# Does Rheumatoid Cachexia Predispose Patients with Rheumatoid Arthritis to Osteoporosis and Vertebral Fractures?

Abdellah El Maghraoui, Siham Sadni, Asmaa Rezqi, Ahmed Bezza, Lahsen Achemlal, and Aziza Mounach

*ABSTRACT* ***Objective.*** To assess the prevalence and risk factors of rheumatoid cachexia (RC) and evaluate its relationship with osteoporosis and vertebral fractures (VF) in patients with rheumatoid arthritis (RA).

***Methods.*** We enrolled into a cross-sectional study 178 consecutive patients with RA (82.6% women) with a mean age of 54.1 ± 11.5 years (25–82) and who fulfilled the American College of Rheumatology criteria for the classification of RA. Body composition, lateral VF assessment images, and scans of the lumbar spine and proximal femur were obtained using dual-energy x-ray absorptiometry. RC was defined by a fat-free mass index below the 10th percentile and a fat mass index above the 25th percentile compared with a reference population. VF were defined using Genant semiquantitative approach.

***Results.*** RC was observed in 96 patients (53.9%) and osteoporosis in 52 patients (29.2%). Comparison between women with and without RC showed that women with RC had a longer disease duration, higher disease activity variables, higher steroid cumulative dose, and higher proportion of patients with erosive arthritis. Women with RC had lower total hip bone mineral density (BMD) and T score than women without RC, while comparison in men found only body mass index to be significantly lower in men with RC. Regression logistic analysis showed an independent and significant association between RC and age and disease activity in women.

***Conclusion.*** Our study showed that half of the patients with RA may have RC, a condition that was significantly associated with disease activity and low hip BMD, but not with VF. (First Release August 1 2015; J Rheumatol 2015;42:1556–62; doi:10.3899/jrheum.141629)

*Key Indexing Terms:*
RHEUMATOID ARTHRITIS DUAL-ENERGY X-RAY ABSORPTIOMETRY
OSTEOPOROSIS VERTEBRAL FRACTURES ADIPOSE TISSUE

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown etiology that is associated with reduced life expectancy and causes destruction of joint cartilage and bone. It affects nearly 1% of the population and predominates among women. Many studies have identified changes in body composition as contributing to the increased morbidity, as well as the mortality, associated with RA[1]. Hypermetabolism and protein degradation linked to the proinflammatory cytokines induced by the disease cause reduction of fat-free mass (FFM), often associated with increased fat mass (FM) and thus with little or no weight loss, and a maintained body mass index (BMI). This combined condition has been called "rheumatoid cachexia" (RC)[2,3]. Because no consensual definition of cachexia exists, the prevalence of malnutrition, including RC, in RA varies with definitions, methods, and populations, and is reported to range between 26% and 71%[4].

It has been shown that lean body mass (LBM) loss is a predisposing factor of osteoporosis and sarcopenia in the elderly and is associated with an increased risk of falls attributed to decreased muscle strength and protective reflexes[5]. Although data on the consequences of this osteosarcopenic obesity in patients with RA are extremely limited, it is reasonable to infer its negative effect in a population that is fragile. It is likely that these individuals will present with poorer clinical outcomes caused by the cascade of metabolic abnormalities associated with these changes in body composition. Clinical outcomes include but are not limited to increased risk of fractures, impaired functional status (including activities of daily living), physical disability, insulin resistance, increased risk of infections, increased length of hospital stay, and reduced survival[6,7].

*From the Rheumatology Department, Military Hospital Mohammed V, Rabat, Morocco.*

*A. El Maghraoui, MD, Professor of Rheumatology; S. Sadni, MD, Fellow of Rheumatology; A. Rezqi, MD, Rheumatologist; A. Bezza, MD, Professor of Rheumatology; L. Achemlal, MD, Professor of Rheumatology; A. Mounach, MD, Rheumatologist, Rheumatology Department, Military Hospital Mohammed V.*

*Address correspondence to Professor A. El Maghraoui, Rheumatology Department, Military Hospital Mohammed V, P.O. Box 1018, Rabat, Morocco. E-mail: aelmaghraoui@gmail.com*

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Several studies have shown an increased prevalence of osteoporosis and vertebral fractures (VF) in patients with RA[8,9,10,11,12,13]. VF are the most common type of fragility fracture. They are associated with chronic back pain, loss of height, kyphosis, reduced pulmonary function, abdominal discomfort, disability, and death[14,15]. VF assessment (VFA) is a relatively new method of diagnosing vertebral deformities[16,17,18]. VFA has demonstrated use for vertebral visualization and thus is an important tool for fracture detection in women[19] and men[20]. The combination of low radiation exposure, high technical reproducibility, and easy data storage renders the method attractive in groups of patients at increased risk of osteoporosis already likely to have to repeated dual-energy x-ray absorptiometry (DEXA) measurements for evaluation of bone mineral density (BMD). The cause of osteoporosis in RA is believed to be multifactorial, with inflammation, inactivity, and the use of corticosteroids contributing to the decreased BMD. There may be a direct link between muscle depletion and osteoporosis in RA because LBM is correlated with BMD of the spine and hip, and is a strong independent predictor of bone mass. However, to our knowledge, the particular role of the relationship between RC and bone loss consequences has never been studied before.

Because of BMI being generally maintained by the parallel body cell mass decline and increase in body FM, the identification of RC relies on measurement of body composition. DEXA is now considered as the gold standard for the evaluation of body composition. This technique permits the assessment of BMD and also the evaluation of asymptomatic VF using VFA. Thus, the purpose of our study was to assess the prevalence and risk factors of cachexia and evaluate its relationship with osteoporosis and VF in patients with RA.

## MATERIALS AND METHODS

*Patients*. The study group consisted of 178 consecutive patients with RA who fulfilled the American College of Rheumatology (ACR) criteria for the classification of RA and who were seen in the Rheumatology Department of the Military Hospital of Rabat, Morocco, between June and December 2013. Demographic, patient, and disease characteristics, including conventional RA disease core measurements, were recorded by interview and clinical examination. Disease duration was defined as the time elapsed between the onset of first disease-related symptoms and enrollment. Joint assessment included 28-joint swollen joint counts and 28–joint tender joint count. The Disease Activity Score at 28 joints (DAS28) was measured[21]. Radiological status was assessed through the clinical file as erosive arthritis or not. The patients signed an informed consent and the study was approved by the local ethics committee and was performed in accordance with the Helsinki declaration.

*BMD measurements*. BMD was determined by a Lunar Prodigy Vision DEXA system (Lunar Corp.). The DEXA scans were obtained by standard procedures supplied by the manufacturer for scanning and analysis. All BMD measurements were carried out by 2 experienced technicians. Daily quality control was carried out by measurement of a Lunar phantom. At the time of the study, phantom measurements showed stable results. The phantom precision expressed as the coefficient of variation percentage was 0.08. Moreover, reproducibility has been assessed in clinical practice and showed a smallest detectable difference of 0.04 g/cm$^2$ (spine) and 0.02 g/cm$^2$ (hips)[22]. Patient BMD was measured at the lumbar spine (anteroposterior projection at L1–L4) and at the femurs (i.e., femoral neck, trochanter, and total hip). Using the US National Health and Nutrition Examination Survey normative data, the World Health Organization (WHO) classification system was applied, defining osteoporosis as T score ≤ –2.5 and osteopenia as –2.5 < T score < –1. Study participants were categorized by the lowest T score of the L1–L4 lumbar spine, femur neck, or total femur.

*VF assessment*. Imaging performance could be obtained by lateral spine imaging when performing BMD measurement using DEXA, with specific software, the so-called VFA. VFA was classified using a combination of Genant semiquantitative (SQ) approach[23] and morphometry in the following manner: each VFA image was inspected visually by 2 readers (AM, SS), who had a previous training session in VFA, to decide whether it contained a fracture in any of the visualized vertebrae. Each vertebra that was judged as fractured by visual inspection was measured using built-in morphometry and assigned a grade based on Genant SQ scale, where Grade 1 (mild) fracture is a reduction in vertebral height of 25%, Grade 2 (moderate) is a reduction of 26–40%, and Grade 3 (severe) is a reduction of over 40%. Subjects with no fractures were included in the nonfracture group, whereas those with Grade 1 or higher fracture were included in the fracture group.

*Cachexia variables assessment*. All anthropometric measures were taken following standard procedures by the same trained investigator. BMI was calculated from weight/height$^2$ (kg/m$^2$). The subjects were weighed to the nearest 0.1 kg, and standing height was measured to the nearest 0.1 cm. In accordance with WHO standards, individuals with BMI values < 18.5 kg/m$^2$ were considered underweight, between 18.5 kg/m$^2$ and 24.9 kg/m$^2$ as normal, 25 kg/m$^2$ and 29.9 kg/m$^2$ as overweight, and with values greater than 30 kg/m$^2$ as obese[24]. Mid-upper arm circumference and waist circumference were measured using a plastic, inelastic, flexible belt-type measuring tape to the nearest 0.5 cm.

Body composition was measured with total body DEXA using the same machine. Using specific anatomic landmarks, legs, arms, and trunk were isolated on the skeletal radiograph anterior view planogram using the DEXA system's automated software. The DEXA software then provided compositional estimates of legs, arms, trunk, head, and whole body. Scans were performed with the subject wearing light indoor clothing and with no detachable metal objects present. DEXA is considered a valid method to estimate body composition in patients with RA[25]. The precision of soft tissue analysis for a Lunar Prodigy is 1% for FFM and 2% for FM[26]. FFM and FM were expressed in absolute kilogram, and FM also as percentage of total mass. The normal reference value for FM percent is 20% to 30% for women and 12% to 20% for men[27]. FFM index (FFMI; kg/m$^2$) and FM index (FMI; kg/m$^2$) were also calculated. Age-matched and sex-matched data from a Swiss population of healthy adults (2986 men and 2649 women) were used to classify low FFM or excess FM[28]. Cutoff values for low muscle mass were defined as FFMI values below the 10th percentile, corresponding to FFMI below 13.7–14.7 kg/m$^2$ for women and 16.9–17.6 kg/m$^2$ for men, depending on age. Obesity was defined as FMI above the 90th percentile, corresponding to FMI above 8.8–13.5 kg/m$^2$ for women and 7.2–9.0 kg/m$^2$ for men, also depending on age. Because there were no established criteria for RC, we used the definition by Engvall, *et al*[29], who categorized the patients as rheumatoid cachectic if FFMI was below the 10th percentile and FMI above the 25th percentile.

*Mini nutritional assessment (MNA)*. The MNA (0–30 points) is a dietary questionnaire including questions related to the number of meals, food and fluid intake, and autonomy of feeding. It is a subjective assessment of self-perception of health and nutrition that also includes questions related to lifestyle, medication, and morbidity, and anthropometrical measurements (e.g., weight, height, and weight loss). The MNA classifies individuals with adequate nutritional status (> 23.5 points), risk for malnutrition (17–23.5 points), and malnutrition (< 17 points)[30].

*Statistical analysis*. Statistics Package for Social Sciences (SPSS Inc.) was used for statistical analyses. Results are expressed in mean ± SD. Prevalence of RC, osteoporosis, and VF was calculated. Data are presented as mean

(95% CI) or median (interquartile range), depending on whether the data were normally distributed. Differences between patient groups were assessed using the Student t test and Mann-Whitney U test, depending on the distribution of the analyzed variable.

Correlations between demographic characteristics and DEXA variables (BMD and body composition) were assessed using the nonparametric Spearman test. Risk factors of RC were tested for significance using the Student t test for quantitative variables and the chi-square test for qualitative variables. Significant risk factors associated with RC in the univariate analysis were entered to a stepwise conditional binary logistic regression analysis and the resulted OR with 95% CI were reported. Finally, classical risk factors associated with osteoporosis were entered to a stepwise conditional binary logistic regression analysis with osteoporosis as the dependent variable.

## RESULTS

*Patient demographics*. In this cohort of 178 patients with RA [147 women (82.6%) and 31 men], the mean ± SD (range) age, weight, and disease duration were 54.1 ± 11.5 years (25–82), 72.2 ± 13.1 kg (42–125), and 8.9 ± 7.4 years (1–36), respectively. All patients were white and were taking low-dose corticosteroids and calcium/vitamin D supplements. Details of clinical, biological, and radiological variables of these patients are reported in Table 1.

*Anthropometrical assessments, BMD, and body composition measurement*. RC, as defined previously, was observed in 96 patients (53.9%): 79/147 (53.7%) in women and 17/31 (54.8%) in men. Osteoporosis (defined as the lowest T score below –2.5) was observed in 52 patients (29.2%). Comparison between women with and without RC showed that the patients with RC were younger and weighed less, and had a longer disease duration, higher RA symptomatic severity variables, higher steroid cumulative dose, and higher proportion of patients with erosive arthritis. They had lower total hip BMD and T scores than women without RC, while comparison between men found only BMI to be significantly lower in men with RC (Table 2).

*Vertebral visualization and fracture identification on VFA*. In these 178 patients, 56.6% of vertebrae from T4–T6 and 99.7% from T7–L4 were adequately visualized on VFA. Grade 2/3 VF were detected in 6.8% (12/178) of these patients while Grade 1 VF were detected in 54/178 (30.3%).

*Data analysis*. Correlations analyses between anthropometric variables and DEXA variables (body composition and BMD) showed that FFMI has a significant positive correlation with BMI, brachial circumference, waist circumference, and total hip BMD (Table 3).

Regression logistic analysis with the presence of RC as the dependent variable showed an independent and significant association with age and disease activity in women with RA (Table 4). Regression logistic analysis with the presence of osteoporosis as the dependent variable showed only independent and significant association with age and BMI in patients with RA (Table 5).

*Table 1*. Demographic and clinical variables of patients with RA (n = 178). Values are mean (SD) unless otherwise specified.

| Variables | Values | Minimum | Maximum |
|---|---|---|---|
| Age, yrs | 54.1 (11.5) | 25 | 82 |
| Female/male | 147 (82.6%)/31 | | |
| Height, cm | 160 (7.6) | 141 | 187 |
| Weight, kg | 72.2 (13.1) | 42 | 125 |
| BMI, kg/m$^2$ | 28.2 (4.7) | 16.6 | 41.3 |
| Disease duration, yrs | 8.9 (7.4) | 1 | 36 |
| Steroid cumulative dose, g | 190.1 (202.9) | 0 | 1240.0 |
| CRP, mg/l | 17.5 (23.0) | 1 | 161 |
| ESR, mm/h | 31.7 (21.4) | 2 | 100 |
| DAS28 | 4.3 (1.6) | 1.0 | 7.9 |
| RF-positive, n (%) | 116/158 (65.2) | | |
| Anti-CCP–positive, n (%) | 110/148 (74.3) | | |
| MNA | 1.1 (0.3) | 1 | 3 |
| WC, cm | 97.8 (12.4) | 43 | 139 |
| BC, cm | 31.4 (9.2) | 20 | 138 |
| LS BMD, g/cm$^2$ | 0.979 (0.19) | 0.509 | 1.980 |
| TH BMD, g/cm$^2$ | 0.881 (0.15) | 0.491 | 1.369 |
| LS T score | –1.52 (1.48) | –5.40 | 2.70 |
| TH T score | –1.17 (1.28) | –4.50 | 2.80 |
| Osteoporosis any site, n (%) | 52 (29.2) | | |
| T score < –1.5, n (%) | 101 (56.7) | | |
| FFMI, kg/m$^2$ | 14.9 (1.9) | 10.6 | 21.7 |

RA: rheumatoid arthritis; BMI: body mass index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; DAS28: 28-joint Disease Activity Score; RF: rheumatoid factor; anti-CCP: anticyclic citrullinated peptide antibodies; MNA: mini nutritional assessment; WC: waist circumference; BC: brachial circumference; LS: lumbar spine; BMD: bone mineral density; TH: total hip; FFMI: fat-free mass index.

*Table 2*. Comparison between patients with and without rheumatoid cachexia. Values are mean (SD) unless otherwise specified.

| Characteristics | Women with Cachexia, n = 79 | Women without Cachexia, n = 68 | p | Men with Cachexia, n = 17 | Men without Cachexia, n = 14 | p | Patients with Cachexia, n = 96 | Patients without Cachexia, n = 82 | p |
|---|---|---|---|---|---|---|---|---|---|
| Age, yrs | 51.8 (10.3) | 56.4 (12.3) | 0.016 | 53.3 (10.7) | 57.0 (12.8) | NS | 52.1 (10.3) | 56.5 (12.4) | 0.011 |
| Weight, kg | 67.1 (9.3) | 75.8 (16.6) | 0.018 | 71.9 (14.1) | 84.0 (14.1) | NS | 68.0 (10.4) | 77.2 (14.2) | 0.0001 |
| Height, cm | 158.4 (5.5) | 157..2 (6.9) | NS | 169.5 (5.0) | 171.7 (4.3) | NS | 160.4 (8.5) | 159.7 (8.5) | NS |
| BMI, kg/m$^2$ | 26.9 (3.6) | 30.6 (4.6) | 0.0001 | 24.8 (4.3) | 28.5 (6.6) | 0.0001 | 26.5 (3.7) | 30.2 (5.0) | 0.0001 |
| Disease duration, yrs | 10.8 (7.9) | 7.5 (7.3) | 0.011 | 7.2 (4.7) | 6.3 (4.1) | NS | 10.2 (7.6) | 7.3 (6.8) | NS |
| Steroid cumulative dose, g | 260.2 (25.0) | 133.2 (14.5) | 0.002 | 137.4 (12.3) | 157.0 (11.5) | NS | 2.38 (2.3) | 1.38 (1.3) | 0.003 |
| RF-positive, n (%) | 43 (63.2) | 51 (64.6) | NS | 12 (70.6) | 10 (71.4) | NS | 54 (87.1) | 66 (82.5) | NS |
| Anti-CCP–positive, n (%) | 44 (78.6) | 46 (73.0) | NS | 12 (80) | 8 (57.1) | NS | 48 (81.4) | 66 (77.6) | NS |
| DAS28 | 4.73 (1.5) | 3.98 (1.5) | 0.006 | 4.10 (1.4) | 4.42 (1.8) | NS | 4.62 (1.5) | 4.06 (1.6) | NS |
| CRP, mg/l | 19.4 (22.4) | 18.5 (27.8) | NS | 9.7 (11.0) | 11.6 (8.7) | NS | 17.7 (21.2) | 17.2 (25.5) | NS |
| Erosive arthritis, n (%) | 63 (84.0) | 42 (67.7) | 0.026 | 10 (62.5) | 6 (46.2) | NS | 73 (80.2) | 48 (64.0) | 0.026 |
| BC, cm | 29.6 (3.8) | 34.0 (13.5) | 0.006 | 30.2 (6.9) | 30.4 (3.7) | NS | 29.7 (4.5) | 33.4 (12.5) | 0.007 |
| WC, cm | 94.1 (11.1) | 102.2 (11.8) | 0.0001 | 93.9 (10.1) | 102.8 (16.4) | NS | 94.0 (10.9) | 102.3 (12.6) | 0.0001 |
| MNA | 1.08 (0.2) | 1.10 (0.3) | NS | 1.29 (0.5) | 1.00 (0.1) | NS | 1.11 (0.3) | 1.09 (0.2) | NS |
| LS BMD | 0.939 (0.17) | 0.997 (0.21) | NS | 1.051 (0.16) | 1.03 (0.19) | NS | 0.958 (0.17) | 1.002 (0.21) | NS |
| LS T score | –1.75 (1.4) | –1.41 (1.5) | NS | –1.07 (1.27) | –1.29 (1.5) | NS | –1.63 (1.4) | –1.39 (1.5) | NS |
| TH BMD | 0.820 (0.14) | 0.917 (0.16) | 0.0001 | 0.938 (0.12) | 0.978 (0.14) | NS | 0.840 (0.14) | 0.928 (0.16) | 0.0001 |
| TH T score | –1.64 (1.1) | –0.89 (1.3) | 0.0001 | –0.71 (1.0) | –0.41 (1.0) | NS | –1.48 (1.1) | –0.81 (1.3) | 0.001 |
| FMI | 12.0 (2.9) | 14.0 (3.7) | 0.0001 | 9.6 (3.9) | 9.5 (4.9) | NS | 11.6 (3.2) | 13.2 (4.2) | 0.005 |
| FFMI | 13.4 (1.0) | 15.7 (1.3) | 0.0001 | 15.8 (2.0) | 18.1 (2.0) | 0.0001 | 13.9 (1.3) | 16.1 (1.7) | 0.0001 |
| Grade 2/3 VF, n (%) | 6 (7.6) | 5 (7.4) | NS | 1 (5.9) | 0 (0.0) | NS | 5 (6.1) | 7 (7.3) | NS |

BMI: body mass index; RF: rheumatoid factor; anti-CCP: anticyclic citrullinated peptide antibodies; DAS28: 28-joint Disease Activity Score; CRP: C-reactive protein; BC: brachial circumference; WC: waist circumference; MNA: mini nutritional assessment; LS: lumbar spine; BMD: bone mineral density; TH: total hip; FMI: fat mass index; FFMI: fat-free mass index; VF: vertebral fractures; NS: not significant.

*Table 3*. Correlations between some patient characteristics, DAS28, and DEXA data in patients with RA.

| Characteristics | BMI | DAS28 | MNA | BC | WC | LS BMD | TH BMD | FFMI | FMI |
|---|---|---|---|---|---|---|---|---|---|
| Age, yrs | 0.10 | 0.12 | 0.05 | –0.3 | –0.24** | –0.36** | –0.26** | 0.12 | 0.04 |
| BMI | | 0.009 | –0.17* | 0.36** | 0.70** | 0.23** | 0.40** | 0.51** | 0.75** |
| DAS28 | | | 0.15* | –0.06 | –0.08 | –0.14 | –0.17* | –0.10 | –0.03 |
| MNA | | | | –0.12 | –0.16* | –0.07 | –0.13 | –0.12 | –0.14 |
| BC | | | | | 0.30** | 0.23** | 0.27** | 0.18* | 0.36** |
| WC | | | | | | 0.06 | 0.23** | 0.45** | 0.53** |
| LS BMD | | | | | | | 0.72** | 0.14 | 0.21** |
| TH BMD | | | | | | | | 0.42** | 0.28** |
| FFMI | | | | | | | | | 0.21** |

* $p < 0.05$. ** $p < 0.01$. DAS28: 28-joint Disease Activity Score; DEXA: dual-energy x-ray absorptiometry; RA: rheumatoid arthritis; BMI: body mass index; MNA: mini nutritional assessment; BC: brachial circumference; WC: waist circumference; LS: lumbar spine; BMD: bone mineral density: TH: total hip; FFMI: fat-free mass index; FMI: fat mass index.

## DISCUSSION

Our study shows that most of our patients with RA had RC while being considered either overweight or obese according to the classical BMI classification. This situation remains similar even if we consider the cutoffs proposed by Stavropoulos-Kalinoglou, *et al*[31] that showed that patients with RA exhibited increased body fat values for a given BMI compared with healthy controls and suggested that BMI cutoff points in the RA population would be more appropriate if they were reduced by about 2 kg/m$^2$ (to 23 kg/m$^2$ and 28 kg/m$^2$ for overweight and obesity, respectively). Moreover, RC was significantly associated with disease activity.

RC has been described and analyzed in a series of studies and reviews that showed evidence of cachexia in two-thirds of patients with RA with muscle wasting and often compensatory increase in FM, the so-called cachectic-obesity, with loss of weight or BMI being uncommon[2]. However, because there is no standard definition of this condition, the frequency of RC varies widely across the studies[32]. Thus, the prevalence

*Table 4*. Regression logistic analysis with the presence of rheumatoid cachexia as the dependent variable. Values are OR (95% CI) unless otherwise specified.

| Variables | Women | p | Men | p | Total Population | p |
|---|---|---|---|---|---|---|
| Age, yrs | 0.962 (0.928–0.977) | 0.033 | 0.957 (0.882–1.039) | 0.299 | 0.963 (0.933–0.993) | 0.018 |
| Disease duration, yrs | 1.009 (0.943–1.078) | 0.8 | 1.050 (0.772–1.429) | 0.754 | 1.008 (0.947–1.073) | 0.804 |
| Active disease, DAS28 > 3.2 | 3.262 (1.385–7.685) | 0.007 | 1.905 (0.288–12.612) | 0.504 | 2.77 (1.298–5.940) | 0.008 |
| Erosive disease | 1.395 (0.535–3.639) | 0.496 | 4.599 (0.537–39.358) | 0.164 | 1.610 (0.711–3.646) | 0.253 |
| Cumulative dose of steroids | 1.003 (1.000–1.006) | 0.062 | 0.994 (0.983–1.006) | 0.334 | 1.002 (1.000–1.005) | 0.112 |

DAS28: 28-joint Disease Activity Score.

*Table 5*. Regression logistic analysis with the presence of osteoporosis any site (T–score ≤ –2.5) as the dependent variable. Values are OR (95% CI) unless otherwise specified.

| Variables | Women | p | Men | p | Total Population | p |
|---|---|---|---|---|---|---|
| Age, yrs | 1.087 (1.044–1.132) | 0.0001 | 1.034 (0.950–1.125) | 0.440 | 1.075 (1.037–1.114) | 0.0001 |
| BMI | 0.894 (0.808–0.989) | 0.029 | 0.754 (0.594–0.956) | 0.020 | 0.892 (0.820–0.970) | 0.008 |
| Disease duration, yrs | 1.021 (0.954–1.093) | 0.543 | 0.858 (0.622–1.183) | 0.349 | 1.024 (0.960–1.092) | 0.474 |
| Cumulative dose of steroids | 1.395 (0.535–3.639) | 0.702 | 0.998 (0.984–1.012) | 0.748 | 0.999 (0.997–1.002) | 0.614 |
| Active disease, DAS28 > 3.2 | 1.451 (0.546–3.856) | 0.456 | 2.822 (0.168–47.401) | 0.471 | 1.426 (0.591–3.437) | 0.430 |
| Rheumatoid cachexia | 1.323 (0.496–3.526) | 0.576 | 0.599 (0.064–5.660) | 0.655 | 1.235 (0.527–2.897) | 0.627 |

BMI: body mass index; DAS28: 28-joint Disease Activity Score.

of RC depends upon the definition used and on what degree of reduction of muscle mass is considered to be significant[33].

Roubenoff, *et al*[34] found that 67% of patients had RC, using the 50th percentile of the reference population as the ideal for arm muscle circumference. Taking 80% of this ideal as a cutoff, cachexia was diagnosed in 14% of the patients by Helliwell, *et al*[35] and 28.8% of the patients by Fukuda, *et al*[36]. Using the more stringent 10th percentile of the reference population as a cutoff, Munro and Capell[37] found that 50% of the RA population was below this level whereas Hernandez-Beriain, *et al*[38] found that 24% of patients with RA were beneath it.

In our study, we used the definition proposed by Engvall, *et al*[29], who categorized the patients as rheumatoid cachectic if FFMI was below the 10th percentile and FMI above the 25th percentile of a reference population from Switzerland[28]. Using the same definition, Elkan, *et al*[39] found RC in 18% of the women and 21% of the men from a series of 80 patients with RA (76% were women). Recently, using the same definition but with skinfold measurements, Lombard, *et al* found RC in 12/117 patients (10.3%) in a South African series of patients with RA[40].

While arm circumference and waist circumference were correlated to DEXA variables in our study, MNA test could not discriminate patients with or without RC, as it was the case in the Elkan, *et al* study[39], which may reflect the fact that MNA is primarily developed to assess malnutrition among the elderly.

Although it is well known that people lose weight during acute or chronic systemic diseases, there are surprisingly few data about weight changes in RA. Clinically, body weight or BMI are used to assess the nutritional status of a patient. It has already been noted that reduction in BMI is a marker for severe rheumatoid disease. However, it is now clear that relying on BMI alone to identify RC is not appropriate because the concurrent presence of a low FFM and a high FM makes BMI an insensitive measure. Thus, in the presence of normal BMI, analysis of body composition may provide valuable insights into disease activity and outcome. Significant correlations have been found between depletion of lean mass and the number of swollen joints, erythrocyte sedimentation rate, C-reactive protein, and the presence of extraarticular disease[38,41,42]. Strong correlations have been found between the degree of depletion of muscle mass and the effect of RA as measured by ACR functional class[43], the Steinbrocker disease stage[38], and the Health Assessment Questionnaire score[41].

Cachexia is different from sarcopenia, a term that is usually reserved for age-related skeletal muscle loss or isolated loss of muscle in the context of dieting, physical immobility, or growth hormone deficiency. The cachexia and muscle wasting found in our study could not reflect only the changes in body composition that occur with age because FFM was lower in younger subjects.

In the present cohort of patients, we found that DAS28 differed between women with and without RC. Thus, the inflammation *per se* might have contributed to the derangement in body composition found here and also described previously[42]. The difference did not reach significance in men, probably because of the low number of men in our series.

Early mortality has decreased among patients with RA

over the past decades, but remained higher than in the general population[44]. It has been estimated that life expectancy in RA is reduced by an average of 3–18 yrs[45]. Most of the excess deaths are attributable to infection, coronary heart disease, and respiratory disease[46]. The underlying cause of accelerated mortality, particularly from cardiovascular disease, may be partly related to metabolic and vascular effects of chronic systemic inflammation, but also to RC[4,47,48]. The majority of our patients, 127/178 (71.3%), displayed central obesity as assessed by waist circumference [9/31 (29.0%) of men > 102 cm and 118/147 (80.3%) of women > 88 cm], a well-known risk factor for developing Type 2 diabetes, coronary heart disease, or hypertension.

We found that RC was associated with low hip BMD in this cohort, but not with VF. This is the first study, to our knowledge, assessing the link between cachexia and osteoporosis in patients with RA. Other studies highlight the role of sarcopenia-related falls and fractures in the elderly[5,49], but few data link sarcopenia and VF[50]. Indeed, it has been shown that denutrition is a predisposing factor of osteoporosis and sarcopenia in the elderly and is associated with an increased risk of falls because of decreased muscle strength and protective reflexes. Further longitudinal studies are warranted to better evaluate the role of RC in the observed bone loss and increased prevalence of fractures in RA.

Our study has strengths and limitations. The assessment of body composition, BMD, and fractures was carefully conducted using standard procedures of acquisition and standard reading of all VFA scans. All the morphometric assessments were made by an experienced investigator after training sessions and after a previous global visualization. The main limitation lies in the chosen definition of RC. However, because no consensual definition exists, we used the definition by Engvall, *et al*[29], who categorized the patients as rheumatoid cachectic if FFMI was below the 10th percentile and FMI above the 25th percentile. The reference population for the classification of FMI and FFMI is a Swiss population that is different from patients with RA in Morocco. To our knowledge, this is the only reference population available for this type of classification. About one-third of the individuals from the reference population were, however, of non-Swiss origin, and therefore may be more representative than people of strictly Swiss nationality. This reference population has been used previously in many important studies.

Our study showed that half of the patients with RA may have RC, even with a normal or high BMI. This condition was significantly associated with disease activity and low hip BMD, but not with VF.


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## REFERENCES


1. Roubenoff R. Rheumatoid cachexia: a complication of rheumatoid arthritis moves into the 21st century. Arthritis Res Ther 2009;11:108.
2. Lemmey AB, Jones J, Maddison PJ. Rheumatoid cachexia: what is it and why is it important? [letter]. J Rheumatol 2011;38:2074.
3. Rajbhandary R, Khezri A, Panush RS. Rheumatoid cachexia: what is it and why is it important? J Rheumatol 2011;38:406-8.
4. Summers GD, Metsios GS, Stavropoulos-Kalinoglou A, Kitas GD. Rheumatoid cachexia and cardiovascular disease. Nat Rev Rheumatol 2010;6:445-51.
5. El Maghraoui A. [Malnutrition, cachexia and osteoporosis]. [Article in French] Rev Rhum Monogr 2013;80:100-4.
6. Ali S, Garcia JM. Sarcopenia, cachexia and aging: diagnosis, mechanisms and therapeutic options - a mini-review. Gerontology 2014;60:294-305.
7. Evans WJ. Skeletal muscle loss: cachexia, sarcopenia, and inactivity. Am J Clin Nutr 2010;91:1123S-7S.
8. Nampei A, Hashimoto J, Koyanagi J, Ono T, Hashimoto H, Tsumaki N, et al. Characteristics of fracture and related factors in patients with rheumatoid arthritis. Mod Rheumatol 2008;18:170-6.
9. Arai K, Hanyu T, Sugitani H, Murai T, Fujisawa J, Nakazono K, et al. Risk factors for vertebral fracture in menopausal or postmenopausal Japanese women with rheumatoid arthritis: a cross-sectional and longitudinal study. J Bone Miner Metab 2006;24:118-24.
10. Ørstavik RE, Haugeberg G, Uhlig T, Falch JA, Halse JI, Høiseth A, et al. Vertebral deformities in 229 female patients with rheumatoid arthritis: associations with clinical variables and bone mineral density. Arthritis Rheum 2003;49:355-60.
11. de Nijs RN, Jacobs JW, Bijlsma JW, Lems WF, Laan RF, Houben HH, et al; Osteoporosis Working Group, Dutch Society for Rheumatology. Prevalence of vertebral deformities and symptomatic vertebral fractures in corticosteroid treated patients with rheumatoid arthritis. Rheumatology 2001;40:1375-83.
12. Peel NF, Moore DJ, Barrington NA, Bax DE, Eastell R. Risk of vertebral fracture and relationship to bone mineral density in steroid treated rheumatoid arthritis. Ann Rheum Dis 1995;54:801-6.
13. El Maghraoui A, Rezqi A, Mounach A, Achemlal L, Bezza A, Ghozlani I. Prevalence and risk factors of vertebral fractures in women with rheumatoid arthritis using vertebral fracture assessment. Rheumatology 2010;49:1303-10.
14. Jalava T, Sarna S, Pylkkänen L, Mawer B, Kanis JA, Selby P, et al. Association between vertebral fracture and increased mortality in osteoporotic patients. J Bone Miner Res 2003;18:1254-60.
15. Naves M, Díaz-López JB, Gómez C, Rodríguez-Rebollar A, Rodríguez-García M, Cannata-Andía JB. The effect of vertebral fracture as a risk factor for osteoporotic fracture and mortality in a Spanish population. Osteoporos Int 2003;14:520-4.
16. El Maghraoui A, Roux C. DXA scanning in clinical practice. QJM 2008;101:605-17.
17. Fuerst T, Wu C, Genant HK, von Ingersleben G, Chen Y, Johnston C, et al. Evaluation of vertebral fracture assessment by dual X-ray absorptiometry in a multicenter setting. Osteoporos Int 2009;20:1199-205.
18. Schousboe JT, Vokes T, Broy SB, Ferrar L, McKiernan F, Roux C, et al. Vertebral fracture assessment: the 2007 ISCD official positions. J Clin Densitom 2008;11:92-108.
19. El Maghraoui A, Morjane F, Nouijai A, Achemlal L, Bezza A, Ghozlani I. Vertebral fracture assessment in Moroccan women: prevalence and risk factors. Maturitas 2009;62:171-5.
20. El Maghraoui A, Mounach A, Gassim S, Ghazi M. Vertebral fracture assessment in healthy men: prevalence and risk factors. Bone 2008;43:544-8.
21. van der Heijde DM, van 't Hof M, van Riel PL, van de Putte LB. Validity of single variables and indices to measure disease activity in rheumatoid arthritis. J Rheumatol 1993;20:538-41.

22. El Maghraoui A, Do Santos Zounon AA, Jroundi I, Nouijai A, Ghazi M, Achemlal L, et al. Reproducibility of bone mineral density measurements using dual X-ray absorptiometry in daily clinical practice. Osteoporos Int 2005;16:1742-8.
23. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res 1993;8:1137-48.
24. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. World Health Organ Tech Rep Ser 1995;854:1-452.
25. Pødenphant J, Gotfredsen A, Engelhart M, Andersen V, Heitmann BL, Kondrup J. Comparison of body composition by dual energy X-ray absorptiometry to other estimates of body composition during weight loss in obese patients with rheumatoid arthritis. Scand J Clin Lab Invest 1996;56:615-25.
26. Kiebzak GM, Leamy LJ, Pierson LM, Nord RH, Zhang ZY. Measurement precision of body composition variables using the lunar DPX-L densitometer. J Clin Densitom 2000;3:35-41.
27. Abernathy RP, Black DR. Healthy body weights: an alternative perspective. Am J Clin Nutr 1996;63 Suppl:448S-51S.
28. Schutz Y, Kyle UU, Pichard C. Fat-free mass index and fat mass index percentiles in Caucasians aged 18-98 y. Int J Obes Relat Metab Disord 2002;26:953-60.
29. Engvall IL, Elkan AC, Tengstrand B, Cederholm T, Brismar K, Hafstrom I. Cachexia in rheumatoid arthritis is associated with inflammatory activity, physical disability, and low bioavailable insulin-like growth factor. Scand J Rheumatol 2008;37:321-8.
30. Vellas B, Guigoz Y, Garry PJ, Nourhashemi F, Bennahum D, Lauque S, et al. The Mini Nutritional Assessment (MNA) and its use in grading the nutritional state of elderly patients. Nutrition 1999;15:116-22.
31. Stavropoulos-Kalinoglou A, Metsios GS, Koutedakis Y, Nevill AM, Douglas KM, Jamurtas A, et al. Redefining overweight and obesity in rheumatoid arthritis patients. Ann Rheum Dis 2007;66:1316-21.
32. van Bokhorst-de van der Schueren MA, Konijn NP, Bultink IE, Lems WF, Earthman CP, van Tuyl LH. Relevance of the new pre-cachexia and cachexia definitions for patients with rheumatoid arthritis. Clin Nutr 2012;31:1008-10.
33. Summers GD, Deighton CM, Rennie MJ, Booth AH. Rheumatoid cachexia: a clinical perspective. Rheumatology 2008;47:1124-31.
34. Roubenoff R, Roubenoff RA, Ward LM, Holland SM, Hellmann DB. Rheumatoid cachexia: depletion of lean body mass in rheumatoid arthritis. Possible association with tumor necrosis factor. J Rheumatol 1992;19:1505-10.
35. Helliwell M, Coombes EJ, Moody BJ, Batstone GF, Robertson JC. Nutritional status in patients with rheumatoid arthritis. Ann Rheum Dis 1984;43:386-90.
36. Fukuda W, Yamazaki T, Akaogi T, Hayashi H, Kusakabe T, Tsubouchi Y, et al. Malnutrition and disease progression in patients with rheumatoid arthritis. Mod Rheumatol 2005;15:104-7.
37. Munro R, Capell H. Prevalence of low body mass in rheumatoid arthritis: association with the acute phase response. Ann Rheum Dis 1997;56:326-9.
38. Hernandez-Beriain JA, Segura-Garcia C, Rodriguez-Lozano B, Bustabad S, Gantes M, González T. Undernutrition in rheumatoid arthritis patients with disability. Scand J Rheumatol 1996;25:383-7.
39. Elkan AC, Engvall IL, Cederholm T, Hafström I. Rheumatoid cachexia, central obesity and malnutrition in patients with low-active rheumatoid arthritis: feasibility of anthropometry, Mini Nutritional Assessment and body composition techniques. Eur J Nutr 2009;48:315-22.
40. Lombard LA, du Plessis LM, Visser J. Body composition of rheumatoid arthritis patients in the City of Cape Town, South Africa. Clin Rheumatol 2014;33:467-76.
41. Arshad A, Rashid R, Benjamin K. The effect of disease activity on fat-free mass and resting energy expenditure in patients with rheumatoid arthritis versus noninflammatory arthropathies/soft tissue rheumatism. Mod Rheumatol 2007;17:470-5.
42. Roubenoff R, Roubenoff RA, Cannon JG, Kehayias JJ, Zhuang H, Dawson-Hughes B, et al. Rheumatoid cachexia: cytokine-driven hypermetabolism accompanying reduced body cell mass in chronic inflammation. J Clin Invest 1994;93:2379-86.
43. Fukuda W, Omoto A, Ohta T, Majima S, Kimura T, Tanaka T, et al. Low body mass index is associated with impaired quality of life in patients with rheumatoid arthritis. Int J Rheum Dis 2013;16:297-302.
44. Dadoun S, Zeboulon-Ktorza N, Combescure C, Elhai M, Rozenberg S, Gossec L, et al. Mortality in rheumatoid arthritis over the last fifty years: systematic review and meta-analysis. Joint Bone Spine 2013;80:29-33.
45. Pincus T, Sokka T, Wolfe F. Premature mortality in patients with rheumatoid arthritis: evolving concepts. Arthritis Rheum 2001;44:1234-6.
46. Kuo CF, Luo SF, See LC, Chou IJ, Chang HC, Yu KH. Rheumatoid arthritis prevalence, incidence, and mortality rates: a nationwide population study in Taiwan. Rheumatol Int 2013;33:355-60.
47. Giles JT, Allison M, Blumenthal RS, Post W, Gelber AC, Petri M, et al. Abdominal adiposity in rheumatoid arthritis: association with cardiometabolic risk factors and disease characteristics. Arthritis Rheum 2010;62:3173-82.
48. Inaba M, Tanaka K, Goto H, Sakai S, Yamada S, Naka H, et al. Independent association of increased trunk fat with increased arterial stiffening in postmenopausal patients with rheumatoid arthritis. J Rheumatol 2007;34:290-5.
49. Hida T, Harada A, Imagama S, Ishiguro N. Managing sarcopenia and its related-fractures to improve quality of life in geriatric populations. Aging Dis 2014;5:226-37.
50. Hida T, Shimokata H, Sakai Y, Ito S, Matsui Y, Takemura M, et al. Sarcopenia and sarcopenic leg as potential risk factors for acute osteoporotic vertebral fracture among older women. Eur Spine J 2015 Feb 18 (E-pub ahead of print).