表3　対象者の背景（開始時）

	非投与群	投与群	p
閉経前/後	2/6	1/7	−
年齢（歳）	62.6 ± 12.6	59.9 ± 10.0	0.6962
BMI（kg/m^2）	22.5 ± 2.9	19.8 ± 2.7	0.0678
収縮期血圧（mmHg）	127.5 ± 13.9	135.5 ± 17.5	0.3286
CRP（mg/dL）	0.450 ± 0.396	1.671 ± 1.598	0.0558
腰椎BMD（g/cm^2）	0.882 ± 0.207	0.846 ± 0.205	0.7560
大腿骨BMD（g/cm^2）	0.761 ± 0.182	0.707 ± 0.193	0.6519
ba PWV（cm/s）	1637 ± 257	1652 ± 538	0.9532
NTX/Cre（nmol BCE/mmol・Cr）	64.2 ± 23.6	60.2 ± 17.2	0.7753
BAP（IU/L）	22.8 ± 8.3	22.8 ± 5.1	0.9973

表4　観察前後での各種パラメータの結果（アレンドロネート非投与群）

	前	後	p
CRP（mg/dL）	0.450 ± 0.396	0.471 ± 0.519	0.7261
腰椎BMD（g/cm^2）	0.882 ± 0.207	0.882 ± 0.181	0.9916
大腿骨BMD（g/cm^2）	0.761 ± 0.182	0.761 ± 0.191	＞0.9999
baPWV（cm/s）	1637 ± 257	1690 ± 241	0.5395
NTX/Cre（nmol BCE/mmol・Cr）	64.2 ± 23.6	90.9 ± 24.9	0.0009†
BAP（IU/L）	22.8 ± 8.3	32.3 ± 9.4	0.0504

† $p<0.05$

表5　観察前後での各種パラメータの結果（アレンドロネート投与群）

	前	後	p
CRP（mg/dL）	1.671 ± 1.598	1.725 ± 1.642	0.9231
腰椎BMD（g/cm^2）	0.846 ± 0.205	0.884 ± 0.203	0.0014†
大腿骨BMD（g/cm^2）	0.707 ± 0.193	0.736 ± 0.168	0.0837§
baPWV（cm/s）	1652 ± 538	1479 ± 306	0.2729
NTX/Cre（nmol BCE/mmol・Cr）	60.2 ± 17.2	35.4 ± 22.8	0.0028†
BAP（IU/L）	22.8 ± 5.1	22.7 ± 16.3	0.9833

† $p<0.05$, § $p<0.1$

おわりに

アレンドロネートは，RA患者で骨吸収を有意に抑制し，骨量を有意に増加することが示された。また，骨量の改善に伴い動脈硬化の進展を予防する可能性が示唆された。

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Osteoporosis Japan

関節リウマチ患者では傍関節性骨粗鬆症の進展が末梢の動脈硬化進展に関与する

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はじめに

関節リウマチ(RA)患者において動脈硬化が進行していることが知られている[1~4]。

われわれはRA患者の超音波Bモード法で測定した総頸動脈内膜中膜肥厚度(CCA-IMT)が有意に増加していることを見出し，RAが動脈壁肥厚度(thickening)の独立した危険因子であることを報告した[5]。さらに，RA炎症と骨吸収亢進がその重要な関与因子であることを示した[6]。今回，これら因子とRA患者の動脈壁の硬化度

表1　関節リウマチ患者群と対照群における臨床パラメータ

	対照群	関節リウマチ患者群	p
人数	49	47	
年齢(歳)	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
喫煙 / 非喫煙	4/45	2/45	0.240
総コレステロール(mg/dL)	209.5 ± 19.0	198.8 ± 34.2	0.058
LDLコレステロール(mg/dL)	116.5 ± 31.5	110.6 ± 24.9	0.346
収縮期血圧(mmHg)	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/hr)	ND	49 (8 ~ 110)	–
血小板数($\times 10^4/\mu L$)	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)	–

表中の数字は平均値±標準偏差を示す。
ND：測定値なし，LDL：low density lipoprotein，CRP：C-reactive protein，ESR：erythrocyte sedimentation rate，DPD：deoxypyridinoline，NTX/Cre：N-terminal telopeptide/creatinine ratio

Involvement of Paraarticular Trabecular Bone Loss at the Ultradistal Radius in Increased Arterial Stiffening in Postmenopausal RA Patients

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Key words：Atherosclerosis, Rheumatoid arthritis, Arterial stiffening, Pulse wave velocity, Paraarticular osteoporosis

大阪市立大学大学院医学研究科代謝内分泌病態内科学

表2　関節リウマチ患者群と対照群における RA 罹患と faPWV，baPWV との関連をみた多変量解析

独立変数	Log faPWV			Log baPWV		
	モデル1	モデル2	モデル3	モデル1	モデル2	モデル3
年齢	0.153	0.190	0.186 #	0.398 *	0.435 *	0.439 *
収縮期血圧	0.339 *	0.328 $	0.378 *	0.418 *	0.423 *	0.427 *
RA 罹患	0.316 $	0.294 $	0.256 $	0.264 *	0.188 *	0.188 #
喫煙 / 非喫煙(− / +)	− 0.049			0.026		
総コレステロール値		− 0.023			− 0.023	
Body mass index			− 0.131			− 0.102
重相関係数	0.318 *	0.301 *	0.328 *	0.541 *	0.539 *	0.552 *

表中の数字は標準偏回帰係数(β)を示す。$^{*}p < 0.001$, $^{\$}p < 0.01$, $^{\#}p < 0.05$

表3　RA 患者47例における臨床パラメータと faPWV, baPWV との単相関

	Log faPWV		Log baPWV	
	標準偏回帰係数	p 値	標準偏回帰係数	p 値
年齢	0.192	0.213	0.520	0.001 *
罹病期間	0.108	0.537	0.110	0.530
Log 橈骨遠位端総骨密度	− 0.078	0.631	− 0.294	0.060
Log 橈骨遠位端海面骨密度	− 0.425	0.007 $	− 0.553	< 0.001 *
Log 踵骨 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
$^{*}p < 0.001$, $^{\$}p < 0.01$, $^{\#}p < 0.05$

(stiffening)と末梢の骨密度の低下との関連を調べた。

1　対象と方法

高血圧，高脂血症など動脈硬化に影響を及ぼす疾患を有さない閉経後の47例の女性RA患者と54人の健常者につき検討した。2群間の年齢，BMI，総コレステロール値，LDLコレステロール値，収縮期血圧に有意差は認めなかった(表1)。動脈壁 stiffening を Colin 社製 form PWV/ABI(model BP-203RPE)を用いて Pulse Wave Velocity(PWV)で評価した。全身性骨粗鬆症として踵骨 osteo-sono index(OSI)を Aloka 社製 AOS-100 による超音波法により測定し算出した。RAの傍関節性骨粗鬆症の指標として橈骨遠位端の骨密度を海綿骨部と皮質骨部とに分けて Stratec 社製 XCT-960 による pQCT 法にて測定した。さらに RA 疾患活動性マーカーとして CRP，ESR，血小板，RFを，骨吸収マーカーとして尿中デオキシピリジノリンとNTXを，さらに動脈硬化の既知因子を測定し検討した。

2　結　　果

RA 患者での femoral-ankle(fa)PWV と brachial-ankle(ba)PWV は1124(range 880～1429) cm/sec，1539(range 946～2501)cm/secで，健

表4　RA患者47例におけるfaPWV, baPWVと臨床パラメータとの関連をみた多変量解析

Independent variables	Log faPWV			Log baPWV		
	モデル1	モデル2	モデル3	モデル1	モデル2	モデル3
年齢	0.193	0.325	0.220	0.337 $^{\$}$	0.421 $^{\$}$	0.421 $^{\$}$
喫煙/非喫煙(−/+)	0.100	0.025	−0.050	0.105	0.076	0.121
収縮期血圧	0.378 $^{\#}$	0.386 $^{\#}$	0.375 $^{\#}$	0.452 *	0.482 *	0.420 $^{\$}$
Log橈骨遠位端海面骨密度	−0.325 $^{\#}$		−0.360 $^{\$}$			
Log橈骨遠位端総骨密度	−0.006	−0.201				
Log踵骨OSI		0.157	−0.081			
重相関係数	0.426 *	0.358 $^{\$}$	0.230 $^{\#}$	0.711 *	0.655 *	0.562 *

表中の数字は標準偏回帰係数(β)を示す。$^{*}p < 0.001$, $^{\$}p < 0.01$, $^{\#}p < 0.05$

常者の982(range 739 ～ 1442)cm/sec, 1322(range 1031 ～ 2212)cm/secに比し，有意な上昇が認められた。RA患者群と対照群において血圧，年齢，喫煙の有無で補正した多変量解析でRA罹患は独立した動脈壁stiffeningの危険因子であった(表2)。RA患者群において橈骨遠位端の海綿骨部の骨密度はfaPWV, baPWVと有意な負の相関を認めた(表3)。

橈骨遠位端の海綿骨部の骨密度はRA患者で健常者に比べて有意な低下を認め，多変量解析で橈骨海綿骨骨密度の低下がRA患者の動脈壁stiffening進展の独立した危険因子であった(表4)。

3　結論と考察

閉経後女性RA患者では傍関節性骨粗鬆症の進展が末梢の動脈壁stiffening進展の危険因子であることが示唆された。橈骨遠位端における海綿骨骨密度の低下はRAの炎症に特徴的である[7]。さらにRAに伴う関節炎のある関節は血清中のピリジノリンとデオキシピリジノリンの上昇に寄与していることも知られている[8]。以上のことより橈骨遠位端における海綿骨骨密度の低下と末梢の動脈壁stiffeningの進展との関連が考えられる。

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Associations between physical activity, peripheral atherosclerosis and bone status in healthy Japanese women

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Abstract

The aim of this cross-sectional study was to investigate whether physical activity and bone status may affect arterial thickening and stiffening in healthy Japanese women. Healthy women ($n=149$; mean age, 54 years) were recruited from those who participated in a local health check program at the Osaka City University Hospital. Physical activity was assessed by physical functioning score of SF-36, and bone status by bone mineral density (BMD) in lumbar spine and calcaneus osteo-sono index (OSI). Arterial wall thickening assessed by intima–media thickness (IMT) in common carotid artery (CA) and femoral artery (FA), and arterial wall stiffening by peak wave velocity (PWV) in heart–carotid (hc) and heart–femoral (hf) as central segment and in heart–brachial (hb) and femoral–ankle (fa) as peripheral segment, respectively. By Spearman Rank correlation, lumbar spine BMD was correlated negatively with CA IMT ($\rho=-0.225$, $p<0.05$) and FA IMT ($\rho=-0.215$, $p<0.05$), and calcaneus OSI with FA IMT ($\rho=-0.330$, $p<0.0001$) but not CA IMT ($\rho=-0051$, $p=0.5335$). Both lumbar spine BMD and calcaneus OSI correlated negatively with PWV in all segments (all $p<0.05$). Physical functioning score correlated weakly but significantly in a negative manner with all PWV segments (all $p<0.05$) but not IMT. Multiple regression analyses revealed a significant association of calcaneus OSI ($\beta=-0.240$, $p=0.0039$) but not lumbar spine BMD ($\beta=-0.067$, $p=0.4541$) with FA IMT, although neither lumbar spine BMD nor calcaneus OSI was associated with CA IMT. Furthermore, physical functioning score was independently associated with hb and fa PWV but not hc and hf PWV, suggesting the preferential association with peripheral segment including lower extremities. Neither lumbar spine BMD nor calcaneus OSI was associated with any segment of PWV.

In conclusion, it was suggested that calcaneus OSI might be associated with arterial wall thickening preferentially in femoral artery, and that physical activity may be associated with arterial wall stiffening in peripheral segment including lower extremity but not in central segment in healthy Japanese women.

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Keywords: Osteoporosis; Quality of life; ADL; Bone mineral density; Atherosclerosis

1. Introduction

Atherosclerosis and osteoporosis progress simultaneously with advancing age [1] and shares common risk factors such as smoking [2] and menopause [3]. There is an association between aortic calcification and BMD in hip or lumbar spine in post-menopausal women, therefore, suggesting the development of osteoporosis as a risk for advanced atherosclerosis after menopause [1,4].

Atherosclerosis has two key components, arterial wall thickening (atherosis) and arterial wall stiffening (sclerosis), which now can be quantified by measuring far wall intimal–medial thickness (IMT) and pulse wave velocity (PWV), respectively. The IMT of the common carotid artery (CA) and femoral artery (FA) has been established as a clinically useful index for identifying early-stage general and local atherosclerosis in lower extremities [5–11], respec-

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tively, since CA IMT is strongly correlated with the presence of coronary artery diseases [5–10] and FA IMT with local atherosclerosis [11]. PWV is also established as a marker of early-stage atherosclerosis [12]. Heart–carotid (hc) PWV and heart–femoral (hf) PWV reflect central segment of atherosclerosis and heart–brachial (hb) PWV and femoral–ankle (fa) PWV peripheral segment, respectively [13].

Physical activity is also one of the important factors affecting atherosclerosis. Weekly fitness activity is a significant profitable factor against the development of aortic calcification [1]. Conversely, arterial stiffening was increased in the paretic lower limb of hemiparetic patients [14]. Recently, the Medical Outcomes Study 36-item Short Form (SF-36), which is a self-administered questionnaire containing 36 items that, when scored, yield eight domains considering physical, cognitive, emotional and social aspects [15,16] has emerged as a valuable index to assess health-related quality of life (HRQL) [17].

Furthermore, lumbar spine (L2–4) BMD and calcaneus osteo-sono-assessment index (OSI) are measured as index of osteoporosis [18,19].

This background prompted us to examine the association of physical activity as reflected by SF-36 score and of bone status as reflected by lumbar spine BMD and calcaneus OSI with general and local arterial wall thickening as reflected by IMT and central and peripheral arteries stiffening as reflected by PWV in healthy Japanese women.

2. Subjects and methods

2.1. Subjects

Healthy Japanese women ($n = 149$) were recruited from people who participated in a local health check program at the Osaka City University Hospital from July to September in 2002 after written informed consent was obtained. The mean age was 54.1 ± 12.3 years. Pre- and post-menopausal women were 46 and 103, respectively. Exclusion criteria are the subjects who are known to be suffering from any major diseases which might affect atherosclerosis and bone metabolism, such as diabetes mellitus (all subjects were HbA1c ≦ 5.7%), cerebral vascular accident impairing seriously activity of daily life (ADL), intermittent claudication, osteoporosis and osteomalacia. The subjects who have been continuously taking medicines were also excluded from the present study.

2.2. IMT measurement

Ultrasonographic examination of the CA and FA was performed in the supine position by high-resolution ultrasonography with a 10 MHz in-line Sectascanner (SSD 610 CL; Aloka Co., Tokyo, Japan), as previously described [20–25]. To avoid inter-observer variability, all measurements were performed by the same examiner (H.Y.) who was unaware of subject characteristics. Briefly, CA and FA were scanned at the level of the bifurcation on both the right and left sides. IMT was measured in the far wall of the CA and FA at sites of the most advanced arterial thickening as diffuse and continuous projection with the greatest distance between the lumen–intimal interface and the media–adventitial interface but without atherosclerotic plaque, which was defined as localized lesions of thickness from 1.3 to 1.5 mm, from digitized still images of the arteries during scanning [26]. These interfaces were all manually traced on the same day to avoid possible variation during the study period and the mean value calculated as the mean of at least 3 still images obtained from the same section of the CA [20,22]. Reproducibility of the IMT measurement was acceptable as shown by coefficients of variation (CV) of 2.8 and 3.4% for CA IMT and FA IMT, respectively. These were calculated from the 40 measurements performed in 20 RA patients on two different occasions according to Bland and Altman [27] using the following formula;

$$\mathrm{CV}(\%) = \frac{100\left(\frac{\mathrm{S.D.}}{\sqrt{2}}\right)}{x}$$

where S.D. is the standard deviation of absolute differences between the two repeated measurements and x is the pooled mean value.

2.3. PWV measurement

PWV was measured in the supine position after 5 min of bed rest using an automatic form analyzer (model BP-203RPE; Colin, Komaki, Japan). Pressure waveforms of the brachial and tibial arteries were recorded by an oscillometric method using the occlusion/sensing cuffs adapted to both arms and both ankles. Pressure waveforms of the carotid and femoral arteries were recorded using multielement tonometry sensors placed at the left carotid and the left femoral arteries. Electrocardiogram was monitored with electrodes placed to both wrists. Heart sound S1 and S2 were detected by a microphone set on the left edge of the sternum at the third intercostals space.

The waveform analyzer measures time intervals between S2 and the notch of carotid pulse wave (Thc), between S2 and the notch of brachial pulse wave (Thb), between pulse wave of the carotid and femoral arteries (Tcf), and between pulse wave waves of the femoral and tibial (ankle) arteries (Tfa). The sum of Thc and Tcf gives the time for pulse waves to travel from the heart (aortic orifice) to the femoral artery (Thf). Also, the waveform analyzer estimates the path lengths of the heart–carotid (Dhc), the heart–brachial (Dhb), the heart–femoral (Dhf) and the femoral–ankle (Dfa) segments based on the height (HT, cm) using the following formulas; $\mathrm{Dhc} = 0.2473 \times \mathrm{HT} - 18.999$; $\mathrm{Dhb} = 0.2195 \times \mathrm{HT} - 2.0734$; $\mathrm{Dhf} = 0.5643 \times \mathrm{HT} - 18.381$; $\mathrm{Dfa} = 0.2486 \times \mathrm{HT} - 30.709$. 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 repeating measurements in 17 healthy subjects on two different occasions. The coefficients of variation were 6.0, 3.3, 4.9 and 3.3% for hc PWV, hb PWV, hf PWV and fa PWV, respectively [13].

2.4. Assessment of health-related quality of life (HRQL)

HRQL was assessed by means of SF-36 [15,16]. The questionnaire consists of 36 items and measures three aspects of health: functional ability, well-being and overall health. These are quantified using eight multi-item domains (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health). The physical functioning domain assesses limitations in physical activities such as walking and climbing stairs. The role-physical and role-emotional domains measure problems with work or other daily activities as a result of physical health or emotional problems. Bodily pain assesses limitations resulting from pain; vitality measures energy and tiredness. The social functioning domain examines the effect of physical and emotional health on normal social activities, and mental health assesses happiness, nervousness and depression. The general health perceptions domain evaluates the personal opinion of one's health compared with that of one's peers, as well as the expectation of changes in health. All domains are scored on a scale from 0 to 100, with 100 representing the best possible health state. Two summary scales (physical and mental component) can also be derived [16,28].

The SF-36 has been validated for use to assess HRQL in osteoporotic patients [29,30].

2.5. BMD measurement at lumbar spine

BMD was measured in the lumbar spine (L2–4) in the anterior–posterior projection by dual-energy X-ray absorptiometry (DEXA; QDR-4500A, Hologic Inc., Waltham, MA), essentially as previously described [31]. The precision of the measurement of lumbar spine BMD using DEXA was less than 1.8%.

2.6. Quantitative ultrasound assessment of calcaneus

Quantitative ultrasound assessment of calcaneus was performed using an ultrasound system (Acoustic Osteo-Screener (AOS-100), Aloka Co. Ltd., Tokyo, Japan), as previously described [20,32]. Briefly, the AOS-100 measures both speed of sound (SOS) and an attenuation-related parameter called the transmission index (TI). These measurements yield a derived parameter, the osteo-sono-assessment index (OSI), which has been proposed to be an estimate of the elastic modulus of the calcaneus [33]. In fact, evidence has been accumulated to indicate that calcaneus OSI, a parameter of quantitative ultrasound assessment of the calcaneus, provides a useful index to estimate elastic modules of the calcaneus [33], and thus a good parameter mostly related to bone mineral density [34]. Precision of the OSI parameter was 2.2% [34].

2.7. Statistical analysis

Values are expressed as mean ± S.D. unless otherwise indicated. Statistical analysis was performed with the Stat View V system (Abacus Concepts, Berkeley, CA) for the Apple computer. The correlation coefficients were calculated by simple regression analysis. p-values of less than 0.05 were considered as statistically significant. Multiple regression analysis was performed to assess independent association with IMTs and PWVs. p-values of less than 0.05 were considered as statistically significant.

3. Results

3.1. Clinical variables, IMT, PWV and bone density of healthy Japanese women

Clinical characteristics of healthy Japanese women ($n = 149$) enrolled in this cross-sectional study are shown in Table 1. The means of systolic and diastolic blood pressure, HDL and LDL cholesterol, and triglycerdides were within normal range. The means of CA and FA IMT were to the value 0.597 ± 0.148 and 0.838 ± 0.385 mm, respectively, and the mean values were 861.6 ± 288.3 cm/s for hc PWV, 867.4 ± 192.1 cm/s for hf PWV, 555.9 ± 70.8 cm/s for

Table 1
Clinical characteristics of 149 women in this study

Age (year)	54.1 ± 12.3
BMI (kg/m^2)	21.8 ± 3 1
Non/menopause	46/103
Systolic BP (mmHg)	121.0 ± 20.1
Diastolic BP (mmHg)	67.5 ± 10.0
Smoking index	36.1 ± 142.9
Smokers/non-smokers	17/132
HDL cholesterol (mg/dl)	66.6 ± 16.0
LDL cholesterol (mg/dl)	133.6 ± 31.7
Triglyceride (mg/dl)	90.1 ± 42.5
CA IMT (mm)	0.597 ± 0.148
FA IMT (mm)	0.838 ± 0.385
hc PWV (cm/s)	861.6 ± 288.3
hf PWV (cm/s)	867.4 ± 192.1
hb PWV (cm/s)	555.9 ± 70.8
fa PWV (cm/s)	940.3 ± 157.4
Lumbar spine BMD (g/cm^2)	0.876 ± 0.146
Calcaneus OSI ($\times 10^6$)	2.54 ± 0.28

Data are expressed as mean ± S.D. BMI: body mass index, BP: blood pressure, HDL: high-density lipoprotein, LDL: low-density lipoprotein, CA IMT: common carotid artery–intima–media thickness, FA: femoral artery, hc PWV: heart–carotid pulse wave velocity, hf: heart–femoral, hb: heart–brachial, fa: femoral–ankle, BMD: bone mineral density, OSI: osteo-sono-assessment index.

Table 2
Unadjusted domain scores of the eight subscales and adjusted domain scores of two summary scales of the SF-36 scores in 149 healthy Japanese women

Scores in SF-36	
Physical functioning	89.9 ± 9 4
Role-physical	90.0 ± 23.1
Bodily pain	75.8 ± 19.5
General health perceptions	65.4 ± 15.8
Vitality	66.2 ± 20.4
Social functioning	89.4 ± 17.5
Role-emotional	89.5 ± 25.8
Mental health	75.7 ± 18.6
Summary scales in SF-36	
Physical components	53.1 ± 6.9
Mental components	47.5 ± 9.6

Data are expressed as mean ± S.D

hb PWV, 940.3 ± 157.4 cm/s for fa PWV. The means of lumbar spine BMD and calcaneus OSI were 0.876 ± 0.146 g/cm^2 and 2.54 ± 0.28 × 10^6, respectively.

3.2. Unadjusted domain scores of the eight subscales and adjusted domain scores of two summary scales of the SF-36 scores

Table 2 represents the HRQL scores assessed by SF-36. Adjusted domain scores of two summary scales, physical and mental components, were both around 50 points, indicating that the subjects enrolled in the present study have not been suffering from major health problems.

3.3. Correlations of IMT and PWV with clinical variables including lumbar spine BMD and calcaneus OSI

Table 3 shows the summary of correlations of IMT and PWV with clinical variables including lumbar spine BMD and calcaneus OSI by Spearman Rank correlation. Age, menopause, smoking index, systolic blood pressure, serum LDL cholesterol and triglyceride, but not HDL cholesterol and physical functioning score of SF-36, were positively correlated with CA and FA IMT. Lumbar spine BMD was negatively correlated with both CA and FA IMT, whereas calcaneus OSI was negatively correlated with FA IMT but not with CA IMT. Age, menopause, systolic blood pressure, serum LDL cholesterol and triglyceride were positively correlated with PWV of all segments. HDL cholesterol was negatively correlated with hc and hf but not hb and fa PWV. Smoking index was positively correlated with hf and fa PWV but not hc and hb PWV. Physical functioning score, lumbar spine BMD and calcaneus OSI correlated significantly in a negative fashion with all PWV.

Table 4
Multiple regression analysis of factors independently associated with IMT

Independent variable	CA IMT		FA IMT	
	Model 1	Model 2	Model 1	Model 2
Age	0.261	0.252	0.598§	0.579§
Menopause	0.158	0.221	−0.138	−0.212
Smoking index	0.112	0.101	0.142	0.174§
Systolic BP	0.046	0.060	−0.146	−0.128
LDL cholesterol	0.200§	0.165§	0.019	0.058
Lumbar spine BMD	0.034	–	−0 067	–
Calcaneus OSI		0.152	–	−0.240§
R^2	0.288‡	0.303‡	0.229‡	0.274‡

Values are standard regression coefficients (s). R^2: multiple coefficient of determination. BP: blood pressure, LDL: low-density lipoprotein, BMD: bone mineral density, OSI: osteo-sono-assessment index, CA IMT: common carotid artery–intima–media thickness, FA: femoral artery.
‡ $p < 0.0001$.
§ $p < 0.05$.

3.4. Multiple regression analysis of factors independently associated with IMT

Table 4 represents the results of multiple regression analysis of various clinical variables which correlated significantly in a simple regression analysis with CA and

Table 3
Correlations of IMT and PWV in each segment with clinical characteristics by Spearman Rank correlation

Clinical variables	CA IMT	FA IMT	hc PWV	hf PWV	hb PWV	fa PWV
Age	0.449‡	0.438‡	0.717‡	0.641‡	0.547‡	0.557‡
Menopause	0.549‡	0.519‡	0.725‡	0.650‡	0.605‡	0.606‡
Smoking index	0.301†	0.311†	0.262	0.253§	0.277	0.217§
Systolic BP	0.297†	0.199§	0.588‡	0.638‡	0.627‡	0.678‡
HDL cholesterol	−0.097	−0.007	−0.172§	−0.167§	−0.079	−0.051
LDL cholesterol	0.328‡	0.277†	0.336‡	0.322‡	0.266§	0.313§
Triglyceride	0.338‡	0.179§	0.333‡	0.372‡	0.242§	0.349‡
Physical functioning score (SF-36)	−0.015	−0.025	−0.160§	−0.157§	−0.148§	−0.192§
Lumbar spine BMD	−0.225§	−0.215§	−0.343‡	−0.283†	−0.289†	−0.281†
Calcaneus OSI	−0.051	−0.330‡	−0.235§	−0.235§	−0.170§	−0.252§

Values indicate bivariate correlation coefficients (Spearman's rho) obtained from 149 healthy Japanese women. BP: blood pressure, HDL: high-density lipoprotein, LDL: low-density lipoprotein, BMD: bone mineral density, OSI: osteo-sono-assessment index, CA IMT: common carotid artery–intima–media thickness, FA: femoral artery, hc PWV: heart–carotid pulse wave velocity, hf: heart–femoral, hb: heart–brachial, fa: femoral–ankle.
‡ $p < 0.0001$.
† $p < 0.001$.
§ $p < 0.05$.

Table 5
Multiple regression analysis of factors independently associated with PWV

Independent variable	hc PWV		hf PWV		hb PWV		fa PWV	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Age	0.582‡	0.570‡	0.411§	0.406§	0.422§	0.411§	0.357§	0.334§
Menopause	0.001	0 036	0.019	−0.018	−0.039	−0.040	−0.028	−0.082
Smoking index	0.075	0.067	0.057	0.058	0.059	0.054	−0.017	−0.016
Systolic BP	0.228§	0.241†	0.323‡	0.334‡	0.354‡	0.375‡	0 431‡	0.455‡
LDL cholesterol	−0.014	−0.040	−0.005	0.009	0.005	10^{-4}	0.037	0.065
Physical functioning score (SF-36)	−0.070	−0.066	−0 054	−0.046	−0.143§	−0.156§	−0.167§	−0.186§
Lumbar spine BMD	0.052	-	0.060	-	0.022	-	0 025	
Calcaneus OSI		0.094		−0.047	-	0.009	-	−0 088
R^2	0.509‡	0.514‡	0.410‡	0.426‡	0.460‡	0.475‡	0 512‡	0.536‡

Values are standard regression coefficients (s). R^2: multiple coefficient of determination. BP: blood pressure, LDL: low-density lipoprotein, BMD: bone mineral density, OSI: osteo-sono-assessment index, hc PWV: heart–carotid pulse wave velocity, hf: heart–femoral, hb: heart–brachial, fa: femoral–ankle.
‡ $p<0.0001$.
§ $p<0.05$.
† $p<0.001$.

FA IMT to evaluate their independent association with CA and FA IMT. In models which included age, menopause, smoking index, systolic BP, serum LDL cholesterol in addition to lumbar spine BMD or calcaneus OSI, neither bone condition failed to emerge as an independent factors significantly associated with CA IMT. In models to evaluate the association with FA IMT, calcaneus OSI but not lumbar spine BMD was significantly associated in a negative manner with FA IMT. Although we performed multiple regression analysis including HDL cholesterol and triglyceride in place of LDL cholesterol in Table 4, these factors failed to emerge as a significant factor independently associated with any of IMT (data not shown).

3.5. Multiple regression analysis of factors independently associated with PWV

Table 5 represents the results of multiple regression analysis of various clinical variables, which correlated significantly in a simple regression analyses, used to evaluate their association with PWV. Model 1 included age, menopause, smoking index, systolic BP, serum LDL cholesterol, physical functioning score and lumbar spine BMD, and model 2 included calcaneus OSI in place of lumbar spine BMD. Age and systolic BP were independent factors significantly associated with PWV of all segments in both models 1 and 2. Lumbar spine BMD and calcaneus OSI failed to emerge as a significant factor associated with PWV of any segment. Physical functioning score associated significantly with hb and fa but not hc and hf PWV, suggesting the preferential association with arterial stiffening in peripheral segment. Although we performed multiple regression analysis including HDL cholesterol and triglyceride in place of LDL cholesterol in Table 5, these factors failed to emerge as a significant factor independently associated with any of PWV (data not shown).

4. Discussion

The present study demonstrated: (i) a significant and negative association of physical functioning score with stiffening of peripheral artery and (ii) a significant and negative association of calcaneus OSI with arterial thickening in femoral artery.

Physical activity is known to suppress increased aortic PWV in the general public [35–39], the mechanism by which is partly explained by the data that regular aerobic exercise augments endothelium-dependent vascular relaxation induced by nitric oxide [40]. Therefore, it is reasonable that the physical functioning domain of SF-36 scores showed a significant and positive correlation with PWV in all segments. In multiple regression analysis, physical functioning score showed an independent association with peripheral segment of PWV, hb and fa PWV, but not with central segment of hc and hf PWV. It was previously reported that, as muscle mass decreases in the paretic lower limb of hemiparetic patients, vascular resistance becomes greater [41]. Increased shear stress due to increased vascular resistance is proposed as a major mechanism by which local atherosclerosis progresses in paretic side by increasing vascular injury [42]. In fact, we have previously found that hemiparetic patients exhibited greater fa PWV in the paretic lower limbs than in non-paretic counterpart [14]. Conversely, an increase of basal vascular resistance in the hindlimb in the sedentary spontaneously hypertensive rat (SHR) is significantly reduced after training [43]. Its mechanism is explained by training-induced increase of venule density in skeletal muscle. Since physical functioning score assesses physical activities such as walking and climbing stairs, it may improve muscle condition preferentially in the peripheral components rather than central components. These backgrounds may rationalize the preferential association of physical functioning score with PWV in peripheral segments.

Another interesting finding in the present study is that calcaneus OSI emerged as an independent factor signifi-

cantly associated with FA IMT but not CA IMT (Table 4). Previous studies have reported that symmetrical training of the upper limbs is accompanied by a greater distensibility of the middle-sized arteries of the more trained side [44] and that improved vascular endothelial function in the upper limb after hand-grip exercise training in the patients with congestive heart failure [45,46], suggesting that the beneficial effect of training on vascular endothelial function may be localized to the side where muscle mass increased. Since calcaneus OSI is a reliable marker of ADL particularly that of lower limb [32], it is reasonable that calcaneus OSI was associated preferentially with FA IMT but not CA IMT. Calcaneus OSI was independently associated with FA IMT but not with CA IMT and all parts of PWV. On the other hand, lumbar spine BMD was not independently associated with either IMT or any parts of PWV in multiple regression analysis in the present study. As IMT indicates arterial thickening and PWV indicates arterial stiffening, respectively, the results of this study indicated that bone loss at calcaneus, but not at lumbar spine, enhanced arterial thickening selectively at femoral artery but not at carotid artery, suggesting the local mechanism of increased bone loss to increase arterial thickening [1].

The limitation of the present study is that the multiple regression model explained only 27.4% of the variance of FA IMT. This may indicate the presence of other factors affecting FA IMT that were not included in the models. Furthermore, due to small numbers of subjects, analyses were performed in subjects including both pre- and post-menopausal women, although calcaneus OSI emerged as a factor independently associated with FA IMT even after adjustment for existence of menopause in the multiple regression analysis. Another limitation of the present study is that the reduced blood flow to the lower extremities resulting from atherosclerotic vascular disease might reduce total hip and calcaneus BMD, as previously described [47]. Furthermore, we have no direct histopathological demonstration that increased IMT and PWV is due to atherosclerosis. The arterial thickening and stiffening measured by ultrasonography and waveform analyzer, respectively, might have been due to another, non-atherosclerotic arteriopathy. However, IMT and PWV measurement is still useful in that these parameters strongly correlated with the presence of coronary artery diseases [8–11].

In summary, it was suggested that physical activity and bone status might be intimately associated with arterial wall condition even in healthy Japanese women. Especially, physical activity may be preferentially associated with arterial stiffening in peripheral arteries and bone status of calcaneus locally with that of femoral artery.

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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.

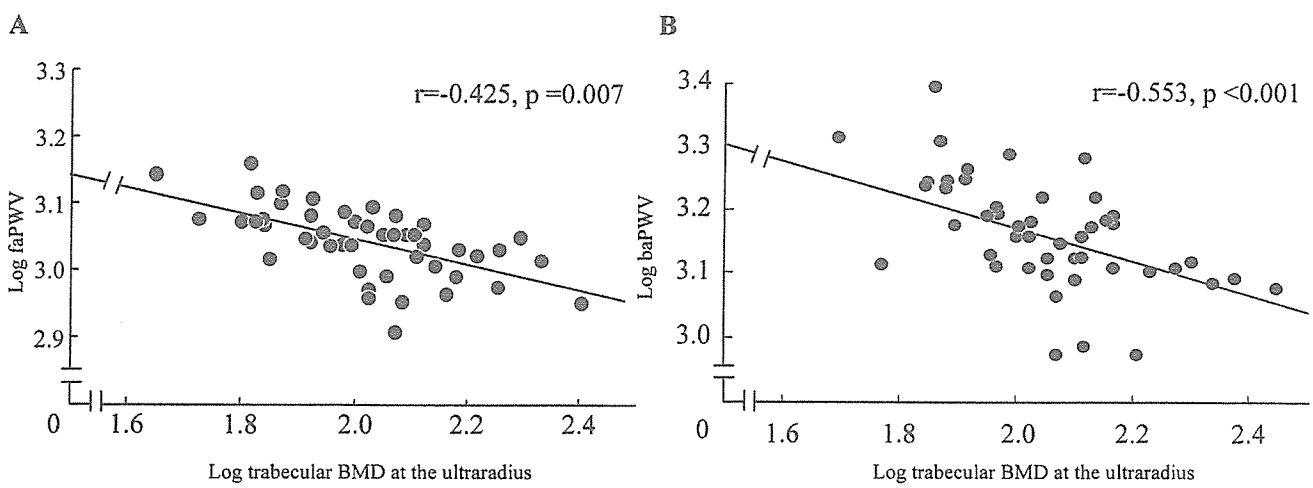

Figure 1. Correlation of trabecular bone density at the ultradistal radius with faPWV (A) and baPWV (B) in 47 RA patients. A significant positive correlation was found between trabecular bone density at the ultradistal radius and faPWV ($r = -0.425$, $p = 0.007$) and baPWV ($r = -0.553$, $p < 0.001$).

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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シンポジウム　各種人工骨の臨床応用と問題点

連通気孔構造を有するハイドロキシアパタイト人工骨の臨床応用 —物理学的特性・臨床的特徴・問題点—*

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はじめに

ハイドロキシアパタイト(hydroxyapatite: HA)をはじめとするリン酸カルシウムセラミックスは骨と化学的に結合するバイオアクティブセラミックスであり，その優れた生体親和性，骨伝導能から人工骨として最も適していると考えられている．緻密体および多孔体HAは1980年代より骨補填剤として広く臨床使用されてきた[1)-7)]．特に多孔体HAは，当初その気孔内に新生骨が侵入し母床骨と完全に同化することが期待されたが，長期の臨床症例の解析から気孔内への新生骨侵入は数ミリ程度に限られることが明らかになってきた[1)]．このような新生骨の侵入していない気孔は強度面で不利であり，多孔体HA移植後2，3年経過してから骨折した症例も報告されている[2),5),7)]．これまでの多孔体HAの気孔構造はいわゆる“軽石状”であり，骨髄腔がすべて連続している海綿骨の骨梁構造とは似て非なるものであった．このような“マクロポア”の構造を制御して，気孔と気孔を組織侵入に十分なサイズの気孔間連通孔でつなげることができれば，多孔体HAの気孔内のbone ingrowthは当然，改善されると考えられる．われわれが物質・材料研究機構(田中順三主任研究員，菊池正紀研究員，生駒俊之研究員)，東芝セラミックス(株)，(株)エム・エム・ティーと共同で開発した連通多孔体ハイドロキシアパタイトセラミックス(interconnected porous calcium hydroxyapatite ceramics: IP-CHA，ネオボーン®，東芝セラミックス(株)製)は，気孔間の連通性に主眼をおいて開発され深部の気孔にまで新生骨が侵入しうる合成多孔体HA骨補填材である[8)]．その特徴は，ほぼすべての気孔が大きい径の気孔間連通孔でつながり組織の侵入が可能であること，そして術前加工性や術中操作性に問題のない強度を同時に実現したことである．

Key words: Hydroxyapatite, Bone substitute, Interconnected porous structure, Tissue engineering, Bone regeneration

*Clinical Application of the Interconnected Porous HA Ceramics: Its Nature and the Point of Issue

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連通多孔体ハイドロキシアパタイトセラミックスの三次元構造

IP-CHAの最大の特徴はその三次元構造にある(図1)．ほぼ球形の気孔が隣接し，気孔間連通孔で互いに連絡する構造になっている．骨補填材として臨床用に開発したネオボーン®の気孔率は75%で，現在市販されている多孔体セラミック人工骨で最も高い気孔率を有する[9)]．走査電子顕微鏡像による検討では，ネオボーン®の気孔は比較的均一なサイズで直径が150-200 μmであり，気孔の内壁には気孔間連通孔が開いており，隣接する気孔と交通している．この気孔間連通孔の直径は90%以上が10-80 μm(平均約40 μm)であり，1つの気孔に通常4-5個以上の連通孔が存在する．高温で焼成されているためHAの粒子が互いに密に結合しており，気孔

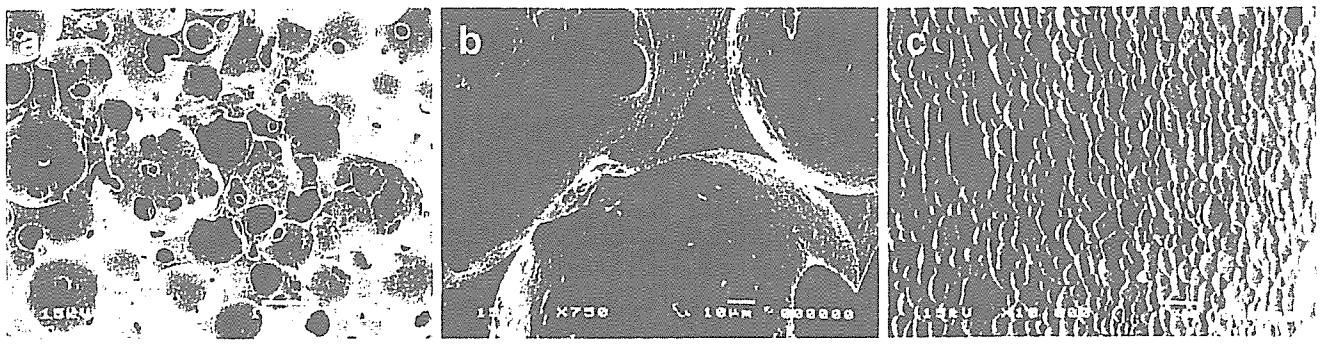

図1 IP-CHA75/ネオボーン®の走査電子顕微鏡像．(a)気孔はほぼ球形で互いに密に隣接しており，(b)気孔壁には多数の気孔間連通孔が観察される．(c)壁の表面はスムーズでHA粒子が密に結合している．

表1 IP-CHAと市販多孔体HAの微細構造および圧縮強度の比較

	試作品			ネオボーン® IP-CHA75	既製多孔体HA
	IP-CHA57	IP-CHA63	IP-CHA69		
全気孔率(%)	57	63	69	75	47.6-64.5
平均気孔径(μm)	58.2	68.5	80.4	191	176-268
気孔間連通孔径(μm)	5	12	25	39	<1-22
実質有効気孔率(%)	40.0	50.2	65.3	67.3	2.5-36.7
圧縮強度(MPa)	68.6	39.8	25.1	12.0	8-60

壁の表面がスムーズである．

気孔率，気孔径，気孔間連通孔の最適化および既製品との比較

このIP-CHAの製造方法の特徴は，起泡ゲル化技術を取り入れたことである[8]．起泡ゲル化技術では，スラリーに起泡剤を加えて撹拌し起泡させたのち，ゲル化させ構造を固定するため，撹拌・起泡過程での種々のパラメーターの調整により気孔および気孔間連通孔の制御が可能である．前臨床の段階でプロトタイプとして作成したIP-CHA57(総気孔率57%)，IP-CHA63(総気孔率63%)，IP-CHA69(総気孔率69%)，臨床用に開発したIP-CHA75(ネオボーン®，総気孔率75%)，および既製の多孔体HA骨補填材の構造的・力学的特性を表1に示す．IP-CHA75(ネオボーン®)の平均気孔径は約190 μm，平均気孔間連通孔径は約40 μmであるが，気孔率を69%に下げたIP-CHA69の平均気孔径は通常のIP-CHAに比べ半分以下の80.4 μm，気孔間連通孔径は約半分の25 μmに低下する．水銀圧入ポロシメーターによる気孔間連通性についての評価では，直径10 μm以上の気孔間連通孔でつながっている気孔による気孔率を「有効気孔率」とすると，IP-CHA75の有効気孔率が67.3%であったのに対し，IP-CHA69で65.3%，IP-CHA63で50.2%，IP-CHA57で40%と総気孔率が低下するにつれ有効気孔率も低下していた．既製の多孔体HA人工骨の有効気孔率は2.5-36.7%となっており，IP-CHA，特にIP-CHA75とIP-CHA69で気孔の連通性がきわめて高いことがわかる．一方，気孔率を下げるとIP-CHAの圧縮強度は高くなる傾向が見られたが，気孔率の高いIP-CHA75でも12 MPa，IP-CHA69で25 MPa程度と海綿骨の2-8倍程度の強度があり，従来の多孔体HA人工骨の中で中間的な値を示していた．IP-CHAがきわめて高い気孔率を有するにもかかわらず比較的高い圧縮強度を有するのは，焼成度が高くHAの粒子が密に結合しており，壁の構造が緻密体HAに類似するためと考えられる．これらの解析からIP-CHA75とIP-CHA69は，既製品と比べ明らかに良好な気孔間連通性を示すと同時に，既製品と同等の圧縮強度を持つことが解った．

IP-CHAの開発コンセプトは，良好な気孔内への骨伝導能(bone ingrowth)を持つ骨補填材であるので，深部気孔内への新生骨形成を評価するためにウサギ大腿骨顆部に径6 mmの円柱形ブロックを埋入し組織学的に検討したところ，IP-CHA75では気孔内の骨組織の