# Paraarticular Trabecular Bone Loss at the Ultradistal Radius and Increased Arterial Stiffening in Postmenopausal Patients with Rheumatoid Arthritis

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***ABSTRACT.*** ***Objective.*** We recently reported enhanced arterial thickening in patients with rheumatoid arthritis (RA) and the importance of increased bone resorption in this process. Our aim was to examine whether arterial stiffening, another aspect of atherosclerosis, is also increased in patients with RA, and to determine if it is an important risk factor.

***Methods.*** The subjects were 47 patients with RA and 49 healthy controls, all postmenopausal women. Subjects having risk factors for atherosclerosis were excluded. Femoral-ankle (fa) pulse wave velocity (PWV) and brachial-ankle (ba) PWV were measured in all patients using a waveform analyzer. Bone mineral density (BMD) at the ultradistal radius was assessed by peripheral quantitative computed tomography. Inflammation markers (C-reactive protein, erythrocyte sedimentation rate, rheumatoid factor, platelet count) and bone resorption markers (urinary excretion of deoxypyridinoline and N-terminal telopeptide) were also measured.

***Results.*** The median values of faPWV and baPWV in RA patients were 1124 cm/s [interquartile range (IQR) 1040–1175] and 1539 cm/s (IQR 1297–1738), respectively, which were significantly greater than the respective values of 982 cm/s (IQR 819–1054; $p < 0.001$) and 1322 cm/s (IQR 1112–1398; $p = 0.004$) in controls. In multiple regression analysis, the presence of RA emerged as an independent factor associated with the greater faPWV and baPWV when adjusted for age, blood pressure, and smoking. In RA patients alone, BMD in the trabecular bone component, but not for the total bone (cortical plus trabecular), at the ultradistal radius correlated significantly with both faPWV and baPWV. Multiple regression analysis showed that trabecular BMD at the distal radius was a significant factor independently associated with greater faPWV and baPWV when adjusted for age, blood pressure, and smoking. None of the measured inflammation markers or bone resorption markers correlated with either faPWV or baPWV in patients with RA.

***Conclusion.*** Patients with RA show increased arterial stiffening, in addition to the arterial thickening we have previously reported, supporting the notion of enhanced atherosclerosis in RA patients. Paraarticular bone loss in the trabecular bone component at the ultradistal radius is a factor significantly associated with increased arterial stiffening in RA patients. (J Rheumatol 2006;33:652–8)

*Key Indexing Terms:*
ATHEROSCLEROSIS RHEUMATOID ARTHRITIS ARTERIAL STIFFENING
PULSE WAVE VELOCITY PARAARTICULAR OSTEOPOROSIS

An accumulation of evidence indicates accelerated atherosclerosis in patients with rheumatoid arthritis (RA)[1-4], and we recently conducted a cross-sectional study that showed patients with RA exhibit greater intima-media thickness (IMT) in the common carotid artery, compared to healthy controls, and that the increase is independently associated with the presence, duration, and severity of RA[5]. Further, we reported in a subsequent longitudinal study that RA patients have a higher rate of increased arterial wall thickening[6], to which increased bone resorption was a contributory factor. Atherosclerosis has 2 key components, arterial thickening (atherosis) and stiffening (sclerosis)[7], which can now be quantified by measuring far-wall IMT by ultrasonography and pulse wave velocity (PWV), respectively[8].

Atherosclerosis and osteoporosis progress simultaneously with advancing age[9] and share common risk factors, such as smoking[10] and menopause[11]. There is an association between aortic calcification and bone mineral density (BMD) in the hip or lumbar spine in postmenopausal women, suggesting that

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development of osteoporosis may be a risk factor for advanced atherosclerosis after menopause[9,12]. We recently reported that even in healthy people a significant association exists between IMT in the femoral artery and the calcaneus osteo-sono assessment index (OSI)[13], and that paraarticular bone in the trabecular bone component at the ultradistal radius and calcaneus is preferentially lost at an early stage of RA, probably due to RA joint inflammation and impairment of physical activity, respectively[14].

This background prompted us to examine (1) whether patients with RA exhibit increased arterial stiffening in addition to arterial thickening; and (2) whether bone loss, and particularly paraarticular trabecular bone loss at the ultradistal radius, might be involved in increased arterial stiffening in patients with RA.

## MATERIALS AND METHODS

*Subjects.* The subjects enrolled in our study were all postmenopausal women. They comprised 47 RA patients and 49 healthy controls; all provided written informed consent to the study protocol. The RA patients were recruited from the Outpatient Clinic of Rheumatology at Osaka City University Hospital, and were diagnosed according to the 1987 revised criteria of the American College of Rheumatology (formerly, the American Rheumatism Association)[15]. Healthy controls were selected from participants in a local health-check program at Osaka City University Hospital. To avoid complication by other known risk factors for atherosclerosis, both groups of subjects were selected on the basis of the following exclusion criteria: (1) hypertension, as defined by blood pressure > 150/90 mm Hg, or use of antihypertensive medication; (2) hyperlipidemia, as diagnosed by the National Cholesterol Education Program ATP III criteria[16] [total cholesterol > 240 mg/dl, low density lipoprotein (LDL) cholesterol > 160 mg/dl, or triglyceride > 150 mg/dl], or use of lipid-lowering medication; (3) diabetes mellitus, based on a history of diabetes or consistency with the criteria of the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus[17], or use of antidiabetic medication; (4) a history of ischemic heart disease or cerebrovascular events; and (5) receiving hormone replacement therapy.

The clinical characteristics of the RA patients and controls are shown in Table 1. No significant difference existed between the 2 groups in age, body mass index (BMI), smoker to nonsmoker ratio, serum level of total cholesterol and LDL cholesterol, or systolic blood pressure. The mean duration of RA was 8.7 years (range 1 to 36 yrs). All 47 RA patients were receiving multiple medications, with 21 patients taking nonsteroidal antiinflammatory drugs (NSAID), 19 receiving methotrexate (MTX), 11 receiving actarit, 8 receiving salazosulfapyridine, 8 receiving bucillamine, 7 receiving MTX supplemented with folate, and 28 receiving low-dose prednisolone (one patient taking 1.0 mg/day, 5 patients 2.0 mg/day, 3 patients 2.5 mg/day, 5 patients 4.0 mg/day, 6 patients 5.0 mg/day, 6 patients 7.5 mg/day, and 2 patients 10.0 mg/day).

*Measurement of clinical variables.* Blood was collected after an overnight fast at the time of PWV measurement. A morning void sample, which subjects were asked to bring to the hospital with them, was used for measurement of urinary parameters. Blood samples were immediately centrifuged and the serum samples were stored at –70°C until analysis. Laboratory variables relevant to RA activity [erythrocyte sedimentation rate (ESR), platelet count (Plt), serum C-reactive protein (CRP), and rheumatoid factor (RF)] were measured by routine methods in RA patients. Serum levels of total cholesterol, triglyceride, and high-density lipoprotein (HDL) cholesterol were determined using an autoanalyzer. LDL cholesterol was calculated by the formula of Friedewald, *et al*[18]. The urinary excretion of deoxypyridinoline (DPD) and N-terminal telopeptide (NTX) was measured as bone resorption markers, as described[19].

Information on smoking habits was obtained using a self-administered questionnaire.

*PWV measurement.* PWV was measured as an index of arterial stiffening as we reported[20,21]. Resting blood pressure was determined in the right arm with a sphygmomanometer after at least 15 min of supine rest at the time of PWV measurement. The systolic blood pressure was taken upon appearance of Korotkoff sounds, and the diastolic blood pressure upon disappearance of such sounds. Results are reported as the average of 3 measurements. PWV was measured in the supine position after 5 min of bed rest, using an automatic waveform analyzer (model BP-203RPE; Colin, Komaki, Japan). Pressure waveforms of the brachial and tibial arteries were recorded by an oscillometric method, using occlusion/sensing cuffs adapted to both arms and both ankles. Pressure waveforms of the femoral arteries were recorded using multi-element tonometry sensors placed at the femoral artery. The electrocardiogram was monitored with electrodes placed on both wrists. Heart sounds S1 and S2 were detected by a microphone positioned at the left edge of the sternum at the third intercostal space. The waveform analyzer measures time intervals between S2 and the notch of the brachial pulse wave (Thb), between

*Table 1.* Clinical characteristics of patients with RA and healthy controls. Values are shown as mean ± SD.

| | Controls | RA Patients | p |
|---|---|---|---|
| No. of subjects | 49 | 47 | |
| Age, yrs | 56.7 ± 7.4 | 59.6 ± 14.1 | 0.198 |
| Body mass index, kg/m$^2$ | 20.4 ± 2.2 | 21.1 ± 2.4 | 0.240 |
| Smoker/nonsmoker | 4/45 | 2/45 | 0.240 |
| Total cholesterol, mg/dl | 209.5 ± 19.0 | 198.8 ± 34.2 | 0.058 |
| LDL cholesterol, mg/dl | 116.5 ± 31.5 | 110.6 ± 24.9 | 0.346 |
| Systolic BP, mm/Hg | 129.3 ± 17.3 | 131.9 ± 21.4 | 0.505 |
| CRP, mg/dl | ND | 1.0 (0.1–8.0) | — |
| RF, IU/ml | ND | 151.1 (9–1270) | — |
| ESR, mm/h | ND | 49 (8–110) | — |
| Platelet count, × 10$^4$/μl | ND | 26.3 (17.2–56.1) | — |
| DPD/Cre, nmol BCE/mmol Cr | ND | 7.9 (4.8–21.2) | — |
| NTX/Cre, nmol BCE/mmol Cr | ND | 69.5 (29.3–153.9) | — |

ND: not determined. LDL: low density lipoprotein; BP: blood pressure; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; DPD: deoxypyridinoline; NTX/Cre: N-terminal telopeptide/creatinine ratio.

pulse waves of the femoral arteries (Tcf), and between pulse waves of the femoral and tibial (ankle) arteries (Tfa). Estimates of the path lengths of the heart-carotid (Dhc), heart-brachial (Dhb), heart-femoral (Dhf), and femoral-ankle (Dfa) segments were obtained based on the height (HT, in centimeters), using the following formulas; Dhc = 0.2437 × HT – 18.999; Dhb = 0.2195 × HT – 2.0734; Dhf = 0.5643 × HT – 18.381; and Dfa = 0.2486 × HT + 30.709. PWV was calculated for each arterial segment as the path length divided by the corresponding time interval. Reproducibility of the PWV measurement was evaluated by repeated measurements in 17 healthy subjects on 2 different occasions. The coefficients of variation were 1.9% and 3.3% for baPWV and faPWV, respectively[20,21], which were significantly lower than the respective value of flow-mediated dilatation (4.3%)[22] or IMT (3.4%)[5].

*Peripheral quantitative computed tomography (pQCT) measurement.* PQCT measurements were performed at 4% to the ulnar length proximal to the end of the radius (ultradistal site) with a single 2.5-mm thick CT slice on the nondominant side, using an XCT-960 scanner (Stratec Inc., Pforzheim, Germany) as described[23-25]. Briefly, the bone mineral content (mg/mm), the cross-sectional bone area, and the BMD (mg/cm$^3$) were determined at the ultradistal site for the entire cross-section, as well as for the trabecular compartment. After determination of the entire bone contour, the outer 65% of voxels were concentrically peeled off. The remaining 35% of voxels were defined as the trabecular region, while the peeled-off area was defined as the cortical plus subcortical area[23,24]. Image processing and calculation of numerical values were performed using the manufacturer's software. The precision of the pQCT procedure ranged from 1% to 2%, depending upon the parameter being assessed[26].

*Quantitative ultrasound assessment of the calcaneus.* Quantitative ultrasound assessment of the calcaneus was performed using an ultrasound system (Acoustic Osteo-Screener, AOS-100; Aloka, Tokyo, Japan) as described[5]. Briefly, the instrument measures both speed of sound (SOS) and an attenuation-related parameter, the transmission index (TI). These measurements yield a derived parameter, the OSI, which has been proposed to be an estimate of the elastic modulus of the calcaneus. The precision of the OSI parameter was 2.2%[13,14,27].

*Statistical analysis.* For categorical data, the difference in prevalence was evaluated by a chi-square test. Variables with a normal distribution were expressed as the mean ± SD, and differences between the mean values were examined by Student t test. Variables showing a non-normal distribution were summarized as the median and the range, and a nonparametric Mann-Whitney U test was used to evaluate differences between the median values. Linear regression analysis was performed to examine univariate correlation, and multiple linear regression analysis was performed to assess independent associations between variables. Variables with skewed distributions were subjected to univariate and multivariate regression models after log-transformation of the data. P values less than 0.05 were considered significant. Statistical analysis was performed with StatView 5.0 for Windows (SAS Institute Inc., Cary, NC, USA).

## RESULTS

*Effects of RA on PWV.* The median faPWV was 1124 cm/s [interquartile range (IQR) 1040–1175] in RA patients, which was significantly greater than the value of 982 cm/s (IQR 819–1054) in healthy controls ($p < 0.001$). The median baPWV was also significantly greater in RA patients (1539 cm/s; IQR 1297–1738) than in controls (1322 cm/s; IQR 1112–1398; $p = 0.004$).

Since PWV values exhibited skewed distribution, the values were log-transformed to fit linear models thereafter. To examine whether the presence of RA was an independent factor associated with the greater faPWV in RA patients, multiple regression analysis was performed. Results of multiple regression analysis of factors associated with log faPWV in the entire group of 96 subjects are shown in Table 2. In model 1, which included age, systolic blood pressure (BP), RA prevalence, and smoking habit as independent variables, RA prevalence and systolic BP were found to be significantly associated with log faPWV. In models 2 and 3, which included total cholesterol and BMI, respectively, in place of smoking habit, RA prevalence still emerged as an independent factor associated with log faPWV. Examination of the association with log baPWV, using the same models, showed that RA prevalence was again a significant and independent factor associated with log baPWV (Table 2). These data indicated that RA prevalence was a significant factor independently associated with increased log faPWV and log baPWV, when classical cardiovascular factors were adjusted.

*Univariate analysis of factors correlated with PWV in RA patients.* Because of the non-normal distribution, logarithmic transformations of various clinical variables were performed (Table 3). Log trabecular bone density at the ultradistal radius in RA patients correlated significantly in a negative manner with log faPWV and log baPWV ($r = –0.425$, $p = 0.007$, and $r = –0.553$, $p < 0.001$, respectively; Table 3 and Figure 1), although log total bone density at the ultradistal radius failed to correlate significantly with both log faPWV and log baPWV (Table 3). Log calcaneus OSI correlated significantly with log baPWV ($r = –0.357$, $p = 0.017$), but not with log faPWV ($r = –0.021$, $p = 0.893$). Neither inflammation markers including serum log CRP, log ESR, and log RF, nor bone resorption markers including urinary log NTX/Cre and log DPD/Cre were significantly correlated with either log faPWV or log baPWV (Table 3).

*Multiple regression analysis of factors associated with the level of PWV.* Finally, we evaluated factors independently associated with the level of faPWV and baPWV in the RA patients, using multiple regression models (Table 4). Three variables (age, smoking habit, and systolic BP) in these models were included as classical risk factors for atherosclerosis. Factors that had shown a significant correlation or tendency to correlate with log PWV were included as the fourth variable, in order to determine whether the variable was independently associated with log PWV. These variables included the log trabecular density (model 1) and the log total bone density (model 2) at the log ultradistal radius and the log calcaneus OSI (model 3), and the models were tested for association with log faPWV and log baPWV. Of all the variables examined, systolic BP and log trabecular density at the ultradistal radius were found to be significant factors independently associated with log faPWV and log baPWV.

*Association of NSAID, corticosteroid, and MTX treatment with arterial stiffening in RA patients.* As shown in Table 5, the differences in faPWV and baPWV did not reach statistical significance between the RA patients who were taking NSAID, corticosteroids, or MTX and those who were not. This lack of association between PWV values and the treatment for RA was also found by multiple regression analysis (data not shown).

*Table 2.* Multiple regression analysis to evaluate the association of RA and other risk factors with log femoral-ankle pulse wave velocity (faPWV) and log brachial ankle (ba)PWV in controls and patients with RA. Standard regression coefficients (ß) are given in the table.

| Independent Variables | Log faPWV | | | Log baPWV | | |
|---|---|---|---|---|---|---|
| | Model 1 | Model 2 | Model 3 | Model 1 | Model 2 | Model 3 |
| Age | 0.153 | 0.190 | 0.186† | 0.398* | 0.435* | 0.439* |
| Systolic BP | 0.339* | 0.328** | 0.378* | 0.418* | 0.423* | 0.427* |
| RA | 0.316** | 0.294** | 0.256** | 0.264* | 0.188* | 0.188† |
| Smoking habit (–/+) | –0.049 | | | 0.026 | | |
| Total cholesterol | | –0.023 | | | –0.023 | |
| BMI | | | –0.131 | | | –0.102 |
| $R^2$ | 0.318* | 0.301* | 0.328* | 0.541* | 0.539* | 0.552* |

BP: blood pressure; BMI: body mass index; $R^2$: multiple coefficient of determination. * $p < 0.001$, ** $p < 0.01$, † $p < 0.05$.

*Table 3.* Univariate analysis of factors correlated with femoral-ankle pulse wave velocity (faPWV) and brachial ankle (ba) PWV in patients with RA.

| | Log faPWV | | Log baPWV | |
|---|---|---|---|---|
| | r | p | r | p |
| Age | 0.192 | 0.213 | 0.520 | 0.001* |
| Duration of RA | 0.108 | 0.537 | 0.110 | 0.530 |
| Log total density at the ultradistal radius | –0.078 | 0.631 | –0.294 | 0.060 |
| Log trabecular density at the ultradistal radius | –0.425 | 0.007** | –0.553 | < 0.001* |
| Log calcaneous OSI | –0.021 | 0.893 | –0.357 | 0.017† |
| Log CRP | –0.059 | 0.711 | 0.002 | 0.988 |
| Log RF | –0.001 | 0.997 | 0.017 | 0.630 |
| Log ESR | 0.096 | 0.588 | 0.115 | 0.519 |
| Log DPD/Cre | –0.011 | 0.965 | 0.065 | 0.799 |
| Log NTX/Cre | –0.076 | 0.642 | 0.046 | 0.779 |

BMD: bone mineral density; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; DPD: deoxypyridinoline; NTX: N-terminal telopeptide; Cre: creatinine; OSI: osteo-sono assessment index. * $p < 0.001$, ** $p < 0.01$, † $< 0.05$.

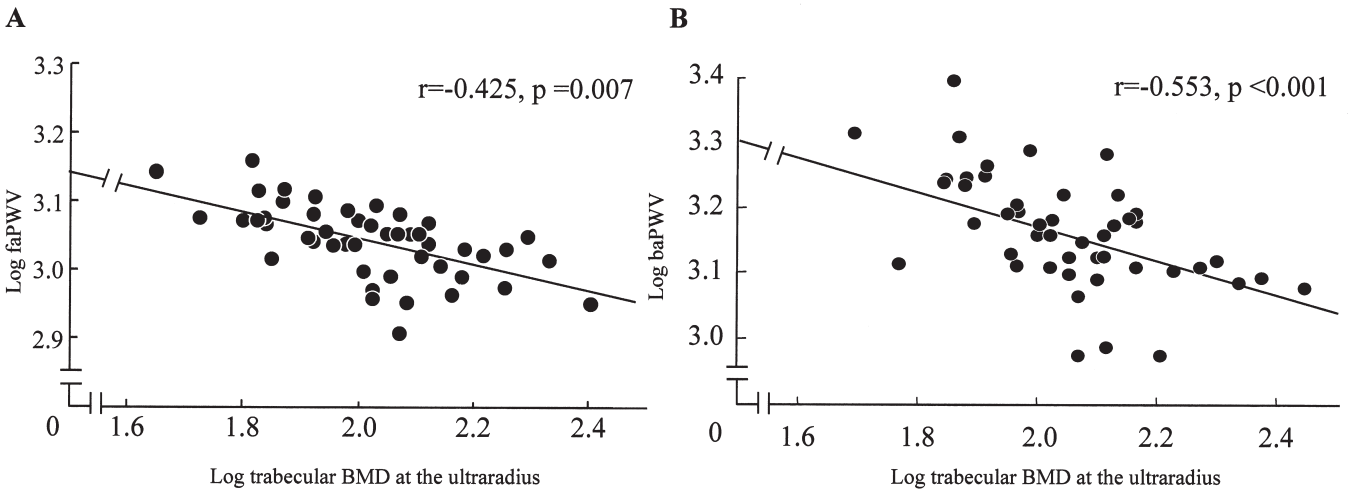


*Figure 1.* Correlation of trabecular bone density at the ultradistal radius with faPWV (A) and baPWV (B) in 47 RA patients. A significant positive correlation was found between trabecular bone density at the ultradistal radius and faPWV (r = –0.425, p = 0.007) and baPWV (r = –0.553, p < 0.001).

*Table 4.* Multiple regression analysis to evaluate the association of bone status and other risk factors with log femoral-ankle pulse wave velocity (faPWV) and log brachial ankle (ba)PWV in patients with RA. Standard regression coefficients (ß) are given in the table.

| Independent Variables | Log faPWV | | | Log baPWV | | |
|---|---|---|---|---|---|---|
| | Model 1 | Model 2 | Model 3 | Model 1 | Model 2 | Model 3 |
| Age | 0.193 | 0.325 | 0.220 | 0.337** | 0.421** | 0.421** |
| Smoking/nonsmoking (–/+) | 0.100 | 0.025 | –0.050 | 0.105 | 0.076 | 0.121 |
| Systolic BP | 0.378† | 0.386† | 0.375† | 0.452* | 0.482* | 0.420** |
| Log trabecular density at the ultradistal radius | –0.325† | | | –0.360** | | |
| Log total density at the ultradistal radius | | -0.006 | | | –0.201 | |
| Log calcaneous OSI | | | 0.157 | | | –0.081 |
| $R^2$ | 0.426* | 0.358** | 0.230† | 0.711* | 0.655* | 0.562* |

BP: blood pressure; OSI: osteo-sono assessment index; $R^2$: multiple coefficient of determination. * $p < 0.001$, ** $p < 0.01$, † $p < 0.05$.

*Table 5.* Association between arterial stiffening and treatment with NSAID, corticosteroid, and methotrexate in 47 patients with RA. Values are shown as mean ± SD.

| | Treated | Not Treated | p |
|---|---|---|---|
| NSAID | | | |
| No. | 21 | 26 | |
| Age, yrs | 59.8 ± 9.8 | 61.0 ± 2.1 | 0.702 |
| faPWV, cm/s | 1130.5 ± 216.4 | 1102.7 ± 116.8 | 0.999 |
| baPWV, cm/s | 1614.1 ± 669.5 | 1549.9 ± 319.6 | 0.526 |
| Corticosteroids | | | |
| No. | 28 | 19 | |
| Age, yrs | 60.6 ± 9.5 | 60.3 ± 10.0 | 0.918 |
| faPWV, cm/s | 1077.1 ± 120.4 | 1149.5 ± 202.8 | 0.212 |
| baPWV, cm/s | 1489.3 ± 300.0 | 1659.2 ± 645.4 | 0.358 |
| Methotrexate | | | |
| No. | 19 | 28 | |
| Age, yrs | 59.0 ± 9.2 | 61.7 ± 10.2 | 0.372 |
| faPWV, cm/s | 1073.9 ± 122.0 | 1155.5 ± 203.1 | 0.169 |
| baPWV, cm/s | 1465.1 ± 277.9 | 1688.7 ± 657.5 | 0.129 |

faPWV: femoral-ankle pulse wave velocity; baPWV: brachial-ankle pulse wave velocity.

## DISCUSSION

We observed that patients with RA exhibit increased arterial stiffening specifically associated with the prevalence of RA, as reflected by significant increases of baPWV and faPWV in these patients and an independent association of RA prevalence with increases in baPWV and faPWV when adjusted for age, systolic blood pressure, smoking habit, total cholesterol, and BMI. In a recent cross-sectional study, we showed that RA patients exhibit increased IMT of the common carotid artery, compared to healthy controls[5,6]. In a subsequent longitudinal study, we found that the annual increase in IMT of the common carotid artery was significantly greater in RA patients than in healthy controls, and that inflammation markers and increased bone resorption were significantly and independently associated with the increased rate of IMT[6]. Taken collectively, these data strongly suggest that RA patients might exhibit increased arterial stiffening in addition to arterial thickening through either RA-associated inflammation or increased bone resorption. Since RA patients might preferentially lose bone from the trabecular bone component at the ultradistal radius and calcaneus[14], we examined which site of bone loss might be important for increased arterial stiffening in RA patients. Multiple regression analysis revealed the trabecular BMD of the ultradistal radius, but not the calcaneus OSI, as an independent factor negatively associated with the greater PWV, even after adjustment for major risk factors for atherosclerosis, such as age, smoking habit, and systolic blood pressure (Table 4), indicating the importance of paraarticular bone loss in increased arterial stiffening in patients with RA. Trabecular bone density at the ultradistal radius, where bone loss occurs specifically for RA inflammation[14], may provide further support for the theory of independent association of RA prevalence with increased PWV values. The major mechanisms through which bone loss occurs in the trabecular bone component at the ultradistal radius and calcaneus are RA inflammation and impairment of activities of daily living (ADL), respectively[14]. Further, we reported that bone resorption around RA-inflamed joints contributes to an increase of the serum bone resorption markers pyridinoline and deoxypyridinoline[28]. These observations may explain the sig-

nificant association of ultradistal trabecular BMD with PWV values. In contrast, calcaneus OSI was not found to be associated with either baPWV or faPWV. These data may suggest the lesser importance of impairment of ADL in the increased arterial stiffening of patients with RA[14].

We previously described a positive association between the Larsen score for metacarpophalangeal joints and IMT of the common carotid artery in a cross-sectional study, suggesting the simultaneous progression of arterial wall thickening with bone destruction in RA patients[5]; and showed that in patients with early-stage RA, reductions in the trabecular BMD, but not the cortical BMD, at the ultradistal radius occurred when there was no decrease in BMD of the lumbar spine, suggesting the ultradistal radius as a major site of bone loss in patients with RA. In accord with the recent hypothesis on an intimate association of bone loss and atherosclerosis in non-RA patients[9,11,29], our study illustrates the relationship between bone loss at the ultradistal radius and increased arterial stiffening in patients with RA.

Administration of bisphosphonate, a bone antiresorptive drug, prevents an increase in IMT in diabetic patients, along with promoting an increase in BMD of the lumbar spine[30]. Further, in postmenopausal women, estrogen derivatives are known to protect against the development of atherosclerosis, while increasing the BMD of the lumbar spine and femur[12]. Although these patients exhibit generalized bone loss, while RA patients exhibit focal bone loss at the paraarticular trabecular bone in RA-involved joints[28], these data suggest that bone loss, either systemically or locally, might play an important role in the stiffening of arterial walls.

The possible mechanism underlying the association between bone loss and atherosclerosis may be explained by the similarity of several aspects of these processes. Recent studies have shown that atherogenic stimulation can induce the expression of molecules originally found in skeletal tissue, such as type I collagen, proteoglycans, osteonectin, osteopontin[31], osteocalcin[32], and also hydroxyapatite[31]. It was recently reported that smooth muscle cells, which derive from bone marrow, exist in atherosclerotic lesions. These results suggest that preferential differentiation of bone marrow cells into smooth muscle cells, rather than osteoblasts, may be one of the mechanisms linking bone loss and atherosclerosis.

Inflammatory cytokines such as tumor necrosis factor-α (TNF-α) play an important role in osteoporosis and atherosclerosis in patients with RA[33,34]. Increased production of TNF-α causes paraarticular bone loss and enhances arterial stiffening simultaneously in patients with RA. However, we found that bone resorption markers (DPD, NTX) and inflammation markers (CRP, ESR) were not significantly correlated with the PWV values. Since it is assumed that a long time period is required for RA inflammation and bone resorption to enhance atherosclerosis, the lack of a significant association between a single measurement of inflammation or bone resorption markers and PWV values in a cross-sectional study may be possible. In contrast, since paraarticular bone loss is assumed to reflect the sum of longterm effects of RA inflammation and bone loss, a significant association between paraarticular trabecular BMD and PWV values might be anticipated.

As a series of epidemiological studies showed that corticosteroid treatment is not associated with increased cardiovascular disease in RA patients[35,36], the use of corticosteroid, in addition to NSAID and methotrexate, did not affect the PWV value in the RA subjects in our study, as we previously described[5,6].

The limitation of our study is the small number of subjects and the restriction of subjects to postmenopausal women. However, since a significant association was observed between paraarticular bone loss at ultradistal radius and arterial stiffening in postmenopausal patients with RA, our study clearly demonstrates the relationship between metabolisms of bone and vessel in postmenopausal patients with RA, as well as in patients with other disease status[37], although a large-scale study is needed to draw a final conclusion.

We demonstrate that patients with RA have increased arterial stiffening, and we suggest that such stiffening may be explained in part by paraarticular trabecular bone loss at the ultradistal radius in these patients.

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