Loss of Cortical Bone from the Metacarpal Diaphysis in Patients with Rheumatoid Arthritis: Independent Effects of Systemic Inflammation and Glucocorticoids

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ABSTRACT. ***Objective.*** To identify factors associated with the loss of cortical diaphyseal bone over time in patients with rheumatoid arthritis (RA).

Methods. We measured the combined cortical thickness (CCT) of the second metacarpal bone from digitized hand radiographs in an RA cohort. We estimated the rate of loss of CCT, and tested the effect of factors that could accelerate the rate.

Results. We studied 649 patients, who had 2990 hand radiographs. The median interval between the first and last followup radiograph was 2 years (range 0 to 23 yrs). The mean CCT at baseline was 4.04 mm (standard deviation 1.18). CCT loss was greatest during the earliest observation stages, following a square-root function of time at a rate of 0.393 mm/year^{½} (95% CI 0.360, 0.423). Patients with a mean erythrocyte sedimentation rate (ESR) < 30 mm/h lost CCT at a rate of 0.303 mm/year^{½} (95% CI 0.247, 0.358); those with a mean ESR > 30 and ≤ 60 mm/h lost CCT at 0.395 mm/year^{½} (95% CI 0.345, 0.446); and those with ESR > 60 mm/h lost CCT at 0.554 mm/year^{½} (95% CI 0.480, 0.628). Patients who received a cumulative dose of glucocorticoids ≥ 11.7 g lost CCT at 0.659 mm/year^{½} (95% CI 0.577, 0.742), compared to 0.361 mm/year^{½} (0.323, 0.401) in patients who did not receive glucocorticoids. In a multivariable model, the effect of the ESR and cumulative glucocorticoids was independent of age at RA onset, RA duration, sex, ethnic group, body mass index, presence of rheumatoid nodules, rheumatoid factor, and the HLA-DRB1 shared epitope.

Conclusion. Early rapid loss of cortical diaphyseal bone occurs in patients with RA, followed by gradual slowing. Systemic inflammation and glucocorticoids seem to accelerate bone loss independently of other risk factors. Cortical diaphyseal bone may be an important target of the disease process in RA. (J Rheumatol 2006;33:508–16)

Key Indexing Terms:

RHEUMATOID ARTHRITIS	OSTEOPOROSIS	INFLAMMATORY MARKERS
BONE DIAPHYSIS	CORTICAL BONE	BONE TURNOVER

Bone loss is one of the pathological consequences of rheumatoid arthritis (RA)[1-3]. Most characteristically, it occurs in the form of bony erosions in diarthrodial joints[4-6]. Bone loss in patients with RA also occurs in the form of generalized and axial osteoporosis[7,8]. This type of bone loss affects mostly trabecular bone. It is made worse by glucocorticoids[9-11], but affects patients with RA even in the absence of these agents[7,12]. A third type of bone loss in patients with RA affects cortical diaphyseal bone[13-17]. This type of bone loss has received less attention. It is a matter of concern because of the load-bearing properties of cortical diaphyseal bone[18,19]. Its loss may increase the risk of bone fractures to a greater extent than does the more thoroughly studied loss of trabecular bone[20,21]. Moreover, in cross-sectional studies, cortical diaphyseal bone has been noted to relate closely to the extent of joint damage[13,22], suggesting that the 2 processes may be related.

Cortical bone can be quantified with a measurement of the combined cortical thickness (CCT), obtained from plain hand radiographs. The CCT is the difference between the medullary and cortical diameters at the midpoint of the bone diaphysis (Figure 1). The second metacarpal is a convenient location to measure the CCT in patients with RA, because it is usually well imaged in plain hand radiographs obtained to assess the outcome of RA[23-26].

We examined the CCT at several times in a cohort of patients with RA. Our objective was to quantify the rate of

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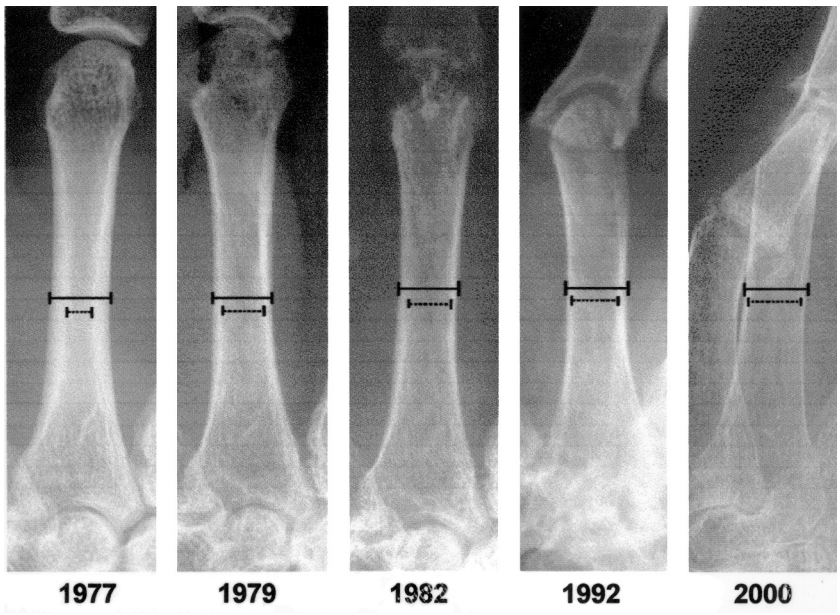

Figure 1. The combined cortical thickness (CCT) of the second metacarpal is provided by the difference between the periosteal (solid line) and endosteal (broken line) diameters, and is expressed in millimeters. In this example, the patient's CCT gradually decreased from 5.0 mm in 1977 to 0.69 mm in 2000.

change in CCT, and to test the role of potential factors that could influence this rate.

MATERIALS AND METHODS

Patients. From 1996 to 2000, we enrolled consecutive patients who met the 1987 American College of Rheumatology classification criteria for RA[27] into ÓRALE (Outcome of Rheumatoid Arthritis Longitudinal Evaluation), a study of the disablement process in RA[28]. We have described the ÓRALE cohort in previous publications[29-32].

We enrolled consecutive patients from 6 rheumatology clinics in San Antonio, Texas: (1) A county-funded clinic; (2) a Veterans Administration clinic; (3) a private, university-based faculty practice; (4) a community-based, 7 rheumatologist private practice; (5) an army clinic; and (6) an air force medical center. At enrollment, all patients resided in Bexar County, Texas, or nearby communities.

Data collection procedures. All patients gave written, informed consent to participate in the study. We performed all interviews and clinical evaluations at the clinic where patients were recruited. Patients received a postero-anterior (PA) hand and wrist radiograph at the site of the study visit. We also obtained previous hand radiographs from files at the study locations. A physician or a trained research nurse examined all patients and reviewed the medical records. We recorded current and past use of medications, including glucocorticoids. We inspected patient's current medication bottles, and reviewed pharmacy and medical records. We estimated the cumulative glucocorticoid dose by multiplying the number of days since a glucocorticoid was first prescribed by the daily dose in use at the time of the initial ÓRALE evaluation.

Data Elements

Demographic information. We ascertained age, sex, and race/ethnicity by self-report, as described[30,31]. For race/ethnicity, we employed the question, "In which of the following race or ethnic groups do you feel you belong?". Patients could chose among "White," "Black," "Asian," "Hispanic," and "Other."

Anthropometric characteristics. We recorded height and used standard clinical scales to measure weight. We calculated the body mass index (BMI) as the weight (kilograms) divided by the square of the height (meters).

Onset of RA. We recorded the ages or dates of symptom onset and the diagnosis of RA, confirmed by the medical records.

Musculoskeletal examination. One of 3 examiners, a rheumatologist, a physician, or a research nurse, all trained in joint examination techniques, assessed 48 joints in each patient for joint tenderness or pain on motion, swelling or deformity, as described[32,33]. Reliability of the joint examination, tested in 28 patients from the ÓRALE sample who were examined by 3 raters, was 0.94 for the tender joint count, 0.90 for the swollen joint count, and 0.98 for the deformed joint count[29,31]. The examiner also recorded the presence or absence of subcutaneous nodules.

Radiographic measurements. We digitized the hand radiographs using a Hewlett Packard ScanJet 4c scanner equipped with a transparency adapter (Hewlett Packard, Palo Alto, CA, USA). We used the Image Tool analysis software package version 2.3 (Dental Diagnostic Science, UTHSCSA, San Antonio, TX, USA) to perform CCT measurements on magnified images (2x), after optimizing contrast. One of us (JFR) measured the CCT as the difference between the endosteal and periosteal diameters at the midpoint of the left and right second metacarpals (Figure 1). Using a personal computer, the reader placed marks on cortical edges using a standard computer mouse. The imaging program measured the distance between cortical edges in pixels, which we converted to millimeters. We used a mean of both sides in the analysis. We estimated the intrarater reliability by measuring agreement between the right and the left hand cortical diameters and CCT, using each patient's first available radiograph. Since the right and left hands resemble, but are not identical to each other, this agreement coefficient is a conservative estimate of the intrarater reliability. The reliability of the patient-averaged endosteal and periosteal diameters was 0.93 for both, and for the CCT the reliability was 0.91. These values represent Spearman-Brown reliability coefficients[34].

Laboratory studies. The erythrocyte sedimentation rate (ESR) and titers for serum rheumatoid factor (RF) were measured in each hospital laboratory. A manual Westergren ESR technique was used in 5 of the centers, the sixth using an automated analyzer (Diesse Diagnostic Senese, Milano, Italy). Agreement between these 2 techniques is very high[35,36]. Latex agglutination was used to measure RF in 5 hospitals, the sixth using an ELISA technique[37].

In each hospital, a positive RF was defined as a titer occurring in < 5% of normal people. Most patients with negative results for RF were tested on several occasions.

HLA-DRB1 typing. HLA-DRB1 genotyping was performed by Biosynthesis, Inc. (Lewisville, TX, USA), a clinically certified laboratory, using polymerase chain reaction-sequence specific primer (PCR-SSP) amplification with Fastype kits (Bio-Synthesis, Inc.)[38]. HLA-DRB1 types were classified using the 1996 World Health Organization Nomenclature Committee for Factors of the HLA System update[39]. Subjects were classified as shared epitope-positive if they had any of the following HLA-DRB1 subtypes: *0101, *0102, *0401, *0404, *0405, *0408, *0409, *0410, *1001, *1402, or *1406. We describe our methods in detail elsewhere[29,31,40].

Statistical analysis. We conducted cross-sectional, 2-group comparisons between patients' characteristics at baseline, using Student's t test, chi-square, or Pearson correlation coefficients as indicated. For assessment of change in CCT over time, we used generalized estimating equations (GEE) with disease duration at the time of the radiograph as the independent variable. We specified an exchangeable correlation structure, identity link, and Gaussian distribution[41]. To select the best model, we tested simple straight-line, quadratic, and square-root transformations of disease duration, using the model that provided the highest Wald chi-square value. To contrast the effect of candidate risk factors on the rate of loss of cortical bone, we tested risk factor x disease duration interactions. We provide bivariate and multivariable estimates of the effect of each candidate predictor. Our study's power to detect a 10% or greater difference in slope-over-time between patients exposed and unexposed to a given risk factor was greater than 90%, given the available sample size, the number of observations, the observed intrapatient correlation in the CCT measurements of 0.84, and a 2 sided p value set at 0.05, and assuming the proportion of exposed patients was ≥ 0.3 and ≤ 0.5[42]. All p values shown are 2-sided to $\leq 10^{-3}$, without modification for multiple testing. We used the Stata 8 statistical software package (Stata Corp., College Station, TX, USA) for all analyses.

RESULTS

We enrolled 779 patients with RA into the ÓRALE study. At the time of the present analysis, hand radiographs were available for 649 (83%) patients, for a total of 2990 hands radiographed. The CCT is a patient-level variable representing the mean cortical thickness of the second metarcarpal of the right and left hands. Therefore, we obtained 1455 patient-level CCT measurements from these radiographs. The mean number of CCT measurements per patient was 2.2 (median 2, range 1 to 10). One patient each had 10 and 9 CCT measurements, 4 patients had 6, 43 had 4, 149 had 3, 298 had 2, and 142 patients had one CCT measurement. The median interval between the first and followup radiographs was 2.0 years (mean 3.4, range 0 to 23 yrs). The cumulative time period covered by the available radiographs was 1588 person-years. The first radiograph was taken at a median of 8 years after the diagnosis of RA (mean 10.9, range 0 to 50 yrs). The 130 patients who were enrolled in the cohort but who lacked radiographs at the time of the present analysis were slightly older and more likely to be White. They also had slightly longer disease duration and had more joint deformities than the patients for whom radiographs were available. However, the 2 groups did not differ in a number of other important variables (Table 1).

The mean CCT on the first available radiograph was 4.04 mm (standard deviation 1.18). Both the periosteal and endosteal diameters of the second metacarpal were significantly greater in the right hand, by a mean of about one-tenth of a millimeter (Table 2). However, the CCT itself did not differ between the right and left hands.

The CCT was cross-sectionally associated with a number of variables (Table 3). Most of these were to be expected: age, sex, height and weight, disease duration, and use of glucocorticoids. Of greater interest was the association between CCT and variables indicating RA disease activity and damage, such as RF, subcutaneous nodules, ESR, and joint deformities. Of note, the association was weak and not significant for the race/ethnicity, HLA-DRB1 shared epitope, and the tender and swollen joint counts (Table 3).

There was a notable decrease in the CCT over time in most patients. The reduction in cortical bone thickness was sometimes dramatic (Figure 1). To model the loss of CCT statistically, we tested untransformed, quadratic, and square-root transformations of disease duration as predictors of the CCT. A model including the untransformed disease duration as the predictor of CCT had a Wald chi-square of 425; the corresponding value for a model that included only a quadratic transformation of disease duration was 183; a model that included the natural log of disease duration had a chi-square of 460; and a model with a square-root transformation of disease duration had a chi-square of 530. Thus, we employ the square-root transformation of disease duration in all subsequent estimates of the rate of cortical bone loss. This transformation of time implies a more rapid loss of CCT during the earliest period of observation, with a gradual slowing of the bone loss over time. More specifically, the amount of bone loss per unit of time is halved in each successive period of observation. Our estimate from this model was that CCT was lost at a rate of 0.393 mm/year$^{1/2}$ (95% CI 0.360, 0.428). This is illustrated in Figure 2, which shows curves that are steeper near the origin and then gradually flatten out.

We examined several candidate factors for their effect on rate of CCT loss. We tested age, sex, race and ethnic background, presence of the HLA-DRB1 shared epitope, RF status, the cumulative dose of prednisone, and the mean ESR, averaged over the period of study. The results of this analysis are shown in Table 4. Factors that resulted in a more rapid rate of CCT loss included non-Hispanic Black race-ethnicity, the ESR, and the cumulative glucocorticoid dose. Black patients lost CCT at a rate that was 0.230 mm/year$^{1/2}$ faster than the rate among non-Hispanic Whites. The rate of loss of CCT increased with the ESR. Patients whose mean ESR (mm/h) was below 30 lost CCT at a rate of 0.303 mm/year$^{1/2}$; those with mean ESR > 30 and < 60 lost CCT at 0.395 mm/year$^{1/2}$ ($p = 0.02$ compared to those with ESR < 30). Patients with ESR > 60 lost CCT at 0.554 mm/year$^{1/2}$ ($p \leq 0.001$ vs ESR < 30; Table 4 and Figure 2).

The glucocorticoid cumulative dose also displayed a dose-response effect, with patients in higher exposure categories showing progressively steeper declines in CCT over time (Figure 3). Compared to patients who were not exposed to

Table 1. Characteristics of 779 patients enrolled in the ÓRALE study, according to availability of hand radiographs.

Variable	Hand Radiographs Present	Hand Radiographs Absent	p
No.	649	130	—
Age, yrs, mean (SD)	55 (12.8)	58 (16)	0.04
Women, n (%)	456 (70)	94 (72)	0.6
White, n (%)	211 (33)	61 (47)	0.002
Black, n (%)	44 (7)	9 (7)	0.9
Hispanic, n (%)	380 (59)	54 (42)	≤ 0.001
RA disease duration, yrs, mean (SD)	11 (10)	12 (11)	0.07
RA disease duration, $yrs^{1/2}$ (SD)	2.8 (1.7)	3.1 (1.7)	0.1
Tender joints, mean (SD)	15 (13)	14 (13)	0.7
Swollen joints, mean (SD)	7 (6.8)	7 (7)	0.7
Deformities, mean (SD)	10 (10.8)	12 (12.8)	0.003
Rheumatoid nodules, n (%)	194 (29)	39 (30)	0.9
MHAQ, mean (SD)	1.9 (0.7)	1.9 (0.7)	0.6
ESR, mean (SD)	41 (27)	42 (26)	0.3
Rheumatoid factor, n (%)	571 (89)	113 (87)	0.7
HLA-DRB1 shared epitope, n (%)	467 (72)	85 (75)	0.6
Prednisone, n (%)	320 (49)	65 (52)	0.6
Cumulative glucocorticoid dose, g, mean (SD)‡	12.3 (16.6)	11.3 (14)	0.6

* Patients who received glucocorticoids only. MHAQ: modified Health Assessment Questionnaire; ESR: erythrocyte sedimentation rate.

Table 2. Baseline combined cortical thickness and cross-sectional diameters (mm) of the second metacarpal in 649 patients with RA. Values represent means (standard deviations).

	Right Hand, mm	Left Hand, mm	Difference	p*
Combined cortical thickness, mm	4.041 (1.231)	4.045 (1.28)	0.003 (0.703)	0.9
Periosteal diameter, mm	8.023 (0.976)	7.919 (0.983)	0.103 (0.491)	≤ 0.001
Endosteal diameter, mm	3.981 (1.337)	3.874 (1.348)	0.107 (0.665)	≤ 0.001

* Paired Student t test.

Table 3. Cross-sectional CCT associations.

Variable	r*	p**
Age	0.38	≤ 0.001
Sex	0.18	≤ 0.001
Race/ethnicity	0.07	0.2
Height	0.21	≤ 0.001
Weight	0.29	≤ 0.001
HLA-DRB1 shared epitope	0.08	0.07
Rheumatoid factor	0.16	≤ 0.001
Rheumatoid nodules	0.22	≤ 0.001
ESR	0.25	≤ 0.001
BMI	0.18	≤ 0.001
Prednisone use	0.14	0.001
Cumulative glucocorticoid dose	0.18	≤ 0.001
Disease duration	0.34	≤ 0.001
Tender joint count	0.04	0.3
Swollen joint count	0.03	0.4
Deformed joint count	0.50	≤ 0.001

* For categorical variables (sex, race/ethnicity), r values are the square-root of a linear regression R^2 using the listed variable as predictor. ** Adjusted for intrasubject correlation. ESR: erythrocyte sedimentation rate; BMI: body mass index.

glucocorticoids, patients in the lower two-thirds of the cumulative dose distribution (i.e., ≤ 11.5 g) had a steeper decline in CCT, although the difference did not reach statistical significance. However, the rate of CCT loss among patients in the top one-third of glucocorticoid exposure was nearly twice the rate among unexposed patients, a highly significant difference statistically (Table 4 and Figure 3).

Upon multivariable adjustment, both an ESR > 60 and a cumulative glucocorticoid dose in the top one-third of the distribution (i.e., ≥ 11.7 g), remained independently associated with acceleration of CCT loss. After multivariable adjustment, the effect of Black race-ethnicity was attenuated, losing statistical significance (Table 4).

DISCUSSION

Measurement of the CCT of the metacarpal and other long bones is a useful way to assess cortical bone[14-17,20-26]. Despite evidence that it is comparable to standard dual x-ray absorptiometry[43,44], the technique is underused. We measured the second metacarpal CCT at several times among members of a cohort of patients with RA. We found significant reductions in

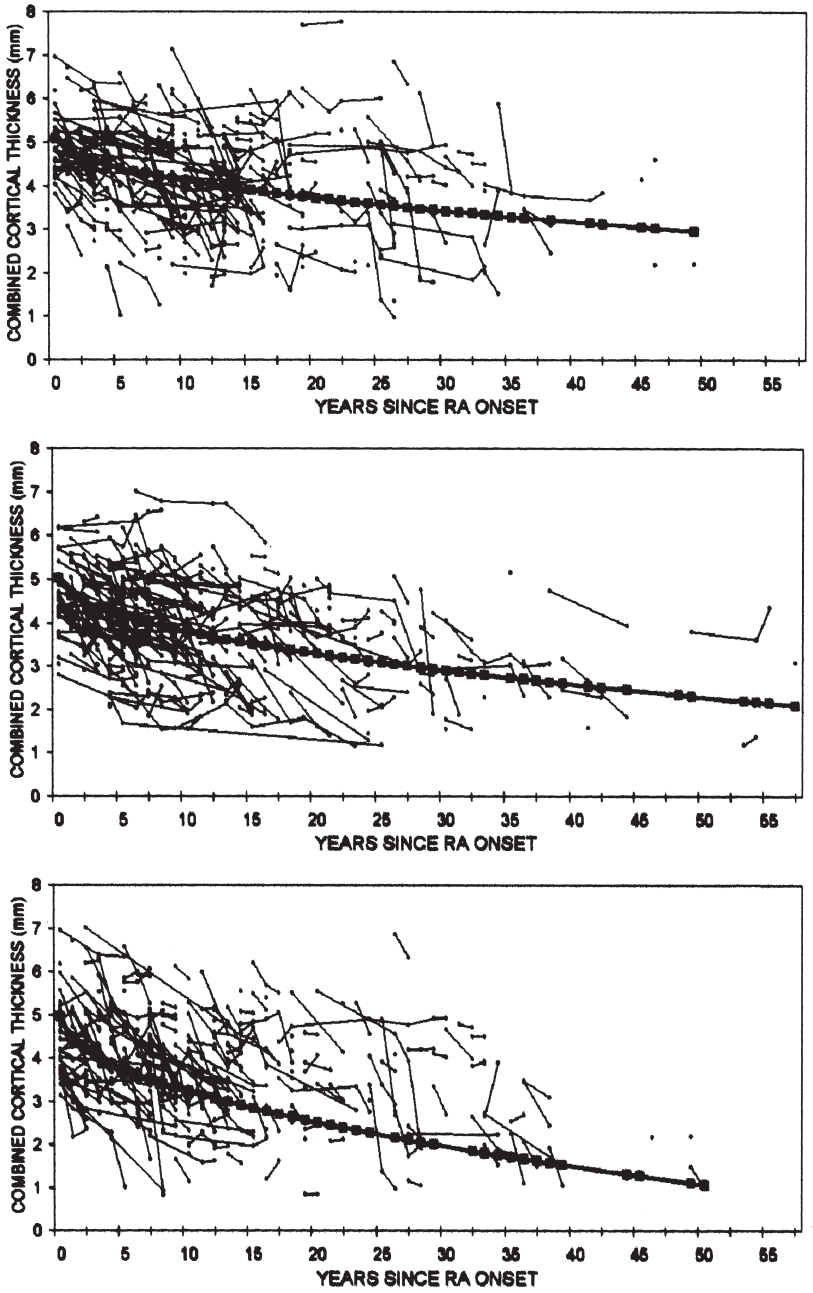

Figure 2. Loss of combined cortical thickness (CCT) over time in 649 patients with RA, grouped according to mean erythrocyte sedimentation rate (ESR). Patients with ESR < 30 mm/h lost CCT at a rate of 0.303 mm/yr$^{1/2}$ (95% CI 0.247, 0.358; top panel). Patients with ESR 30–60 mm/h lost CCT at a rate of 0.395 mm/yr$^{1/2}$ (95% CI 0.345, 0.446; P = 0.02 compared to ESR < 30; middle panel). Patients with ESR > 60 mm/h had the highest rate of CCT loss, 0.554 mm/year (95% CI 0.480, 0.628; p ≤ 0.001 compared to ESR < 30; bottom panel). The differences remained significant after adjustment for covariates listed in Table 4.

CCT over time. The evidence suggested more rapid bone loss early in the observation period, and that the speed with which bone was lost gradually decreased over time. Bone loss was more rapid in patients with elevated ESR and patients who received glucocorticoids. These associations were independent of other covariates including age, sex, ethnic group, body mass, the HLA-DRB1 shared epitope, the presence of subcutaneous nodules, and serum RF status.

We used the ESR to measure systemic inflammation. The association between CCT loss and elevation of ESR was significant, and displayed a biological gradient or dose-response effect. Patients in successively higher thirds of the ESR distri-

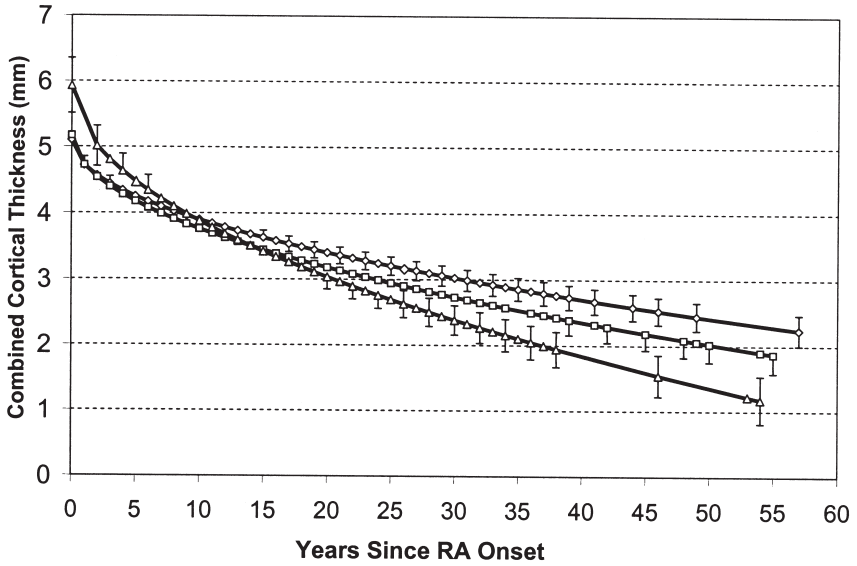

Figure 3. Loss of CCT over time in 649 patients with RA, according to the cumulative glucocorticoid dose. The 329 patients who did not receive glucocorticoids (◇), lost CCT at a rate of 0.362 mm/yr^{½} (95% CI 0.323, 0.401). The 215 patients in the lower and middle thirds of the glucocorticoid exposure distribution (□), who received up to 11.5 g prednisone, lost CCT at a rate of 0.412 mm/yr^{½} (95% CI 0.360, 0.465). The 105 patients in the highest glucocorticoid exposure tertile (△), who received ≥ 11.7 g prednisone, lost CCT at a rate of 0.659 mm/yr^{½} (95% CI 0.577, 0.742). Graph shows the unadjusted means, estimated from a generalized estimating equation with the square-root of disease duration as an independent variable. Bars represent 95% CI.

bution displayed increasingly rapid CCT loss. Our findings provide evidence that systemic inflammation is associated with cortical bone loss. Studies have suggested systemic inflammation also correlates strongly with joint damage in patients with RA[45-48]. Interleukin 1, receptor activator of nuclear factor- B (known as RANK), RANK-ligand, and other inflammatory mediators circulate in the blood of patients with RA, where they can reach and activate osteoclasts in cortical bone, causing bone resorption[49,50]. We had no information on the status of cortical bone elsewhere in the body. Such data would be useful to confirm a role for systemic inflammation in cortical bone loss.

An alternative explanation for the association between systemic inflammation and the CCT is that cortical diaphyseal bone could be a primary target of disease-induced damage in RA, as is the case for articular cartilage and subchondral bone. The cross-sectional associations of the CCT with RF, subcutaneous nodules, and joint deformities support this possibility. However, it is not clear how the pathologic process of RA could reach the metacarpal cortical diaphyseal bone. Synovial tissue and pannus do not appear to come into direct contact with the metacarpal mid-diaphyseal cortical bone. We are not aware of studies of the pathologic anatomy of the metacarpal bone marrow or endosteal surface, or other types of mechanistic studies focusing on cortical diaphyseal bone in patients with RA. The physical proximity of the metacarpophalangeal and wrist joints, which are both prime RA targets, may allow inflammatory mediators to influence osteoclasts in the mid-diaphysis. Further research to determine the mechanism of cortical diaphyseal bone loss in RA would be of great interest.

A limited number of studies have focused on cortical bone in RA. Most have had a cross-sectional design[13,51]. Some studies of metacarpal bone mass in RA that used a longitudinal design have suggested that treatment with disease modifying antirheumatic drugs or glucocorticoids had a sparing effect on metacarpal bone loss[13,52]. An association with systemic inflammation markers, such as we have found, is consistent with this finding, and extends it on several fronts. We had access to a larger and more diverse cohort of RA patients, who also had more CCT measurements over time. We used a multivariable modeling technique that is better suited for analyzing longitudinal data. These advantages allowed us to test a variety of curves to describe the dynamics of bone loss. We found that the best fit was provided by a square-root function of time. We believe the square-root function of time is more biologically plausible than the straight-line models tested previously. The square-root function posits an asymptotic, gradual slowing of bone loss that is more consistent with a finite supply of metacarpal bone.

In contrast with the study by Haugeberg, *et al*[52], in which a low dose of prednisolone was associated with a reduction in the rate of bone loss, we found that glucocorticoid accelerated thinning of the CCT. The reasons for this discrepancy are probably related to differences in study design. Haugeberg, *et al* employed a randomized trial of low-dose prednisolone over 2 years. Our patients' treatment was not randomly assigned, and thus was probably driven by disease severity. Moreover, the mean daily dose was higher, and followup longer. It is

Table 4. Rate of bone loss according to candidate predictors in 649 patients with RA.

Risk Factor	Rate of Loss, mm/yr$^{1/2}$	Bivariate p	Multivariate p*
Sex			
Men	–0.426 (–0.476, –0.376)		
Women	–0.406 (–0.442, –0.369)		
Difference	0.020 (–0.042, 0.082)	0.5	0.1
Race/Ethnicity			
Non-Hispanic White	–0.337 (–0.406, –0.269)		
Hispanic	–0.392 (–0.435, –0.348)		
Difference	–0.054 (–0.135, 0.027)	0.2	0.5
Non-Hispanic Black	–0.568 (–0.714, –0.422)		
Difference	–0.230 (–0.392, –0.070)	0.005	0.054
HLA-DRB1 shared epitope			
Negative	–0.393 (–0.456, –0.330)		
Positive	–0.394 (–0.433, –0.355)		
Difference	–0.001 (–0.076, 0.073)	0.9	0.7
Rheumatoid nodules			
Absent	–0.371 (–0.412, –0.331)		
Present	–0.423 (–0.479, –0.366)		
Difference	–0.051 (–0.120, 0.018)	0.1	0.1
Rheumatoid factor			
Negative	–0.314 (–0.437, –0.190)		
Positive	–0.396 (–0.431, –0.360)		
Difference	–0.082 (–0.211, 0.046)	0.2	0.3
ESR, mm h			
< 30	–0.303 (–0.358, –0.247)		
30–60	–0.395 (–0.446, –0.345)		
Difference	–0.093 (–0.168, –0.018)	0.02	0.04
ESR > 60	–0.554 (–0.628, –0.480)		
Difference	–0.251 (–0.344, –0.159)	≤ 0.001	≤ 0.001
BMI, kg/m^2			
< 20	–0.417 (–0.582, –0.252)		
20–25	–0.433 (–0.508, –0.357)		
Difference	–0.016 (–0.197, 0.165)	0.9	0.6
25–30	–0.386 (–0.443, –0.330)		
Difference	0.030 (–0.143, 0.205)	0.7	0.4
> 30	–0.342 (–0.398, –0.286)		
Difference	0.075 (–0.099, 0.249)	0.4	0.2
Prednisone††			
Absent	–0.341 (–0.386, –0.295)		
Present	–0.450 (–0.500, –0.399)		
Difference	–0.109 (–0.176, –0.041)	0.002	0.001
Cumulative glucocorticoid dose, g††			
Absent	–0.362 (–0.401, –0.323)		
> 0 to 11.5**	–0.412 (–0.465, –0.360)		
Difference	–0.050 (–0.116, 0.015)	0.1	0.2
11.7 to 119†	–0.659 (–0.742, 0.577)		
Difference	–0.298 (–0.389, –0.206)	≤ 0.001	≤ 0.001

* Adjusted for age at RA onset, RA disease duration, and all other variables included in this table; ** lower and middle third of cumulative glucocorticoid dose distribution; † top third of cumulative glucocorticoid dose distribution. †† Prednisone and cumulative glucocorticoid dose were entered in separate multivariable models. ESR: erythrocyte sedimentation rate; BMI: body mass index.

remarkable that differences in CCT between glucocorticoid exposure categories did not appear until about 20 years of disease (Figure 3).

Although cortical bone accounts for 80% of the bone mass, it has received less attention than trabecular bone[53,54]. Cortical bone is stronger[18]. It provides structural support to the body. Trabecular bone is more metabolically active than cortical bone, but its structural role is less prominent. These structural properties suggest that loss of cortical bone may enhance fracture risk to a greater extent than does loss of trabecular bone.

In this RA cohort, cortical bone was lost at a more rapid rate in the initial periods of observation, but continued even after more than 2 decades. This contrasts with what occurs in persons without RA, among whom cortical bone loss is a late finding[55]. The square-root function of time implies more rapid

bone loss early in the observation period, with slowing of bone loss in the later stages of followup. This finding may have clinical implications, because it suggests that preventive and therapeutic intervention would have the greatest influence if undertaken early. This supports the recommendation to initiate aggressive RA treatment and osteoporosis prevention early in the disease course[56,57].

In contrast to findings in the general population[14], among whom handedness may explain a difference in CCT between the right and left sides, we found no such difference in this RA cohort. This may be a consequence of disease-induced bone loss that overshadows the effect of handedness. However, we did find that both the cross-sectional metacarpal diameters (i.e., the periosteal and endosteal diameters) had larger dimensions on the right side.

The lack of hand radiographs for some patients of our cohort is a potential source of selection bias. Indeed, patients without radiographs had more deformed joints at enrollment (Table 1). These patients are thus likely to have had more advanced metacarpal bone loss than the patients for whom radiographs were available. This would place patients lacking radiographs in a flatter, slower segment of the bone-loss curve. Because we did not have radiographs from these patients, our analysis may overestimate the rate of metacarpal bone loss in RA. It should be noted that anthropometric characteristics, prednisone use, and ESR were not statistically different between patients with and those without radiographs (Table 1). The sample size we studied can detect cross-sectional effect sizes of 0.27 or greater with 80% power. It is thus unlikely that differences between patients with and without radiographs in characteristics other than deformed joints and ethnicity are large or even moderate. This suggests that the extent of bias from these sources was modest in our study. The hand radiographs in this study were taken with several different x-ray machines, which could in theory affect the reliability of our CCT measurements. We believe this is unlikely. The technology for plain radiography of the bones is well standardized, allowing comparisons between bone radiographs obtained with different machines. Moreover, as shown in Figure 1, the periosteal and endosteal diameters are readily visualized, and the relationship between one and the other is unlikely to be altered from one x-ray machine to the next. We aimed to increase the accuracy of our CCT measurements by digitally enhancing the radiographs. Despite this, it can be difficult to determine the exact mid-shaft diameter in patients with advanced joint destruction, because the proximal and distal ends of the bone may be destroyed. Also, irregularity of the endosteal margin can pose difficulties for measuring the endosteal diameter. Despite this, our CCT measurements appear to be reliable, as suggested by the agreement in CCT between right and left sides.

We observed that cortical diaphyseal bone is lost over time in patients with RA, with early rapid loss, followed by gradual slowing that nevertheless continues even after more than 2 decades. Systemic inflammation and glucocorticoid use have significant deleterious effects on the rate of cortical bone loss from the metacarpal diaphysis. At this time it is unclear how an anatomical location that seems to lack synovium can be affected by an inflammatory process centered in the joints. Further research is needed to elucidate the mechanisms of cortical bone loss in RA, and its potential relevance as an outcome marker.

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