
BMD (gr/cm^2)	L_2-L_4	1.02±0.23	1.11±0.17	**0.049**
	Femur Ward's	0.69±0.14	0.82±0.19	**<0.001**
	Femur neck	0.84±0.12	0.93±0.15	**0.002**
	Femur trochanter	1.03±0.20	1.14±0.17	**0.009**
	Femur total	0.86±0.12	0.97±0.14	**<0.001**
	Right foot talar	0.74±0.20	0.80±0.18	0.131
	Left foot talar	0.71±0.22	0.78±0.18	0.120
	Right foot 1. MTP	0.57±0.14	0.65±0.15	**0.008**
	Left foot 1. MTP	0.56±0.15	0.66±0.15	**0.003**
	Right foot 2. MTP	0.32±0.2	0.36±0.2	**0.014**
	Left foot 2. MTP	0.33±0.2	0,36±0,2	**0.025**
	Right foot 3. MTP	0.31±0.2	0,34±0,2	**0.001**
	Left foot 3. MTP	0.33±0.2	0,32±0,2	0.312
	Right foot 4. MTP	0.30±0.2	0,30±0,2	0.709
	Left foot 4. MTP	0.30±0.2	0,31±0,2	0.156
	Right foot 5. MTP	0.29±0.2	0,31±0,2	**0.026**
	Left foot 5. MTP	0.29±0.2	0,31±0,2	0.198
	Right foot 2. MTP (distal)	0.33±0.2	0,37±0,2	**0.015**
	Left foot 2. MTP (distal)	0.35±0.2	0,38±0,2	**0.032**
	Right foot total	0.58±0.10	0,64±0,2	**0.003**
	Left foot total	0.56±0.11	0.65±0.2	**<0.001**

BMD: Bone mineral density, MTP methotarsophalangial

Table 4. Relationship between foot BMD and axial BMD

	Right Foot Total BMD		Left Foot Total BMD	
	RA (n=50)	Control (n=40)	RA (n=50)	Control (n=40)
$Lumbar_2$ -$Lumbar_4$	0.572*	0.742*	0.516*	0.779*
Femur neck	0.752*	0.737*	0.711*	0.681*
Femur trochanter	0.674*	0.743*	0.679*	0.677
Femur ward's	0.714*	0.725*	0.650*	0.686*
Femur total	0.724*	0.752*	0.694*	0.740*

*p<0.001, BMD: Bone mineral density, RA: Rheumatoid Arthritis

Periarticular bone loss has been demonstrated in certain body areas using different methods (21-22). Hand joints are the target joints in RA and assessment using radiographic or other imaging techniques gives detailed information about disease status and outcome. It is clear that hand BMD measurement using DEXA is a precise, repeatable and reliable method. The hand BMD has been shown to correlate with BMD at other parts of the body (23). Different radiographic scoring methods have been developed to evaluate the disease progression in RA however they had restricted ability to evaluate bone mineralization (23).

Many studies (18, 20, 24-26) have been published about the assessment of BMD in hand and forearm of RA patients. However to our knowledge, there is no study assessing periarticular and/or total foot BMD in RA using the DEXA method. Foot joints are weight bearing joints and also target for inflammation in RA. BMD measurements of calcaneus by DEXA have been considered to have low long-term consistency (27). However, it was noted that heel DEXA can be used to scan OP in risk groups (28).

Peel et al. (20) reported that the hand BMD was lower with respect to other areas in the postmenopausal patients with RA. Devlin et al. (24) showed correlation between CRP levels, an activity marker, and hand BMD. In our study, there was a negative correlation between right and left foot BMD and ESR.

Shibuya et al. (21) reported that BMD measurements on mid radius and calcaneus were significantly lower in postmenopausal patients with RA than patients with osteoarthritis except BMD at lumbar spine. These authors also showed close correlation between BMD in all areas and severity markers for the disease and body mass.

Shenstone et al. (29) reported correlation between BMD and HAQ score, and also showed relationship between lumbar BMD and baseline Stoke Index. The BMD loss was found to be higher in femur neck in early stages

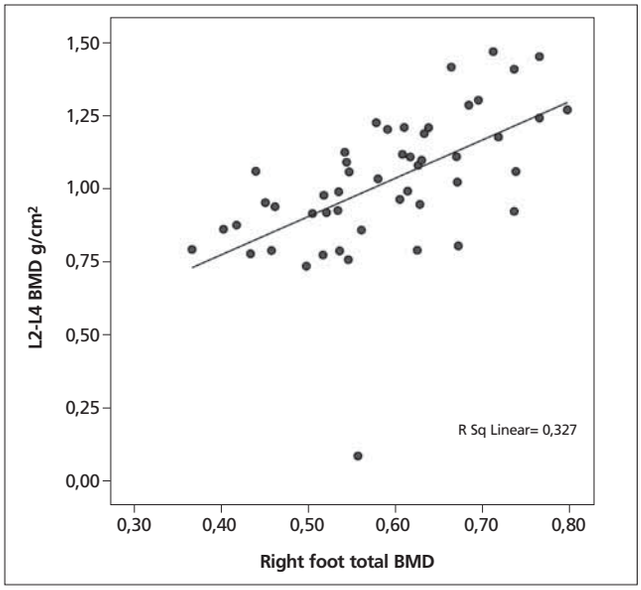

Figure 2. Relationship between right foot and L2-L4 BMD (gr/cm^2) in the study group

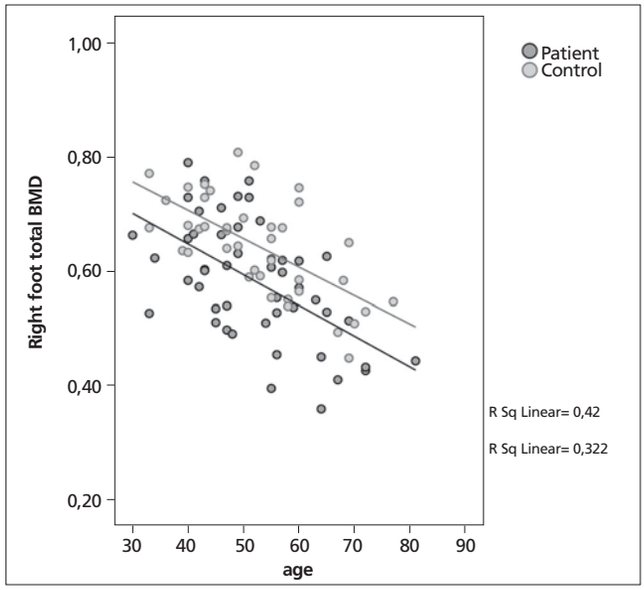

Figure 3. Relationship between right foot total BMD (gr/cm^2) and age in the study group

Table 5. Relationship between age and BMD in patients

	Age	
	RA	**Control**
$Lumbar_2$ -$Lumbar_4$	-0.44**	-0.53**
Femur Ward's	-0.52***	-0.71***
Femur neck	-0.59***	-0.71***
Femur trochanteric	-0.45**	-0.59***
Femur total	-0.53***	-0.63***
Right 1. MTP	-0.53***	-0.64***
Left 1. MTP	-0.56***	-0.44***
Right 2. MTP distal	-0.41**	-0.46**
Left 2. MTP distal	-0.37**	-0.34*
Right foot total	-0.56***	-0.64***
Left foot total	-0.50***	-0.59***

*p<0.05 **p<0.01 ***p<0.001, MTP: methotarsophalangial, BMD: Bone mineral density, RA: Rheumatoid Arthritis

of the RA regardless of disease activity and functional loss. But, in our study, there was no relation between BMD with Stoke Index.

We found that FFI was positively related to disease duration, ESR, VAS pain, morning stiffness, RAI and HAQ. The femur trochanter BMD and FFI were negatively correlated. It is considered that hip BMD is more related to disability, pain and functional limitation in patients with RA in accordance with above mentioned studies.

Ozgocmen et al. (30) compared HAQ and Larsen scores with BMD measurements from axial, total hand and 2.metacarpal middle shaft in 30 RA patients and 29 healthy females, no correlation was found between HAQ and other parameters. They reported that Larsen score had slightly negative correlation with BMD of second. metacarpal middle shaft and the total hand BMD had positive correlation with lomber spine and femur neck BMD. In accordance with the previous studies, we found a negative correlation between foot BMD and SJSN and SES but not with Larsen score.

Plain radiographs are routine methods to evaluate joint damage and disease progression in RA. They are beneficial in pursuing natural continuity of disease and detecting treatment. Radiographic evaluation has many advantages. It reflects time of joint pathology and allows repeated evaluations. Also it has advantages like repeatability, highly assessed validity and sensitivity to change (10). Many scoring methods only include hand radiographs; but it was reported that erosions may develop earlier on the foot region of patients with RA (31). Paimela et al. (31) suggested that radiographic modifications of feet are more sensitive than modifications of hand in early RA and for this reason radiographic evaluations should be included in the RA classification criteria. Particularly, diagnostic sensitivity increases when hand and foot radiographs were evaluated together in early disease (2, 26, 31-36). Foot joints are frequently involved in RA and results in functional limitations. Bone loss in the feet results from combined effects of localized and generalized inflammation. We also consider other concomitant effects like menopausal status and glucocorticoid use. It was noted in most publications that in order to increase sensitivity of radiological criteria, feet should be analyzed along with hands (33). In addition to this, radiological modifications occur in time (34, 35).

In our previously published study (10), we measured hand, spine and femur BMD by DEXA in patients with RA and healthy controls. We found a moderate relationship between radiographic scores and hand BMD with Larsen, Sharp/van der Heijde and SENS (simple erosion narrowing score). While the hand BMD was found to be lower in the RA patients, there was no difference between the axial

Table 6. Relationship between radiographic scores and foot BMD in patients with RA

	Larsen		SJNS		SES	
	Hand	Foot	Hand	Foot	Hand	Foot
Right foot total BMD	-0.558**	-0.250	-0.514**	-0.401*	-0.576**	-0.375*
Left foot total BMD	-0.591**	-0.278	-0.561**	-0.427*	-0.602**	-0.418*

*p<0.01 **p<0.001 SJNS: Sharp-joint narrowing score, SES: Sharp-erosion score BMD: Bone Mineral Density, RA: Rheumatoid arthritis

BMD. As the hand BMD correlated significantly with disease duration and CRP levels, we suggested that radiographic scores were beneficial in estimating hand BMD (10).

Our results reveal that foot BMD measurement using DEXA is a practical, repeatable and easy method. Foot BMD measurement may reflect both localized and generalized bone loss and may be a potential outcome measure particularly in patients with marked foot involvement.

Conflict of Interest

No conflict of interest is declared by the authors.

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