Independent Association of Increased Trunk Fat with Increased Arterial Stiffening in Postmenopausal Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** We recently reported increased arterial thickening and stiffening in patients with rheumatoid arthritis (RA) to which inflammation and increased bone resorption contributed. The current study examined the possible involvement of trunk fat in increased arterial stiffening in postmenopausal patients with RA.

Methods. RA patients (n = 30) and healthy controls (n = 30), all postmenopausal women, were examined for body adiposity and brachial-ankle pulse wave velocity (baPWV) by dual-energy x-ray absorptiometry and waveform analyzer, respectively. Subjects having other diseases and predisposed to atherosclerosis were excluded. Trunk:peripheral fat ratio was calculated as the fat mass of the trunk divided by the sum of the fat mass of arms and legs. Bone mineral density (BMD) at ultradistal radius was measured by peripheral quantitative computed tomography. Inflammation markers and bone resorption markers were also measured.

Results. Age, body mass index, and systolic blood pressure (BP) of RA patients were 60.8 ± 9.8 years, 22.5 ± 3.3, and 129.6 ± 20.8 mm Hg, respectively, which did not differ from data from healthy controls. Duration of RA was 10.4 years with mean daily dose of prednisolone 3.02 ± 3.85 mg. RA patients exhibited a significantly greater trunk:peripheral fat ratio (1.041 ± 0.253 vs 0.839 ± 0.223; $p < 0.001$) and baPWV value (1544.7 ± 304.9 vs 1373.8 ± 256.1; $p < 0.005$) than healthy controls. In RA patients, age ($r = 0.588$, $p < 0.001$), systolic BP ($r = 0.553$, $p < 0.005$), trabecular BMD at ultradistal radius ($r = –0.346$, $p = 0.061$), and trunk:peripheral fat ratio ($r = 0.366$, $p = 0.046$) were correlated with baPWV. Trunk:peripheral fat ratio did not differ significantly between RA patients with and those without prednisolone treatment. In multiple regression analysis that included age, systolic BP, and trunk:peripheral fat ratio as independent variables, the trunk:peripheral fat ratio emerged as an independent factor significantly associated with baPWV in RA patients. When trabecular BMD at ultradistal radius was inserted in place of trunk:peripheral fat ratio, it emerged as a factor that was significantly associated with baPWV.

Conclusion. We showed that increased trunk fat was significantly and independently associated with increased arterial stiffening in postmenopausal patients with RA. (J Rheumatol 2007;34:290–5)

Key Indexing Terms:

RHEUMATOID ARTHRITIS | ATHEROSCLEROSIS | ARTERIAL STIFFENING
PULSE WAVE VELOCITY | METABOLIC SYNDROME | CENTRAL OBESITY

Large epidemiological studies showed that one of the most important causes of death in patients with rheumatoid arthritis (RA) is cardiovascular disease[1-3]. We recently reported that RA prevalence by itself is a risk factor for accelerated atherosclerosis by cross-sectional[4] or longitudinal study[5], and that RA inflammation and enhanced bone loss, particularly at the paraarticular trabecular component, is responsible for the increased arterial wall thickening and stiffening[5,6]. Recently, evidence has accumulated that excess body fat, particularly visceral fat, is associated with the prevalence of the metabolic syndrome that increases cardiac risk[7,8]. Obesity might also promote preclinical atherosclerotic changes by a direct effect on vascular physiology[9,10]. We have reported that bone loss at weight-bearing bones, such as calcaneus, was significantly associated with impairment of physical activity in patients with RA, where it occurs preferentially[4,11], as well as in healthy subjects[12]. Therefore, the reduction of calcaneus osteo-sono index might result from the impairment of physical activity in patients with RA. It has been increasingly recognized that visceral obesity is intimately involved in the pro-

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gression of atherosclerosis due partly to the lack of physical activity[13]. RA patients' physical activity decreases as joint destruction progresses[14], and thus the loss of muscle mass is assumed to occur preferentially in the limb region as a result of impaired joint function. Although computed tomography is the gold standard to measure visceral fat mass, the amount of radiation exposure is too great for use in the general population. Alternatively, dual-energy x-ray absorptiometry (DEXA) allows us to determine the fat mass separately in trunk and peripheral regions; the resultant trunk:peripheral fat ratio provides a clinically relevant measure of central obesity[15].

These assumptions prompted us to examine whether patients with RA exhibited increased trunk:peripheral fat ratio, and to determine the involvement of central obesity in development of increased arterial wall stiffening in RA.

MATERIALS AND METHODS

Subjects. The subjects were all postmenopausal women, comprising 30 patients with RA and 30 healthy controls; all provided written informed consent to the study protocol. RA patients were recruited from the Outpatient Rheumatology Clinic 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)[16]. Healthy controls were selected from participants in a Local Health Check Program at Osaka City University Hospital. The study was approved by the Institutional Review Board of Osaka City University Graduate School of Medicine.

To avoid confounding by other known risk factors for atherosclerosis, both groups were selected on the basis of the following exclusion criteria: (1) hypertension, defined as blood pressure > 150/90 mm Hg, or use of antihypertensive medication; (2) hyperlipidemia, as diagnosed by the NCEP ATP III criteria[17] [total cholesterol > 240 mg/dl, low-density lipoprotein (LDL) cholesterol > 160 mg/dl, high-density (HDL) cholesterol < 35 mg/dl, or triglyceride > 150 mg/dl], or use of lipid-lowering medication; (3) diabetes mellitus, based on a history of diabetes or the expert committee criteria[18], or use of antidiabetic medication; (4) history of ischemic heart disease or cerebrovascular events; and (5) receiving hormone replacement therapy. Further, to avoid the effect of joint destruction on ultradistal radius bone mineral density (BMD) by peripheral quantitative computerized tomography (pQCT), RA patients whose bone structure of distal radius was destroyed as shown by radiographic examination were also excluded. All 30 RA patients were receiving multiple medications — 19 taking nonsteroidal antiinflammatory drugs, 13 methotrexate (MTX), 4 actarit, 1 salazosulfapyridine, 3 bucillamine, 5 MTX supplemented with folate, and 15 low-dose prednisolone (2 patients taking 1.0 mg/day, 2 patients 3.0 mg/day, 1 patient 4.0 mg/day, 6 patients 5.0 mg/day, 1 patient 6.0 mg/day, 1 patient 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 urine sample, which subjects were asked to bring to the hospital, was also used. Blood samples were immediately centrifuged and the resultant serum samples were stored at –70°C until analyzed. Laboratory variables relevant to RA activity [erythrocyte sedimentation rate (ESR), platelet count, serum C-reactive protein (CRP), and rheumatoid factor (RF)] were measured by routine methods in RA patients. Serum levels of total cholesterol, triglyceride, and HDL cholesterol were determined using an autoanalyzer. LDL cholesterol was calculated by the formula of Friedewald, *et al*[19]. Urinary excretion of deoxypyridinoline and N-terminal telopeptide was measured as bone resorption marker, as described[20].

Measurement of body fat by DEXA. The percentage of body fat of the total body, trunk, arms, and legs was measured by DEXA (QDR-4500A, Hologic, Waltham, MA, USA)[21,22] (Figure 1). Fat from arms and legs was first summed to estimate peripheral fat, and a trunk:peripheral fat ratio variable was created by dividing trunk regional fat (g) by peripheral regional fat (g), as described[15]. The precision of measurements of fat mass are 1.5%, 0.8%, and 1.1% for the arms, legs, and trunk, respectively, according to the report of the manufacturer.

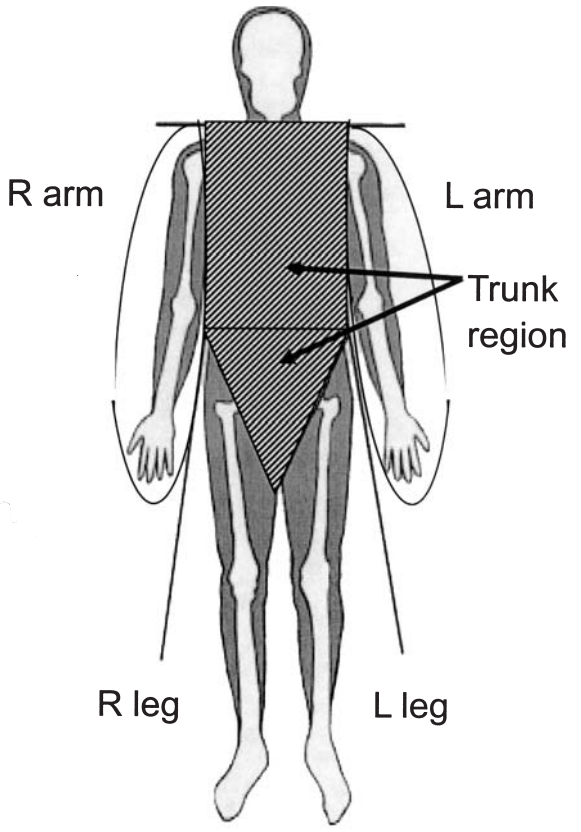

Figure 1. Estimation of trunk:peripheral fat ratio. Fat from both arms and legs was first summed to estimate peripheral fat. A trunk:peripheral fat ratio variable was created by dividing trunk regional fat (g) by peripheral regional fat (g).

Measurement of arterial stiffening by PWV. PWV was measured as an index of arterial stiffening as reported[6,23]. 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 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 subject's height (HT, in cm), using the following formulas: Dhc = 0.2437 × HT – 18.999; Dhb = 0.2195 × HT – 2.0734; Dhf = 0.5643 × HT – 18.381; 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% for baPWV and 3.3% for faPWV[21,24].

Measurement of BMD by pQCT. pQCT measurements were performed at 4% to the ulnar length proximal to the end of the radius (ultradistal site) with a single CT slice 2.5 mm thick on the nondominant side, using an XCT-960 scanner (Stratec Inc., Pforzheim, Germany) as described[11]. Briefly, the bone mineral content (mg/mm), cross-sectional bone area, and 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 the subcortical area[25]. 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 variable being assessed[26].

Statistical analysis. Variables with a normal distribution were expressed as mean ± SD, and differences between mean values were examined by Student's t test. Variables showing a non-normal distribution were summarized as median and range, and a nonparametric Mann-Whitney U-test was used to evaluate the differences between the median values. Linear regression analysis was performed to examine univariate correlation, and multiple linear regression analysis 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 < 0.05 were considered statistically significant. Statistical analysis was performed with StatView 5.0 for Windows (SAS Institute Inc., Cary, NC, USA).

RESULTS

Clinical characteristics of patients and controls. Clinical characteristics of the RA patients and healthy controls are shown in Table 1. The mean duration of RA was 10.4 ± 14.3 months (range 0.33–50 mo), with daily dose of prednisolone 3.02 ± 3.85 mg (range 0–15 mg). There was no significant difference between the 2 groups in age, body mass index, or systolic blood pressure, although trunk:peripheral fat ratio, faPWV, and baPWV were all significantly greater in RA patients than in controls. Trunk:peripheral fat ratio did not differ significantly between RA patients using and those not using steroid therapy (data not shown).

Factors correlated with PWV in RA patients. In RA patients, age (r = 0.588, p < 0.001) and systolic blood pressure (r = 0.553, p = 0.0015) showed a significant and positive correlation with baPWV, as reported[6] (Table 2). Trabecular, but not total, BMD at ultradistal radius showed a tendency to a negative correlation with baPWV (r = –0.346, p = 0.061), essentially as previously reported[11]. Of interest, the trunk:peripheral fat ratio showed a significant and positive correlation with baPWV (r = 0.366, p = 0.046).

Multiple regression analysis of factors associated with the level of PWV. Next, we tried to elucidate the factor independently associated with increased PWV value in RA patients. In multiple regression analysis that included age, systolic blood pressure and trunk:peripheral fat ratio as independent variables, the trunk:peripheral fat ratio and systolic blood pressure emerged as independent factors significantly associated with baPWV in RA patients. When trabecular or total BMD at ultradistal radius was inserted in place of the trunk:peripheral fat ratio, trabecular, but not total BMD, emerged as a significant factor (Table 3).

Table 1. Clinical characteristics of healthy controls and patients with RA.

Clinical Variables	Controls	RA Patients
No. of subjects	30	30
Age, yrs	65.6 ± 10.8	60.8 ± 9.8
Body mass index, kg/m^2	22.8 ± 4.1	22.5 ± 3.3
Systolic BP, mm Hg	139.3 ± 20.8	129.6 ± 20.8
Total cholesterol	210.3 ± 35.8	203.9 ± 35.9
HDL cholesterol	56.6 ± 16.3	63.5 ± 14.8
Triglyceride	113.0 ± 48.5	104.7 ± 36.1
Trunk:peripheral fat ratio	0.839 ± 0.223	1.041 ± 0.253
baPWV, cm/s	1373.8 ± 256.1	1544.7 ± 304.9
pQCT		
Total BMD at ultradistal radius (Z score, %)	101.2 ± 13.6	93.3 ± 26.0
Trabecular BMD at ultradistal radius (Z score, %)	121.2 ± 33.4	83.3 ± 45.0
RA duration, mo	—	10.4 ± 14.3
Prednisolone, mg/day	—	3.02 ± 3.85
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)
Platelets (× 10^4/μl)	ND	26.3 (17.2–56.1)
DPD/Cre, nmol/mmol Cr	ND	7.9 (4.8–21.2)
NTX/Cre, nmol BCE/mmol Cr	ND	69.5 (29.3–153.9)

Values are shown as mean ± SD. Values of CRP, RF, ESR, platelets, DPD, and NTX are median (range). ND: not determined. HDL: high density lipoprotein; BP: blood pressure; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; DPD: deoxypyridinoline; NTX:/Cre, N-terminal telopeptide/creatinine ratio; baPWV: brachial-ankle pulse wave velocity; pQCT: peripheral quantitative computerized tomography.

Table 2. Univariate analysis of factors correlated with baPWV in patients with RA.

	baPWV	
	r	p
Age	0.588	0.0006*
Systolic blood pressure	0.553	0.0015*
RA duration	0.156	0.564
Total BMD at the ultradistal radius	–0.237	0.208
Trabecular BMD at the ultradistal radius	–0.346	0.061
Trunk:peripheral fat ratio	0.366	0.046**

* $p < 0.01$, ** $p < 0.05$.

DISCUSSION

Our study showed that trunk:peripheral fat ratio was significantly greater in patients with RA than in healthy controls, and that increased trunk:peripheral fat ratio in RA patients was independently associated with increased arterial stiffening observed in those patients. These data showed that an increase of abdominal fat might contribute to the increased arterial stiffening in RA patients, and also probably to increased cardiovascular mortality.

Inflammatory disease activity in RA is frequently accompanied by loss of body cell mass, known as rheumatoid cachexia[27]. This condition may manifest as low BMI and can also potentially contribute to excess cardiovascular burden. Recently, an epidemiological study confirmed that low BMI is associated with a significantly increased cardiovascular death rate[28], although no data were shown on RA disease activity. When the treatment of RA is not sufficient to suppress disease activity, patients with RA should lose body weight due to persistence of RA-associated inflammation. Since sustained inflammation is known to accelerate atherosclerosis in RA patients, those patients should have higher cardiovascular risk. We examined RA patients with their RA activity almost controlled, as reflected by their serum median CRP levels around 1.0 mg/dl, thanks to the introduction of MTX into the RA therapeutic regimen. Therefore, the effect of RA inflammation on atherosclerosis should have been attenuated in the patients enrolled in this study. As RA activity has been controlled, patients might easily gain body weight to develop central obesity, leading to increased arterial stiffening. These data raise the possibility that recent improvements of RA disease control by new therapeutic regimens may induce patients to gain body weight preferentially in the trunk region and to develop metabolic syndrome, which might contribute to the increased arterial stiffening, and possibly to the increased cardiovascular risk in patients. Although the metabolic syndrome is defined as those having abdominal circumference > 90 cm, RA patients in our study did not show such a great circumference on the basis of their normal BMI of 22.5 ± 3.3. However, the older age of patients with RA might play a role in development of central obesity. Further, the smaller amounts of muscle due to ethnic variation may be partly responsible.

Trunk fat is known as a risk factor for chronic diseases including metabolic syndrome, such as diabetes mellitus and cardiovascular diseases[29]. Although overall obesity increases the cardiovascular risk, central adiposity contributes to it to a greater extent by several specific mechanisms[30]. Trunk adipose tissue is reported to secrete various adipocytokines[31] that may induce endothelial dysfunction, impaired metabolic state[32], and atherogenic serum lipid profile[33], to increase cardiovascular risk[34]. Excess subcutaneous trunk fat and abdominal adiposity have also been shown to induce insulin resistance to enhance atherosclerosis[35,36].

An exercise intervention study reported a greater reduction in total abdominal and subcutaneous abdominal fat in the exercise weight-loss group than in the diet weight-loss group[37]. Another study clearly showed that mean BMI, the percentage of body fat, and the waist:hip ratio were significantly lower for each increasing physical activity level[38], suggesting that impaired physical activity often observed in patients with RA might enhance deposition of adipose tissue in the trunk region. Supporting this notion is our previous finding that bone mass at calcaneus was preferentially reduced even in the early stage of RA[11], and that this had a significant negative correlation with the score on the modified Health Assessment Questionnaire[4], suggesting that impairment of patients' physical activity occurs even in the early stage of RA.

Our study confirmed our previous finding[6] that trabecular

Table 3. Multiple regression analysis to evaluate the association of bone status and other risk factors with baPWV in patients with RA. Standard regression coefficients (ß) are given.

Independent Variables	baPWV		
	Model 1	Model 2	Model 3
Age	0.270	0.386**	0.270**
Systolic blood pressure	0.325*	0.336	0.294
Trabecular bone density at the ultradistal radius	–0.328*		
Total bone density at the ultradistal radius		–0.083	
Trunk:peripheral fat ratio			0.321**
R^2	0.514*	0.315*	0.423**

* $p < 0.01$, ** $p < 0.05$. R^2, multiple coefficient of determination.

bone loss, but not cortical bone loss, at the paraarticular ultradistal radius was associated with increased arterial wall stiffening. The reduction of physical activity in patients with RA might cause loss of muscle mass in the limb region, as described[39]. Glucocorticoid is known to increase visceral fat, as observed in Cushing syndrome, since fat cells in the abdominal region have been thought to be more sensitive to hormonal factors than fat cells in other regions[40]. However, the effect of glucocorticoid in increasing abdominal fat could be negated in patients with RA receiving low-dose prednisolone, since no essential difference was observed in the trunk:peripheral fat ratio between RA patients with and those without prednisolone therapy. The limitation of our study is that it is not possible to conclude that the increased fat was involved in the development of increased arterial stiffening in postmenopausal patients with RA, since the study design was cross-sectional. Thus, a longitudinal study is needed to draw conclusions about the significance of central obesity in arterial stiffening in RA.

In summary, postmenopausal patients with RA who had success with drug treatment had significantly higher trunk:peripheral fat ratios that were independently associated with increased baPWV values; these findings suggest that increased trunk fat, as well as paraarticular bone loss, might be involved in the increased arterial stiffening in postmenopausal patients with RA.

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