Original Article

Relationship between Carotid Atherosclerosis and Lumbar Spine Bone Mineral Density in Postmenopausal Women

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Osteoporosis and increased carotid intima-media thickness (IMT) have been associated with atherosclerosis. We investigated the correlation between carotid IMT and lumbar spine bone mineral density (BMD) in postmenopausal women. We studied the carotid IMT in 175 postmenopausal women, including 43 women (control) with normal spinal BMD, 73 women with osteopenia, and 59 women with osteoporosis. Carotid IMT was assessed by ultrasonography. BMD at the lumbar spine (lumbar 2 to 4 vertebrae) was measured by dual-energy X-ray absorptiometry. Age, years since menopause, and carotid IMT were significantly greater in the osteoporosis group than in the control (all $p<0.01$) and osteopenia groups (all $p<0.01$). Estradiol was significantly lower in the osteoporosis group than in the control group ($p<0.05$). BMD was significantly lower in the osteoporosis group than in the osteopenia or control group (both $p<0.01$) and in the osteopenia group than in the control group ($p<0.01$). After adjusting for age, years since menopause, and estradiol, women with osteoporosis had significantly greater carotid IMT than controls ($p<0.05$). The univariate linear regression analysis revealed that carotid IMT was significantly positively correlated with age, years since menopause, and low-density lipoprotein (LDL) cholesterol (all $p<0.05$) and was significantly negatively correlated with estradiol and BMD (all $p<0.05$), but showed no significant association with other clinical variables. In multivariate regression analysis, the carotid IMT was significantly positively correlated with LDL cholesterol ($p<0.01$) and negatively correlated with BMD ($p<0.01$), but not with other variables. Carotid atherosclerosis might be associated with lumbar spine bone mass in postmenopausal women, suggesting that postmenopausal women with osteoporosis may have more advanced carotid atherosclerosis than those with a normal bone mass. (*Hypertens Res* 2008; 31: 1191–1197)

***Key Words*: bone mass, carotid atherosclerosis, menopause, women**

Introduction

Cardiovascular disease (CVD) and osteoporosis are known to be major causes of morbidity and mortality in postmenopausal women (*1–3*). In recent years, several studies have examined the association between atherosclerosis at different sites and osteoporosis or low bone mineral density (BMD) in

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women (*4*–*7*). We have also recently demonstrated that postmenopausal women with osteoporosis have elevated arterial stiffness and impaired brachial arterial endothelial function (*8*, *9*). These reports suggested that the development of osteoporosis might be related to a risk for advanced atherosclerosis after menopause. However, the nature of the association between osteoporosis or low BMD and atherosclerosis remains unknown. Therefore, some common factors may influence the development of both atherosclerosis and bone metabolism.

An increased intima-media thickness (IMT) of the carotid artery, measured noninvasively by ultrasonography, has been reported to be associated with cardiovascular risk (*10*) and the severity of coronary atherosclerosis (*11*), and also to predict cardiovascular events, such as myocardial infarction and stroke, in several populations (*12*). A few studies have reported that the lumbar spine BMD is inversely correlated with the maximum thickness of the carotid IMT in postmenopausal women (*6*). However, it is not known whether postmenopausal women with osteoporosis have a higher carotid IMT than those with normal BMD.

In order to investigate the possible relationship between osteoporosis and carotid atherosclerosis and to clarify whether some common factors might contribute to bone mineral loss and carotid atherosclerosis, we compared the carotid IMT among postmenopausal women with normal lumbar spine BMD, osteopenia, and osteoporosis, and evaluated the correlation between the carotid IMT and the lumbar spine BMD and some clinical factors in postmenopausal women.

Methods

Subjects

Of 325 consecutive Japanese postmenopausal women who came to our clinic for a checkup that included examination for possible osteoporosis, 175 subjects (mean age: 59.3±8.6 years; range: 43 to 77 years) participated in this study. At least 1 year had passed since the last menstrual period in each of the subjects. The menopausal status was confirmed by a serum estradiol concentration of <20 pg/mL. Patients with alcohol or caffeine use were excluded from the study since alcohol or caffeine drinking affect BMD (*13*, *14*). None of the subjects had diseases (fractures, cardiovascular diseases, liver disorders, renal disorders, *etc*.) that interfered with the activities of normal daily life. Six subjects were smokers. Ninety-one subjects with essential hypertension, 76 with dyslipidemia, and 17 with type 2 diabetes mellitus were included. None of the subjects had received hormone replacement therapy or had taken any steroids or medications known to influence bone metabolism. Of these subjects, 18 were treated with angiotensin II type 1 receptor blockers (ARBs), 12 with angiotensin-converting enzyme (ACE) inhibitors, 10 with α1-blockers, 26 with β-blockers, 55 with calcium antagonists, 10 with diuretics, 38 with statins, 2 with fibrates, and 1 with sulfonylureas. Written informed consent was obtained from each of the participants prior to admission into the study, and the study protocol was approved by the Ethics Committee of the Cardiovascular Hospital of Central Japan.

Table 1. Complications and Drugs of the Control, Osteopenia, and Osteoporosis Groups

Variables	Control	Osteopenia	Osteoporosis
n	43	73	59
Hypertension (*n* (%))	20 (47)	40 (55)	31 (53)
ARBs (*n* (%))	4 (9)	8 (11)	6 (10)
ACE inhibitors (*n* (%))	3 (7)	6 (8)	3 (5)
α1-Blockers (*n* (%))	2 (5)	5 (7)	3 (5)
β-Blockers (*n* (%))	6 (14)	13 (18)	7 (12)
Calcium antagonists (*n* (%))	12 (28)	25 (34)	18 (31)
Diuretics (*n* (%))	2 (5)	5 (7)	3 (5)
Dyslipidemia (*n* (%))	18 (42)	34 (47)	24 (41)
Statins (*n* (%))	10 (23)	16 (22)	12 (20)
Fibrates (*n* (%))	0 (0)	1 (1)	1 (2)
Diabetes mellitus (*n* (%))	4 (9)	8 (11)	5 (8)
Sulfonylureas (*n* (%))	1 (2)	0 (0)	0 (0)

ARBs, angiotensin II type 1 receptor blockers; ACE, angiotensin-converting enzyme.

The study subjects were assigned to one of three groups according to the BMD at the lumbar spine: a control group (normal BMD; 43 women), an osteopenia group (BMD 1–2.5 SD below the mean value for young adults; 73 women), and an osteoporosis group (BMD more than 2.5 SD below the mean value for young adults; 59 women). This classification system based on the BMD was established by an expert panel of the World Health Organization (*15*).

Physical Examination

The height and weight of the subjects were measured, and the body mass index was calculated. The blood pressure was measured in the morning after the patient had fasted overnight (12 h). The measurement was conducted by the same investigator with a sphygmomanometer in the right arm of the subject, after she had rested for 10 min in the supine position.

Measurement of BMD

The validity of this method has been demonstrated in a previous study (*16*). The BMD was evaluated at the lumbar spine (using the central portion of a lateral scout view of the lumbar 2 to 4 vertebrae) by dual-energy X-ray absorptiometry (DXA) (QDR-1000W; Hologic, Waltham, USA), and expressed as g/cm^2. All the measurements were performed by two operators, and one technician analyzed all of the scans. The inter- and intra-operator coefficients of variation were less than 1%.

Table 2. Clinical and Laboratory Characteristics of the Control, Osteopenia, and Osteoporosis Groups

Variables	Control	Osteopenia	Osteoporosis
Age (years)	53.1±4.7	56.8±7.1*	66.9±6.8**,†
Years since menopause (years)	3.8±3.6	6.8±6.2*	15.7±7.5**,†
Body mass index (kg/m^2)	22.4±3.0	22.9±3.5	22.4±2.7
Smokers (*n* (%))	2 (5)	3 (4)	1 (2)
Estradiol (pg/mL)	12.3±3.2	11.7±3.3	10.8±2.0*
Systolic blood pressure (mmHg)	126.7±15.4	126.2±15.9	129.8±13.6
Diastolic blood pressure (mmHg)	81.2±11.5	77.9±10.4	78.2±8.7
Heart rate (bpm)	67.7±7.9	66.9±7.3	66.1±6.6
HDL cholesterol (mg/dL)	54.6±13.0	55.7±14.0	58.0±11.4
Triglyceride (mg/dL)	108.4±48.3	110.7±47.4	92.6±40.5
LDL cholesterol (mg/dL)	124.6±28.3	133.0±36.1	127.2±26.7
Fasting plasma glucose (mg/dL)	100.9±14.6	97.0±9.4	95.1±13.2
Creatinine (mg/dL)	0.74±0.17	0.74±0.17	0.71±0.14
Calcium (mg/dL)	9.1±0.4	9.0±0.6	9.1±0.5
Phosphate (mg/dL)	3.6±0.4	3.5±0.5	3.6±0.4
Carotid IMT (mm)	0.69±0.17	0.74±0.16	0.84±0.13**,†
BMD (g/cm^2)	1.00±0.07	0.81±0.06**	0.64±0.04**,†

HDL, high-density lipoprotein; LDL, low-density lipoprotein; IMT, intima-media thickness; BMD, bone mineral density. All the results are presented as means±SD. *$p<0.05$,**$p<0.01$ *vs*. control. †$p<0.01$ *vs*. osteopenia.

Measurement of the Carotid IMT

The wall thickness of the carotid arteries was evaluated bilaterally with an ultrasonograph (Power Vision 6000; Toshiba, Tokyo, Japan) using a 7.5-MHz linear type-B–mode probe (*17*, *18*). After the subject had rested for at least 10 min in the supine position with the neck in slight hyperextension, the optimal visualization of the common carotid arteries, carotid bulb, and extracranial internal and external carotid arteries of both sides was evaluated. The end-diastolic IMT of the far wall of the common carotid artery was measured bilaterally from the anterior, lateral and posterior aspects 10 mm proximal to the bulb, and averaged to obtain the mean IMT. The detection limit of the echo system at 7.5-MHz was 0.1 mm. All the scans were evaluated by a physician who was unaware of the clinical characteristics of the subjects. The variability of the ultrasonographic measurements was assessed by performing 5 measurements over a period of 1 month in 12 volunteers. The intra-observer coefficient of variation for the IMT measurement was 5.5±0.8%.

Assays

Blood samples were drawn from the antecubital vein in the morning after the subject had fasted for 12 h. The subjects were allowed to rest in the supine position for at least 10 min prior to the sample collection. The fasting blood samples were centrifuged at 4°C for 15 min at 3,000× *g*, within 1 h of collection. The serum concentrations of estradiol were measured by radioimmunoassay. The serum total cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride, creatinine, calcium, and phosphorus concentrations were determined by standard laboratory techniques (Medca Japan, Konosu, Japan). The concentrations of low-density lipoprotein (LDL) cholesterol were calculated using the Friedwald formula. Plasma glucose was measured in duplicate with an automatic analyzer by the glucose oxidase method (Medca Japan). The intra- and inter-assay coefficients of variation were <5% for estradiol, <6% for lipids, and <7% for plasma glucose.

Table 3. Carotid Artery IMT and Lumbar Spine BMD of the Control, Osteopenia, and Osteoporosis Groups (Analysis of Covariance, Adjusted for Age, Years Since Menopause, and Estradiol)

Variables	Control	Osteopenia	Osteoporosis
Carotid IMT (mm)	0.71±0.17	0.75±0.15	0.82±0.18*
BMD (g/cm^2)	0.99±0.07	0.81±0.06**	0.65±0.07**,†

IMT, intima-media thickness; BMD, bone mineral density. All the results are presented as means±SD. *$p<0.05$, **$p<0.01$ *vs*. control. †$p<0.01$ *vs*. osteopenia.

Statistical Analysis

Data are expressed as the means±SD. The χ^2 test and Fisher's exact test were used to compare categorical data. One-way analysis of variance (ANOVA) was used to compare the clinical characteristics among the three groups. The laboratory data of the three groups were compared by analysis of covariance (ANCOVA), after adjusting for age, and years since menopause. Pearson's correlation coefficient analyses

Table 4. Correlations of Carotid IMT and Lumbar Spine BMD with Clinical Variables by Pearson's Correlation

Variables	Carotid IMT		Lumbar spine BMD	
	r	*p*	*r*	*p*
Age	0.316	0.001	−0.603	0.001
Years since menopause	0.315	0.001	-0.584	0.001
Body mass index	0.083	0.274	0.036	0.637
Estradiol	−0.180	0.017	0.171	0.024
SBP	0.045	0.552	−0.122	0.109
DBP	−0.025	0.742	0.076	0.316
Heart rate	−0.089	0.241	0.130	0.086
HDL cholesterol	−0.059	0.440	−0.140	0.066
Triglyceride	0.069	0.367	0.128	0.092
LDL cholesterol	0.178	0.020	−0.020	0.797
Fasting plasma glucose	0.068	0.375	0.134	0.079
Creatinine	0.089	0.240	0.030	0.696
Calcium	−0.034	0.653	−0.067	0.377
Phosphate	0.026	0.731	−0.068	0.374
BMD	−0.417	0.001	—	—

IMT, intima-media thickness; BMD, bone mineral density; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

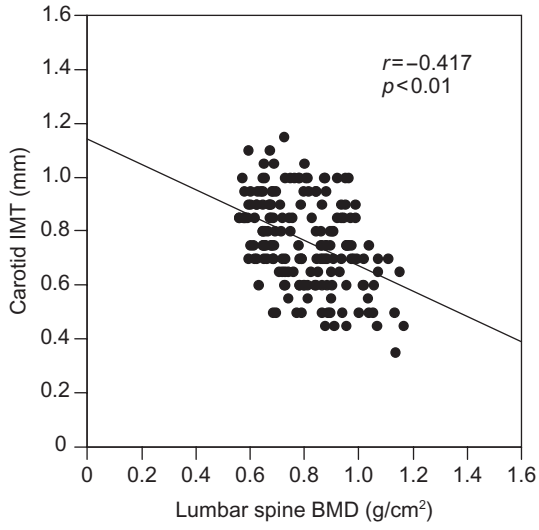

Fig. 1. *Correlation between carotid intima-media thickness (IMT) and lumbar spine bone mineral density (BMD) in postmenopausal women.*

were used to examine the relationships between the values of carotid IMT and the values of BMD and other clinical variables and between the values of BMD and the values of carotid IMT and other clinical variables. In addition, multiple regression analysis was performed among the values of carotid IMT and the values of BMD and other clinical variables. All the probability values were 2-tailed. A value of $p<0.05$ was considered significant. All statistical analyses were performed using the SPSS software (v11.0; SPSS, Chicago, USA).

Results

Three groups had similar complications and received similar drugs (Table 1). Age and years since menopause were significantly greater in the osteoporosis group than in the control ($p<0.01$ for both) and osteopenia groups ($p<0.01$ for both) and in the osteopenia group than in the control group ($p<0.05$ for both). Estradiol was significantly lower in the osteoporosis group than in the control group ($p<0.05$). Carotid IMT was significantly greater in the osteoporosis group than in the control ($p<0.01$) and osteopenia group ($p<0.01$). As expected, BMD was significantly lower in the osteoporosis group than in the osteopenia or control group ($p<0.01$ for both) and in the osteopenia group than in the control group ($p<0.01$). However, there were no significant differences in other characteristics among the three groups (Table 2).

After adjusting for age, years since menopause, and estradiol, carotid IMT was found to be significantly higher in the osteoporosis group than in the control group (0.82±0.18 mm *vs*. 0.71±0.17 mm; $p<0.05$). Furthermore, BMD was significantly lower in the osteoporosis group than in the osteoporosis or control group ($p<0.01$ for both) and in the osteopenia group than in the control group ($p<0.01$; Table 3).

The results of the univariate regression analysis revealed that carotid IMT was significantly positively correlated with age ($r=0.316$, $p<0.01$), years since menopause ($r=0.315$, $p<0.01$), and LDL cholesterol ($r=0.178$, $p<0.05$) and was significantly negatively correlated with estradiol ($r=-0.180$, $p<0.05$) and BMD ($r=-0.417$, $p<0.01$), but showed no significant association with other clinical variables (Table 4, Fig. 1). In addition, lumbar spine BMD was significantly positively correlated with estradiol ($r=0.171$, $p<0.05$) and was significantly negatively correlated with age ($r=-0.603$, $p<0.01$) and years since menopause ($r=-0.584$, $p<0.01$), but showed no significant association with other clinical variables (Table 4).

Table 5 shows the results of multiple regression analysis of various clinical variables to evaluate their independent association with carotid IMT. In model 1, which included age, years since menopause, estradiol, LDL cholesterol, and lumbar spine BMD, only LDL cholesterol and lumbar spine BMD were independent factors significantly associated with carotid IMT. There was a tendency toward lower estradiol with higher carotid IMT. In model 2, which included age, years since menopause, LDL cholesterol, and lumbar spine BMD, LDL cholesterol and lumbar spine BMD were independent factors significantly associated with carotid IMT. In model 3, which included age, years since menopause, estradiol, LDL cholesterol, lumbar spine BMD, and the use of antihypertensive drugs and statins, LDL cholesterol and lum-

Table 5. Independent Predictors of Carotid IMT with Clinical Variables by Multiple Regression Analysis

Variables	Model 1			Model 2			Model 3		
	β	t	p	β	t	p	β	t	p
Age	0.34	0.211	0.833	0.038	0.229	0.819	0.011	0.067	0.947
Years since menopause	0.099	0.619	0.537	0.097	0.599	0.550	0.110	0.675	0.501
Log (Estradiol)	−0.126	−1.807	0.073	—	—	—	−0.124	−1.761	0.080
LDL cholesterol	0.186	2.710	0.007	0.171	2.499	0.013	0.184	2.668	0.008
BMD	−0.318	−3.664	0.001	−0.340	−3.937	0.001	−0.313	−3.593	0.001
Antihypertensive drugs	—	—	—	—	—	—	0.055	0.783	0.435
Statins	—	—	—	—	—	—	0.075	1.077	0.283
		r^2=0.233			r^2=0.218			r^2=0.242	
		p=0.001			p=0.001			p=0.001	

IMT, intima-media thickness; LDL, low-density lipoprotein; BMD, bone mineral density.

bar spine BMD were independent factors significantly associated with carotid IMT.

Discussion

The present study showed that the carotid IMT was greater in postmenopausal women with osteoporosis than in those with normal bone mass. The carotid IMT was significantly negatively correlated with lumbar spine BMD and was significantly positively correlated with LDL cholesterol.

An association between carotid atherosclerosis and lumbar spine BMD has been shown in a few studies (*6*, *7*). Uyama *et al*. (*6*) reported that in postmenopausal women, the lumbar spine BMD, measured by DXA, was inversely correlated with the plaque score, which was computed by adding the maximum thickness of the IMT (plaque thickness), of the carotid arteries of both sides, as determined by ultrasonography. Jorgensen *et al*. (*7*) also demonstrated that among elderly men and postmenopausal women, the likelihood of visualizing echogenic calcified atherosclerotic carotid plaques on ultrasonography was higher in subjects with a low forearm BMD, as assessed by single X-ray absorptiometry, than in subjects with high BMD. Although there were differences in the methods and sites of measurement of the BMD, the study populations, and the methods used to assess carotid atherosclerosis between the aforementioned study and the present study, the findings of the two studies were consistent. Accordingly, it is likely that postmenopausal women with osteoporosis have more advanced carotid atherosclerosis than postmenopausal women with normal bone mass.

The nature of the association between BMD and carotid atherosclerosis is not yet clearly understood. However, we can speculate on several possible explanations. Epidemiological data have suggested that estrogen deficiency is a risk factor for cardiovascular disease and osteoporosis (*19*, *20*). Bone and arteries are target organs for estrogen actions. Estrogen receptors have been demonstrated on osteoblasts (*21*), osteoclasts (*22*), and vascular endothelial and smooth muscle cells (*23*), suggesting direct effects of estrogen on vascular endothelial cells and bone cells. Hormone replacement therapy in postmenopausal women increases the BMD (*24*, *25*) and reduces the carotid IMT (*17*, *26*). Estrogen may be one of the important factors explaining the relationship between bone mass and the carotid IMT. The present study showed that the serum estradiol level tended to be negatively correlated with carotid IMT, although this relation was not statistically significant. The sensitivity of serum estradiol measurement was 10 pg/mL in this study. Ninety-one of 175 subjects had serum estradiol concentrations below 10 pg/mL, which was not surprising, since postmenopausal women have low concentrations of estradiol. Therefore, the sensitivity of serum estradiol measurement might be related to the lack of an association between serum estradiol and carotid IMT.

There are other possible explanations for the present findings. Oxidized lipids promote atherogenesis (*27*) and inhibit differentiation and mineralization of bone cells (*28*). The present study showed that LDL cholesterol concentrations were positively associated with carotid IMT, but were not related to lumbar spine BMD. Accordingly, LDL cholesterol might be a risk factor for the formation of carotid atherosclerosis, but not for a decrease in bone mass. Thus LDL cholesterol could not be a common factor contributing to both bone mineral loss and carotid atherosclerosis.

Increased carotid IMT is associated with several cardiovascular risk factors, including smoking, blood pressure, hypertension, total cholesterol, and diabetes mellitus (*29*). On the other hand, anti-atherosclerotic effects of antihypertensive treatment and lipid- and glucose-lowering therapy on carotid IMT have been reported. In the ELVERA trial (*30*), amlodipine and lisinopril reduced carotid IMT in elderly hypertensive patients. Furthermore, in the LIPID Atherosclerosis Substudy (*31*), pravastatin reduced the carotid IMT in subjects with coronary heart disease. Zhu *et al*. (*32*) have demonstrated that micronized fenofibrate inhibits the progression of carotid IMT in patients with hypertrigryceridemia and essential hypertension. Katakami *et al*. (*33*) have shown that gliclazide attenuates progression of carotid IMT in subjects with type 2 diabetes. However, in the present study there were no

differences in smoking, complications, or received drugs among the three groups. Thus, we speculate that the effects of smoking, complications, and received drugs on carotid IMT may have been similar among the three groups.

In conclusion, carotid atherosclerosis might be associated with lumbar spine bone mass in postmenopausal women, suggesting that postmenopausal women with osteoporosis may have more advanced carotid atherosclerosis than those with a normal bone mass. However, we could not find any common factors which might contribute to bone mineral loss and carotid atherosclerosis. Further study is needed to explore the relationship between carotid atherosclerosis and bone mass in postmenopausal women and the potential common factors.

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