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ABSTRACT. Objective. To investigate the relationship among focal bone erosions and bone mineral density (BMD), 25(OH) vitamin D (25OHD), and parathyroid hormone (PTH) values in patients with rheumatoid arthritis (RA).

Methods. The study included 1191 RA patients (1014 women, 177 men, mean age 58.9 ± 11.1 yrs) participating in a multicenter, cross-sectional study.

Results. Radiographic evidence of typical bony erosions on hands or forefeet was found in 64.1% of patients. In those with bone erosions as compared to those without, mean BMD Z score values were significantly lower at both the spine (-0.74 ± 1.19 vs -0.46 ± 1.31 ; $p = 0.05$) and the hip (-0.72 ± 1.07 vs -0.15 ± 1.23 ; $p < 0.001$). In the subgroup of patients not taking vitamin D supplements, PTH levels were significantly higher in those with erosive arthritis (25.9 ± 14.0 vs 23.1 ± 11.6 pg/ml; $p = 0.01$); whereas the 25OHD concentrations were very similar in the 2 groups. The mean differences for BMD and PTH among the erosive and nonerosive RA remained statistically significant when values were simultaneously adjusted for all disease and mineral metabolism factors (i.e., age, sex, menopause, disease duration, Disease Activity Score 28-joint count, Health Assessment Questionnaire, activities of daily living, Steinbrocker functional state, glucocorticoid therapy, body weight, and bisphosphonate treatment).

Conclusion. Our results suggest that the presence of bone erosions in RA correlates with low BMD levels and high PTH levels, and that these associations are independent of the degree of functional impairment and other common determinants of bone mass and mineral metabolism in adults with RA. These findings suggest that treatments to prevent bone loss or suppress PTH levels might positively affect the progression of bone erosions in RA. (First Release April 1 2011; J Rheumatol 2011;38:997–1002; doi:10.3899/jrheum.100829)

Key Indexing Terms:

RHEUMATOID ARTHRITIS
VITAMIN D

BONE EROSIONS
BONE MINERAL DENSITY

PARATHYROID HORMONE
DISEASE ACTIVITY

Five years after onset of disease, 30%–50% of patients with rheumatoid arthritis (RA) exhibit focal bone erosions^{1,2}. A number of clinical and biological markers have been identified as baseline risk factors for the progression of joint damage in RA^{3,4,5,6,7}. Bone erosions develop as a result of complex interactions between cells and cytokines/chemokines in

the synovium and in surrounding tissues. As well as joint destruction, RA is also associated with generalized bone loss, with a higher prevalence of osteoporosis. Patients with RA were reported to be at higher risk for both hip⁸ and vertebral fractures⁹, but this has not been confirmed in all studies¹⁰. Both focal bone erosions and generalized osteoporosis are related to an imbalance between osteoblast and osteoclast activity^{11,12}. Inflammatory cytokines involved in the pathophysiology of RA, such as tumor necrosis factor- α (TNF- α) and RANKL (receptor activator of nuclear factor- κ B ligand), are also associated with generalized bone loss^{13,14}.

Vitamin D deficiency and the associated secondary hyperparathyroidism are strong risk factors for osteoporosis¹⁵. Vitamin D deficiency has been found to be associated with a higher incidence of RA¹⁶ as well as more active disease progression^{17,18,19}, but this was not confirmed in other studies^{20,21}. It may therefore be that the increased risk of developing focal bone erosions in patients with RA is related with low bone mineral density (BMD), low levels of 25(OH) vitamin D (25OHD), and secondary hyperparathyroidism.

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The aim of our study was to investigate the relationship between focal bone erosions and bone mass or mineral metabolism in a large cohort of RA patients. We hypothesized that lower BMD or 25OHD or higher parathyroid hormone (PTH) levels would be associated with higher prevalence of typical RA erosions.

MATERIALS AND METHODS

The study population included 1191 consecutive patients (1014 women, 177 men) from 22 rheumatology centers uniformly distributed across Italy (6 northern, 8 central, 8 in southern Italy). All patients fulfilled the 1987 American College of Rheumatology (ACR) revised criteria²² for RA. The inclusion criteria were a diagnosis of established RA and an age range of 30 to 75 years, irrespective of menopausal status. Exclusion criteria were insulin-dependent diabetes and severe hepatic or severe renal impairment (serum creatinine > 2 mg/dl). Patients unable to walk without assistance and those with total bilateral hip replacement were excluded, being considered unfit for a thorough clinical investigation.

All patients were interviewed and went through a full physical examination by rheumatologist at each clinical center for information on disease and treatment history.

Disease-related findings included disease duration and counts of 28 tender and swollen joints. Radiographs of hands and feet were analyzed locally using the van der Heijde modification of the Sharp erosion score²³, and subjects were categorized by the presence or absence of radiographic erosions (erosion score ≥ 1 vs erosion score = 0). This threshold was selected since the total erosion score was thought to be mostly dependent on disease duration.

Clinical measurements of RA disease activity included the Italian version of the Health Assessment Questionnaire Disability Index (HAQ)²⁴, the Steinbrocker functional state²⁵, and mobility in activities of daily life (mobility ADL)²⁶. The 3-variable Disease Activity Score 28-joint count (DAS28) was calculated using C-reactive protein (CRP) and by the Nijmegen algorithm (available online: <http://www.reuma-nijmegen.nl/www.das-score.nl/index.html>).

The ACR criteria were used to classify patients as in remission or not in remission at the time of observation. Surgical or natural menopausal age and smoking habit were also recorded. Information was collected on RA-specific treatments, including disease modifying antirheumatic drugs (DMARD: methotrexate, cyclosporine, sulfasalazine, antimalarials, and azathioprine) and TNF blockers. Patients were classified as not supplemented with vitamin D if they have been taking on average during the last year < 200 IU vitamin D daily. Glucocorticoid treatment was evaluated in detail; patients were divided into users and nonusers at the time of observation. Patients were classified as nonusers when they had never been treated with glucocorticoid or when treatment had been discontinued for more than 6 months. Information on the current dose, treatment duration, and cumulative doses (time per daily dose) was also obtained for each user from the clinical notes, and when required by specifically interviewing the patient.

Patients were interviewed on past and current use of drugs affecting bone metabolism including bisphosphonates, calcium, and vitamin D supplements. Daily intake of calcium was assessed by a simplified validated questionnaire²⁷. In all subjects, body weight and height (Harpender stadiometer) were assessed and body mass index (BMI; kg/m²) was calculated.

CRP, erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), and cyclic citrullinated peptide antibody (anti-CCP) and routine biochemistry were measured locally.

Individual aliquots of serum samples were collected from June 2007 to May 2008 from each patient, with a time lag of 0 to 16 months between X-ray or dual-energy X-ray absorptiometry (DEXA) examination. Four aliquots were sent on dry ice by courier to the University of Verona laboratory and kept at -50°C until measurements of serum intact PTH and

25OHD were taken using commercial ELISA kits (IDS Co., Bolden, UK), with interassay coefficients of variation ranging from 5% to 15%.

Hologic (17 centers) and Lunar (2 centers) instruments were used for DEXA evaluations of BMD at the lumbar spine and/or femoral neck in 449 patients. The values obtained with the Lunar instruments were standardized to those of the Hologic instruments²⁸. The *in vivo* coefficients of variation, tested in each center before the start of the study, ranged from 0.6% to 1.2% at the spine and 0.95% to 2.2% at the hip.

This study was approved by the local ethics committees, and the subjects' written consent was obtained according to the Declaration of Helsinki.

Statistical analysis. The per-protocol main objective of the study used for determining the sample size was the association between PTH and 25OHD levels with disease activity and the presence of bone erosions on standard radiographs of hands and feet.

All continuous variables are reported as mean \pm standard deviations (SD). The clinical characteristics of patients with and without erosions were compared by chi-square test for categorical variables and Student t test for continuous variables. Analysis of covariance was used to adjust the values for any confounding factor: BMD or PTH or 25OHD were the dependent variables and erosions (yes vs no) the fixed factors. All potential interfering factors (covariates age, sex, menopausal state, disease duration, DAS28, HAQ, mobility ADL, functional state, glucocorticoid therapy, BMI, bisphosphonate treatment) were included altogether in the models. All analyses were performed with SPSS, version 13.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Clinically relevant characteristics of the patients are listed in Table 1. The mean age was 58.9 \pm 11.1 years (range 30 and 75 yrs). Seventy-five percent of female patients had been postmenopausal for a mean of 15 \pm 8 years; 82 of these women had undergone oophorectomy.

Seventy-nine percent of the patients were in Class I or II Steinbrocker functional class, 19.0% were in Class III, and 1.8% were in Class IV. HAQ was < 1 in 46%, between 1 and 2 in 32%, and between 2 and 3 in 22% of patients. The

Table 1. Characteristics of the 1191 patients (1014 women, 177 men). Data are mean \pm SD.

Characteristic	Women	Men
Age, yrs	58.7 \pm 11.1	59.9 \pm 10.8
Height, cm	160.4 \pm 6.7	170.9 \pm 6.3
Weight, kg	64.4 \pm 12.2	75.9 \pm 12.2
Body mass index, kg/m ²	25.0 \pm 4.5	25.9 \pm 3.7
Duration of RA, mo	138 \pm 104	138 \pm 108
No. swollen joints	3.1 \pm 5.0	2.0 \pm 3.0
C-reactive protein, mg/dl	2.6 \pm 5.5	2.8 \pm 5.7
DAS28	3.96 \pm 1.00	3.55 \pm 0.97
ESR, mm ³ /h	30.7 \pm 21.3	26.7 \pm 22.4
Serum calcium, mg/dl	9.0 \pm 1.1	8.9 \pm 1.3
Serum phosphate, mg/dl	3.4 \pm 0.7	3.2 \pm 0.7
Serum 25OHD, ng/ml	24.1 \pm 14.4	24.7 \pm 12.4
Serum PTH, pg/ml	25.0 \pm 14.1	24.9 \pm 11.6
Lumbar spine BMD T score	-1.70 \pm 1.25	-1.40 \pm 1.65
Lumbar spine BMD Z score	-0.68 \pm 1.18	-0.35 \pm 1.65
Total hip BMD T score	-1.50 \pm 1.15	-1.18 \pm 1.17
Total hip BMD Z score	-0.58 \pm 1.14	-0.23 \pm 1.22

RA: rheumatoid arthritis; DAS28: Disease Activity Score 28-joint count; ESR: erythrocyte sedimentation rate; PTH: parathyroid hormone; BMD: bone mineral density.

mobility ADL score was 0–6 in 35%, 6–10 in 42%, and > 10 in 35% of the patients.

Mean dietary calcium intake was 750 ± 330 mg/day. Twenty-two percent of the patients were being treated with calcium supplements and 45% were taking vitamin D supplements. RF was positive in 63.7% of patients. Anti-CCP measurements were available for 758 patients, and were positive in 66.3%.

At the time of recruitment to the study, 88.2% of patients were taking DMARD: 50.8% methotrexate, 15.9% leflunomide, 10.9% antimalarials, and 3.2% either cyclosporine or sulfasalazine. In total, 502 patients (45.5%) were being treated with anti-TNF- α , generally in association with methotrexate. Eighty-six percent of patients were on glucocorticoid treatment (mean daily dose 5.4 ± 3.5 mg prednisone equivalents). Mean duration of steroid treatment was 33 ± 52 months and cumulative prednisone equivalent intake was 11.7 ± 14.2 g.

Twenty-three percent of the patients were found to be in clinical remission according to the ACR criteria.

The frequency of osteoporosis (i.e., T score less than -2.5) in the overall sample was 28% for lumbar spine, 26% for femoral neck, and 20% for total hip. At the time of recruitment, 27.2% of the patients were being treated with bisphosphonates.

Evidence of typical bony erosions on radiographs of hands or forefeet was found in 64.1% of patients.

A DEXA evaluation was obtained for patients from only 10 of the 22 study centers. The patients in whom a DEXA examination was obtained or not obtained were comparable for all the characteristics listed in Table 1 (results not shown).

The prevalence of the main clinical indices of disease activity, and of the characteristics considered potentially associated with BMD for patients with or without erosions, are listed in Tables 2 and 3. The patients with bone erosions generally had more severe and longer-lasting disease and were more often taking anti-TNF- α and bisphosphonate therapy. Both hip and spine BMD T scores and Z scores were significantly lower in patients with bone erosions than in those without erosions.

In the entire study population and also in the subgroup not taking vitamin D supplements, PTH levels were significantly higher in those with erosive arthritis, while 25OHD concentrations were very similar in the 2 groups of patients.

Mean values for BMD, for serum 25OHD, and for PTH, adjusted in a comprehensive model for all factors potentially associated with disease activity and mineral metabolism, are listed in Table 4. The differences between patients with and those without erosions decreased, but remained statistically significant for hip BMD and for PTH. The individual contribution of each covariate was very small and non-significant, with the only exception for age as adjustment factor for BMD values (results not shown). The exclusion of

Table 2. Comparison between patients with and without bone erosions for continuous variables (mean \pm SD).

Characteristic	Erosions		p
	Yes	No	
No.	763	428	
Age, yrs	59.2 \pm 11.0	58.4 \pm 11.4	NS
Height, cm	161.4 \pm 7.4	163.0 \pm 7.8	< 0.001
Weight, kg	65.2 \pm 12.7	67.5 \pm 13.1	0.004
Body mass index, kg/m ²	25.0 \pm 4.5	25.4 \pm 4.4	NS
Calcium intake, mg/day	771 \pm 392	805 \pm 391	NS
Duration of RA, mo	155 \pm 107	107 \pm 92	< 0.001
No. swollen joints	3.3 \pm 5.1	2.4 \pm 4.0	0.003
DAS28	4.06 \pm 1.00	3.61 \pm 0.93	< 0.001
Daily dose (mg prednisone equivalents)	5.49 \pm 3.43	5.00 \pm 3.54	NS
Cumulative glucocorticoid dose [†] (g prednisone equivalents)	13.5 \pm 15.2	8.5 \pm 11.7	< 0.001
HAQ	1.24 \pm 0.86	0.96 \pm 0.78	< 0.001
Mobility ADL score	8.53 \pm 3.80	7.71 \pm 2.77	< 0.001
Serum 25OHD, ng/ml	24.8 \pm 15.4	23.9 \pm 12.1	NS
	21.7 \pm 12.0*	20.7 \pm 9.2*	NS
Serum PTH, pg/ml	25.5 \pm 14.4	23.7 \pm 12.3	0.014
	25.9 \pm 14.0*	23.1 \pm 11.6*	0.010
Lumbar spine BMD T score	-1.75 \pm 1.24	-1.50 \pm 1.41	0.05
Lumbar spine BMD Z score	-0.74 \pm 1.19	-0.46 \pm 1.31	0.05
Total hip BMD T score	-1.64 \pm 1.08	-1.10 \pm 1.24	< 0.001
Total hip BMD Z score	-0.72 \pm 1.07	-0.15 \pm 1.23	< 0.001

* Subgroup of patients not on treatment with vitamin D supplements. [†] subgroup of patients classified as users at the time of observation. RA: rheumatoid arthritis; DAS28: Disease Activity Score 28-joint count; HAQ: Health Assessment Questionnaire; ADL: activities of daily living; PTH: parathyroid hormone; BMD: bone mineral density; NS: nonsignificant, p > 0.05.

Table 3. Association between discrete patient variables (percentages) and bone erosions.

Bone Erosions	Yes	No	p
Rheumatoid factor-positive	68.5	55.2	< 0.001
Anti-CCP-positive	71.2	58.1	< 0.001
Smoking	21.0	20.3	NS
Postmenopausal status	77.2	72.4	0.09
DMARD treatment	71.2	73.4	NS
Glucocorticoid treatment	86.2	85.5	NS
TNF blocker therapy	50.7	36.2	< 0.001
Vitamin D supplementation	47.6	40.2	0.014
Bisphosphonate therapy	29.3	23.4	0.026

Anti-CCP: cyclic citrullinated peptide antibody; DMARD: disease-modifying antirheumatic drugs; TNF: tumor necrosis factor; NS: nonsignificant, $p > 0.05$.

Table 4. BMD, 25OHD, and parathyroid hormone (PTH) levels (mean \pm SD) after multiple adjustments (age, sex, menopausal state, disease duration, DAS28, HAQ, mobility ADL, functional state, cumulative and daily glucocorticoid therapy, dietary calcium intake, smoking, BMI, bisphosphonate treatment) in RA patients with and without bone erosions. BMD values were also adjusted for 25OHD levels.

Characteristic	Erosions		p
	Yes	No	
25OHD (ng/ml)	23.3 \pm 12.1	24.8 \pm 11.0	NS
	21.8 \pm 11.1*	20.2 \pm 9.0*	
Parathyroid hormone, pg/ml	25.7 \pm 13.7	23.3 \pm 13.1	0.04
	26.3 \pm 13.1*	22.9 \pm 11.0*	0.009
Lumbar spine BMD T score	-1.67 \pm 1.21	-1.60 \pm 1.43	NS
Lumbar spine BMD Z score	-0.64 \pm 1.71	-0.48 \pm 0.83	NS
Total hip BMD T score	-1.55 \pm 1.04	-1.18 \pm 1.05	0.005
Total hip BMD Z score	-0.65 \pm 1.02	-0.25 \pm 0.99	0.005

*Patients not on treatment with vitamin D supplements. NS: nonsignificant, $p > 0.05$.

men or premenopausal women did not change the statistical significance (results not shown) and there was no interaction with recruitment sites. When PTH levels were adjusted also for 25OHD levels the difference became somewhat more significant (p value from 0.009 to 0.004).

A significant relationship was also found between values for BMD or PTH and erosion score categorized as zero score or quartiles of erosion score. However, this gradient of relationship was completely lost when data were adjusted for disease duration, which was the main determinant of erosion score among patients with erosions (results not shown).

DISCUSSION

In a large cohort of RA patients with a median disease duration of 115 months we found that in patients with focal bony erosions, total hip and lumbar spine BMD were significantly lower than in patients without erosions. An additional novel finding of our study was the association between the presence of erosions and higher PTH levels.

At variance with the values for spine BMD, total hip

BMD values remained significantly related to erosions as shown by values simultaneously adjusted for all available variables potentially associated with bone mass, such as age, disease activity (ESR, CRP, DAS28), functional impairment (HAQ, mobility ADL), BMI, 25OHD levels, and treatment with glucocorticoids or bisphosphonates.

The relationship between focal bone erosions and bone metabolism has been examined in previous studies. An ancillary finding of the COBRA trial²⁹ was the observation that the bone resorption markers urinary pyridinoline and deoxypyridinoline were correlated with erosion scores. A significant positive correlation between hand BMD and erosions was reported in a number of studies, but this is to be expected from the proximity of the erosions to the region of BMD measurement^{13,30,31}. A correlation between BMD at both the hip and the spine and the Larsen score has been observed in a cohort of 204 patients with early-onset RA³², and from a post hoc analysis of the BeSt trial³³. The progression of erosion scores was faster in patients with the lowest BMD values³⁴.

Recently Solomon, *et al*³⁵ reported that the erosion score was significantly correlated with total hip BMD, but not with lumbar spine BMD. This observation, together with our results and previous studies, might be explained by the negative effect of functional impairment associated with erosions and also by the effect of the severity and duration of disease on generalized bone loss. Indeed, in Solomon's study the association between focal erosions and total hip BMD lost statistical significance when BMD values were adjusted for age, BMI, and cumulative oral glucocorticoid dose. However, we did find that the association between erosions and total hip BMD remained statistically significant after adjustment for not only functional status, but also all other potential determinants of BMD. These determinants included disease duration, sex and menopausal status, vitamin D insufficiency, and the use of glucocorticoids or DMARD, which are known to negatively affect bone metabolism. These results may be explained by sample size, as our sample was 7 times larger than that of the previous study³⁵.

We found, similarly to other investigators^{34,35}, that the relationship with bone erosions was stronger for total hip than for lumbar spine BMD. From the larger proportion of trabecular bone content of the vertebral bodies relative to total hip, one would anticipate the opposite, since the perturbation of cytokines occurring in RA would be expected to have more influence on the more metabolically active trabecular bone tissue than on cortical bone. On the other hand, the accuracy of lumbar spine DEXA is affected with advancing age by a number of factors³⁶ that might dilute the relationship between BMD and erosions.

We also found an association between erosions and PTH levels but not with serum 25OHD. Serum 25OHD was, as expected, negatively correlated with PTH (results not

shown), but when serum PTH was adjusted for 25OHD its association with the presence of erosions became even stronger. These findings are difficult to interpret. RA might be associated with decreased 1- α -hydroxylase activity, which is able to convert 25OHD into the active vitamin D metabolite 1.25(OH)₂D, with a consequent sparing effect on vitamin D deposits. Indeed, circulating levels of 1.25(OH)₂D have been found to be negatively associated with disease activity in RA¹⁷. It is also conceivable that in these patients with variable vitamin D intake or sun exposure (even though they were not taking vitamin D supplement), PTH is a better predictor of vitamin D insufficiency, together with calcium intake, than 25OHD itself, over a long time interval²⁷. Finally, it was also found that T lymphocytes may facilitate PTH-induced osteoclastogenesis by increasing the bone marrow responsiveness of stromal cells to PTH³⁷.

This observational study has a number of limitations. With its cross-sectional design we associate measurements (BMD or PTH levels) taken at a given timepoint with erosions that are dependent on the disease duration and on therapy. BMD values were adjusted for all available factors, but other potential confounders (e.g., family history, dietary habits in childhood, etc.) could not be taken into account. The hand and foot radiographs were analyzed using the van der Heijde modification of the Sharp erosion score²³ in each center, without centralized supervision. We also established, per protocol, a definition of typical erosions by a score ≥ 1 , which is less likely to be associated with large inter-site variability. The study included patients receiving bisphosphonates, but this factor could not be excluded since bisphosphonate treatment is likely to reflect previous diagnosis of osteoporosis. Hand and foot radiographs were not taken simultaneously with DEXA evaluation. The time lag between DEXA scanning or serum collection and radiography ranged from 0 to 16 months, but this interval was shorter (< 4 months) in patients with early RA (< 3 years), and > 6 months only in patients with stable longterm disease.

Our results suggest that the presence of bone erosions in RA correlates with low BMD levels, and that this association is independent of both functional impairment and other common determinants of bone mass in adult subjects. It appears that bone erosions and generalized osteoporosis share a common pathophysiological mechanism and that osteoporosis might be an independent risk factor for the development of bone erosions. This might imply that anti-resorption agents should be considered for the management of RA at onset of disease. PTH levels are also associated with the presence of bone erosions by a mechanism that is not associated with vitamin D deficiency. Interventional studies of the effect of treatments aimed at preventing bone loss or suppressing PTH levels on the appearance and progression of bone erosions in RA could shed light on the clinical relevance of these associations.

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