THE INFLUENCE OF SEVERE BONE LOSS ON MITRAL ANNULAR CALCIFICATION IN POSTMENOPAUSAL OSTEOPOROSIS OF ELDERLY JAPANESE WOMEN

NOBUYUKI SUGIHARA, M.D. AND MASUNORI MATSUZAKI, M.D.

We assessed the influence of aging bone calcium metabolism on mitral annular calcification (MAC) and aortic valve calcification (AVC) in 239 septuagenarians (62 men, 177 women; 80.2±4.4 years). Osteoporosis was diagnosed by vertebral bone fracture. Both MAC and AVC were derived by 2-dimensional echocardiography. Bone mineral content (BMC) of the lumbar vertebral body was obtained by single-energy quantitative computed tomography using a calibration phantom. Serum calcium, phosphorus, parathyroid hormone, calcitonin, and osteocalcin were examined. Patients were classified into 3 age-matched groups in each sex: Group-C included patients with MAC (−) and AVC (−) (n=96); Group-A was those with AVC (+) and MAC (−) (n=80); Group-M consisted of those with MAC (+) and AVC (−) or AVC (+) (n=63). Osteoporosis-frequency and BMC in women were significantly higher (p<0.01) and lower (p<0.001) respectively than those in men. Among men, osteoporosis-frequency and BMC showed no difference between the 3 groups. Among women, osteoporosis-frequency (52%) and BMC (32±23 mg/cm³) in Group-M were higher (NS) and significantly less (p<0.01) than those (37%, 49±36) in Group-C, respectively. In both sexes, serum examinations revealed no differences between the 3 groups. These results suggest that: 1) MAC in elderly women can be attributed to ectopic calcium deposits, related to the severe bone loss caused by postmenopausal osteoporosis; 2) there is no significant relationship between the incidence of MAC or AVC and the humoral factors of calcium metabolism; and 3) AVC may be mainly caused by pressure or stress loading.

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PRIMARY (senile or postmenopausal) osteoporosis is more frequently seen in elderly women in Japan than in those in European and American countries! The high incidence of this disease is due to a low nutritional intake of calcium! Elderly women with osteoporosis also have a high incidence of complications with ectopic calcium deposition on arterial walls2--5 Therefore, it is possible that osteoporosis may cause calcium deposition in the cardiovascular system in elderly Japanese women.7

Intracardiac calcifications caused by non-inflammatory or degenerative change in the elderly include mitral annular calcification (MAC), aortic valve calcification (AVC), epicardial coronary artery and papillary muscle calcification.6 Previous reports demonstrated that these intracardiac calcification occur frequently in women, with age, and

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<tbody>
<tr>
<td><strong>Men (n)</strong></td>
<td>62</td>
<td>22</td>
<td>29</td>
<td>11</td>
<td></td>
<td>2</td>
<td>9</td>
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<tr>
<td><strong>Range of age</strong></td>
<td>74~89</td>
<td>76~89</td>
<td>74~89</td>
<td>76~85</td>
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<td>76~85</td>
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<tr>
<td><strong>Age (years old)</strong></td>
<td>80.9±3.9</td>
<td>76.9±3.5</td>
<td>81.7±4.0</td>
<td>80.8±4.0</td>
<td>NS (a)</td>
<td>81.7±4.0</td>
<td>81.8±3.0</td>
<td>NS (a')</td>
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<tr>
<td><strong>Osteoporosis frequency</strong></td>
<td>21% (13/62)</td>
<td>18% (4/22)</td>
<td>24% (7/29)</td>
<td>18% (2/11)</td>
<td>NS (a)</td>
<td>11% (1/9)</td>
<td>NS (a')</td>
<td></td>
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<tr>
<td><strong>Patient by vertebra (n)</strong></td>
<td>(8, 54, 0)</td>
<td>(4, 18, 0)</td>
<td>(3, 26, 0)</td>
<td>(1, 10, 0)</td>
<td></td>
<td>(0, 2, 0)</td>
<td>(1, 8, 0)</td>
<td></td>
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<tr>
<td><strong>BMC (mg/cm²)</strong></td>
<td>72.3±43.3</td>
<td>69.6±41.8</td>
<td>78.1±39.3</td>
<td>62.1±56.8</td>
<td>NS (a)</td>
<td>22.8±17.5</td>
<td>70.8±59.3</td>
<td>NS (a')</td>
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<tr>
<td><strong>Women (n)</strong></td>
<td>177</td>
<td>74</td>
<td>51</td>
<td>52</td>
<td></td>
<td>14</td>
<td>38</td>
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<tr>
<td><strong>Range of age</strong></td>
<td>71~88</td>
<td>71~87</td>
<td>71~87</td>
<td>72~88</td>
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<td>72~86</td>
<td>72~88</td>
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<tr>
<td><strong>Age (years old)</strong></td>
<td>80.0±4.6</td>
<td>79.3±4.5</td>
<td>80.3±4.3</td>
<td>80.1±4.8</td>
<td>NS (a)</td>
<td>79.5±4.8</td>
<td>80.9±4.7</td>
<td>NS (a')</td>
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<tr>
<td><strong>Osteoporosis frequency</strong></td>
<td>40% (71/177)</td>
<td>37% (28/74)</td>
<td>31% (16/51)</td>
<td>52% (27/52)</td>
<td>NS (a)</td>
<td>42% (6/14)</td>
<td>55% (21/38)</td>
<td>NS (a')</td>
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<td><strong>Patient by vertebra (n)</strong></td>
<td>(23, 131, 23)</td>
<td>(8, 59, 7)</td>
<td>(4, 41, 6)</td>
<td>(11, 31, 10)</td>
<td></td>
<td>(4, 8, 2)</td>
<td>(7, 23, 8)</td>
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<tr>
<td><strong>BMC (mg/cm²)</strong></td>
<td>43.5±33.5</td>
<td>46.8±35.6</td>
<td>48.5±36.5</td>
<td>31.7±23.3</td>
<td>p&lt;0.01</td>
<td>34.3±22.7</td>
<td>30.7±23.7</td>
<td>p&lt;0.05</td>
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Abbreviations: n=number of patients; BMC=bone mineral content; L2, L3 and L4=the 2nd, 3rd and 4th lumbar vertebral bodies; Group-C=patients with mitral annular calcification (MAC) (-) and aortic valve calcification (AVC) (-); Group-A=patients with AVC (+) and MAC (-); Group-M=patients with MAC (+) and AVC (-) or AVC (+); P value (a) and (b)=p value of differences between the 3 Groups-C, -A, and -M by one-way analysis of variance (ANOVA) and by chi-square test, respectively; P value (a') and (b')=p value of differences between the 4 Groups-C, -A, -M with AVC(-), and -M with AVC (+) by one-way ANOVA and by chi-square test, respectively; *=p<0.05, **=p<0.01 and ***=p<0.001 differences between the osteoporosis frequencies and between the BMCs of men and women in each group by chi-square test and by Student's t-test, respectively; NS=not significant; values are represented as mean±SD.
in the etiologies of disorders such as hyperlipidemia, diabetes mellitus, hypertension, mitral valve prolapse, hypertrophic obstructive cardiomyopathy, primary hyperparathyroidism and renal failure. In elderly Japanese women also, MAC and AVC are frequently seen. Thus, postmenopausal osteoporosis may be one of many factors or disorders contributing to intracardiac calcification, as a result of the high frequency of osteoporosis in Japanese women.

In the present study, we evaluated the

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contribution of osteoporosis toward calcium deposition in heart tissue, such as MAC or AVC, in elderly subjects.

METHODS

Patients:
The patient population for study consisted of 239 consecutive in- and outpatient of septua- and octogenarians (mean age 80.2 ± 4.4 yr [mean ± SD]; Table I). Sixty-two were men (mean age 80.9 ± 3.9 yr, range 74 to 89), and 177 were women (mean age 80.0 ± 4.6 yr, range 71 to 88). Patients were examined by plain postero-anterior and lateral vertebral roentgenography (chest and lumbar X-ray film), echocardiography, computed tomography (CT) of lumbar vertebrae and serum examinations within a month.

We selected 239 patients with the following basal diseases: 88 with arrhythmia and ischemic heart disease; 82 with cerebrovascular disease; 55 with hypertension; 25 with acute pneumonia and non-inflammatory chronic obstructive lung disease; 2 with acute urinary tract infection; 4 with benign gastrointestinal disease; and 84 patients with spondylosis deformans and osteoarthritis as complications of primary osteoporosis. Osteoporosis was diagnosed by generalized osteopenia and 1 or more non-traumatic vertebral fractures on X-ray film according to the methods of Barnett et al19 and Aloia et al20 Many of these patients had 2 or more concomitant diseases.

We excluded patients with the following inflammatory or atherosclerotic diseases: hyperlipidemia, diabetes mellitus, chronic collagen disease, rheumatic or congenital heart disease, and infectious endocarditis or
myocarditis. In addition, we excluded those with secondary osteoporosis due to endocrine disease, post-oophorectomy and renal failure. Long-term bed-ridden patients with cerebrovascular or osteoarthropathic disease were also excluded. The patients receiving therapy with calcium supplements, vitamin D, calcitonin or hormonal drug, and malnourished patients recovering from gastrectomy or suffering from psychological anorexia were excluded.

**Measurement of MAC and AVC:**

M-mode and 2-dimensional (2-D) echocardiography were performed using a phased-array imaging system with a 3.75 MHz transducer (Toshiba Medical, SSH-60A). As shown in Fig. 1 (Upper figure), MAC was diagnosed by the echocardiographic finding according to the method of Fulkerson et al\textsuperscript{13} and Nestico et al\textsuperscript{17} Anterior MAC was identified as dense echoes between the anterior leaflet of the mitral valve and the posterior wall of the aortic root; posterior MAC was defined as dense echoes behind the posterior leaflet of the mitral valve ahead of and moving parallel to the posterior wall of the left ventricle. MAC was continuously detected as echoes of at least 3 mm thickness and over 5 mm width with a sweep from the aortic root to the left ventricular cavity in both systole and diastole. As shown in Fig. 1 (lower figure), AVC was also determined from the M-mode and 2-D study according to the method of Fujikawa et al\textsuperscript{21} and Wong et al\textsuperscript{22} AVC was defined as widening local echoes in at least 1 cusp of the aortic valve, with multiple dense echoes originating from the aortic valve in diastole.

**Patient groups:**

Patients were classified into 3 age-matched groups in each sex according to echocardiographic findings (Table I): Group-C consisted of 96 patients (22 men, 74 women) with MAC (−) and AVC (−); Group-A comprised 80 patients (29 men, 51 women) with AVC (+) and MAC (−); Group-M was composed 63 patients (11 men, 52 women) with MAC (+) and AVC (−) or AVC (+). And then, Group-M was divided into 2 subgroups of 16 patients with AVC (−) (2 men, 14 women), and 47 patients with AVC (+) (9 men, 38 women).

**Measurement of bone mineral content (BMC) in the lumbar vertebral body:**

Using single-energy CT equipment (Hitachi Medico, CT-W400-20), we scanned the lumbar vertebral bodies and produced images under the following conditions: X-ray voltage 120 KV; current amplitude 250 mA; slice thickness 1 cm scanning field 30 cm; scanning time 4.5 sec; window level +50; window width 250; and calculation matrix.
size 320×320 pixels.

As shown in Fig. 2, we measured the BMC of vertebral bodies with the lumbar CT using a calibration phantom (Chugai Pharmaceutical, B-MAS) according to the method of Fujii et al. During CT examination, the phantom was attached closely to the lumbar back of the patient in a supine position, with CT equipment at an angle for scanning a slice as perpendicular as possible to the midplane of the vertebral body. Thus, both the vertebral body and the phantom system were scanned simultaneously (Fig. 2, upper left). Subsequently, we set the region of interest (ROI) in the spongy bone of the vertebral body using the largest ellipsoidal circle on the display, excluding a cortical bone and a nutritional foramen. Then, we calculated the mean CT value (Hounsfield Unit) in the ROI of the vertebral body (Fig. 2, lower right). Similarly, we set the 5 ROIs on 5 standard substances in the calibrated phantom by using round circles on the display, and calculated the mean CT values within the 5 ROIs (Fig. 2, upper right and lower left). Five standard substances were composed of the following concentrations of CaCO₃: 32.31, 80.17, 133.47, 177.03, and 223.66 mg/cm³, in this order. The first regression line was calculated by the least squares method using the mean CT value of each standard. By applying the mean CT value for the vertebral body to the first regression line, BMC (mg/cm³) was obtained. In all patients, we simultaneously scanned the 2nd, 3rd and 4th vertebral bodies (Fig. 2, upper left). Results from the 3rd body were used as a representative BMC for most patients. In patients with compression fractures or marked callus formation as a complication of trabecular microfracture in the 3rd vertebral body, results from the 2nd or 4th body were used as a representative BMC. Patients with severe compression fractures or marked scoliosis throughout the 3 vertebral bodies were excluded.

**Blood serum examinations:**

The serum calcium-controlling hormones were measured during non-inflammatory periods in each disease. However, we did not perform serum examinations in patients with chronic inflammatory disease. The serum levels of calcium (Ca) and phosphorus (P) were measured by atomic absorption spectrophotometry. The levels of carboxyl-terminal parathyroid hormone (PTH-c), calcitonin (CLT), and calcium-binding protein of osteocalcin (OC) were measured by immunoactive radio-immunooassay. (Normal range of serum examinations in our laboratory were as follows Ca 3.4—5.1 mEq/l; P 1.6—2.6 mEq/l; PTH-c under 1.3 ng/ml; CT under 100 pg/ml; and OC 1.5—6.5 ng/ml. Minimum sensitivity levels were 0.12 ng/ml for PTH-c, 25 pg/ml for CLT, and 0.5 ng/ml for OC.)

**Statistical analysis:**

Data are represented as mean ± standard deviation (SD). The statistical significance of differences between 2 groups and between 3 or more groups were determined using Student's t-test for paired or unpaired values, and using 1-way analysis of variance (ANOVA) and Dunnett's test, respectively. Comparison of categorical variables in frequency was performed by chi-square test. Values of p lower than 0.05 were considered as significant.

**RESULTS**

**Frequency of osteoporosis:**

As shown in Table 1, the frequency of osteoporosis in all women (40%) was significantly higher than that of osteoporosis in all men (21%) (p<0.01). In men, osteoporosis frequency increased in order of Group-C (18%), -M (18%) and -A (24%), but there was no significant difference between the 3 groups. In contrast, the frequency in women increased from Group-A (31%), -C (37%) to -M (52%), again with no statistical difference between the 3 groups. The frequency of osteoporosis in women was significantly higher than men in Group-M (p<0.05), but there was no statistical difference between sexes in Groups-C and A.

After Group-M was divided into 2 groups by the positivity of AVC, the frequency of osteoporosis was compared between the 4 groups in each sex. Among men, osteoporosis frequency of Group-M with AVC (−) (50%) was the highest, and that of Group-M with AVC (+) (11%) was the lowest, but there was no statistical difference between the 4 groups. In contrast, among women,
second highest, but there was no difference between the 4 groups. The osteoporosis frequency of women was significantly higher than men in Group-M with AVC (+) (p<0.05), but there was no statistical difference in Group-M with AVC (−).

**Bone mineral content (BMC):**

As shown in Table I, a representative BMC for each patient was derived based on results from 1 of 3 lumbar vertebrae. Among men, BMC was based on the 2nd vertebral body in 8 patients, the 3rd body in 54 and the 4th body in 0. In Group-C, 4, 18 and 0; In Group-A, 3, 26 and 0; and in Group-M, 1, 10 and 0 patients, respectively (in Group-M with AVC (−), 0, 2 and 0; in Group-M with AVC (+), 1, 8 and 0 patients). Similarly, among women, BMC was based on the 2nd, 3rd and 4th vertebral bodies in 23, 131 and 23 patients, respectively. In Group-C, 8, 59 and 7; in Group-A, 4, 41 and 6; in Group-M, 11, 31 and 10 patients, respectively (in Group-M with AVC (−), 4, 8 and 2; in Group-M with AVC (+), 7, 23 and 8 patients). The 2nd and 4th bodies were used for representative BMCS in women more frequently than in men. Mean regression coefficient using 5 standards of the phantom for the first regression line were 0.971±0.019 in men and 0.976±0.011 in women.

The mean BMC of all women (43.5±33.5 mg/cm²) was significantly lower than that of all men (72.5±43.5 mg/cm²; p<0.001). Among men, BMC decreased in order of Groups-A, -C and -M (78.1±39.3, 69.6±41.8 and 62.1±56.8 mg/cm²). However, there was no statistical difference between the 3 groups (Table I and left figure in Fig. 3). In contrast, BMC in women decreased from Group-C (48.6±35.6), Group-A (48.5±36.5) to Group-M (31.7±23.3 mg/cm²) (p<0.01, Table I). BMC in Group-M was significantly less than that in Group-C (p<0.01) (Right figure in Fig 3). However, there was no difference between BMC of Groups-C and -A. Between BMC of men and women in each group, women were significantly less than men in all groups (p<0.05 in Group-C and p<0.01 in both Groups-A and -M).

After Group-M was divided into 2 groups by AVC positivity, BMC was compared between the 4 groups in each sex. Among
men, BMC of Group-M with AVC (−) (22.8±17.5 mg/cm³) was the lowest, and that of Group-M with AVC (+) (70.8±59.3 mg/cm³) was the second highest value. However, BMC in men showed no statistical difference between the 4 groups. Among women, BMC of Group-M with AVC (+) (30.7±23.7 mg/cm³) was the lowest, and that of Group-M with AVC (−) (34.3±22.7 mg/cm³) was similarly lower. BMC of Group-M with AVC (+) was significantly less than that of Group-C (p<0.05), but there was no difference between the BMC of Group-M with AVC (−) and Group-C. Moreover, between the BMC of men and women, women was significantly less than men in Group-M with AVC (+) (p<0.01), but there was no statistical difference in Group-M with AVC (−).

Serum examinations:
Table II summarizes the results of serum examinations. The mean levels of Ca, PTH-c and CLT in all women (Ca: 4.24±0.36 mEq/l, PTH-c: 0.58±0.47 ng/ml, CLT: 46.71±31.05 pg/ml) were higher than those in all men (Ca: 4.13±0.41 mEq/l, PTH-c: 0.53±0.34 ng/ml, CLT: 44.89±30.02 pg/ml), but these differences were not significant. However, the mean levels of P and OC in all women (P: 1.92±0.30 mEq/l, OC: 10.11±3.40 ng/ml) were significantly higher than those in all men (P: 1.76±0.32 mEq/l, OC: 7.58±4.11 ng/ml; p<0.001 and p<0.01, respectively). In Group-C, mean level of P in women was significantly higher than those in men (p<0.05). In Group-A, mean levels of P and OC in women were significantly higher than those in men (p<0.05 and p<0.001, respectively), and in Group-M, the mean levels of Ca, P and OC in women were significantly higher than those in men (p<0.05; all of these) (Table II).
In both men and women, the levels of Ca and P were almost all within normal limits, with no significant differences between the 3 groups (Fig. 4 and 5). The levels of PTH-c and CLT were almost in the lower normal ranges, with no differences between the 3 groups (Fig. 6 and 7). On the other hand, the levels of OC were in the upper or over normal range, but showed no significant differences between the 3 groups (Fig. 8).

**DISCUSSION**

**Relationship between osteoporosis and MAC:**

In the present study, the frequency of osteoporosis was significantly higher in women than in men. In patients with MAC, osteoporosis frequency and BMC were significantly higher and lower in women than in men, respectively. Among women, osteoporosis frequency and BMC were higher and lower respectively in patients with MAC than in patients without MAC. Elderly women with both MAC and AVC had the lowest BMC complicated with the highest frequency of osteoporosis. These results suggest that the severe bone loss of postmenopausal osteoporosis in elderly women is one of many factors causing MAC. Patients with osteoporosis have a higher incidence of complications with calcium deposition on arterial walls. Similarly, patients with osteoporosis may have intracardiac calcifications. A possible mechanism of MAC formation in elderly women may involve ectopic calcium deposits on mitral ring tissue, probably caused by migration phe-
nomena of ionized calcium associated with aging, due to the decalcification of bone. This mechanism may also affect AVC formation, but may have a weaker influence than on MAC formation. AVC may be caused by other factors, particularly pressure or stress loading. Whereas, our results in men showed a lower frequency of osteoporosis and no relationship between BMC and MAC or AVC.

According to previous reports, serum concentrations of vitamin-D and calcitonin decrease, and those of parathyroid hormone and osteocalcin increase, in proportion to age in elderly men and women. In particular, elderly women with postmenopausal osteoporosis have low serum levels of vitamin-D and calcitonin, but high levels of parathyroid hormone and osteocalcin, due to low calcium intake and decreased female-sex hormone secretion. Among women in our study, serum levels of parathyroid hormone and calcitonin were almost always in the lower normal ranges, and the level of osteocalcin was almost always in the upper or over normal range. The levels of calcitonin and osteocalcin were similar to those in osteoporotic patients in the previous reports. Furthermore, our study showed no significant differences between the 3 groups in both sexes. Our results suggest that serum hormone levels in elderly women with MAC are similar to those in patients with osteoporosis. Previous studies reported that patients of both sexes with arterial wall calcification had low levels of serum estrogen, and that after bilateral oophorectomy women had increased atherosclerosis and a high risk of ischemic heart disease with complications of severe osteoporosis. We consider that a lower level of serum estrogen may be a major background factor contributing to the formation of MAC and AVC, as well as arterial wall calcification, probably by migration phenomena of calcium decalcified from bone. It has been reported that osteocalcin or atherocalcin (an extracellular matrix Ca-binding protein from osteoblast secretion) was seen in a markedly elevated concentration at calcified plaques of arterial walls. However, our data on serum osteocalcin showed no interference in the formation of MAC or AVC.

Measurement of bone mineral content (BMC):

The quantitative CT (QCT) method using a calibration phantom provides a highly accurate measurement of BMC in spongy bone of vertebral bodies. QCT makes it possible to study BMC free from artificial noise factors, such as changes in temperature or humidity, the model of CT equipment, and the body type of the patient. In addition, the measurement of spongy bone by QCT provides more sensitive detection of decreased BMC in osteoporotic patients than the measurement of vertebral cortex or spicular bone by any other method. Nevertheless, some problems with the QCT method should be considered, such as the following: 1) There may be difference in bone decalcification rate between the trunk and extremities. By the method of single-
photon absorption, the decalcification rate from the vertebral body is the same as that from whole body bones. Therefore, we assumed that the bone loss by the BMC of vertebral bone could be interpreted as a reflection of general osteopenia. 2) With the single-energy QCT we used, a beam hardening phenomenon at the cortical bone of the vertebral body and the fatty tissue of spongyous bone affects the CT value, resulting in an underestimated negative value in some patients. Dual-energy QCT is used to resolve this phenomenon, but exposes the patients to much more X-ray irradiation. In practice, there is little difference between the results by single- and dual-energy QCT in values of the mean and standard deviation. 3) Elderly patients frequently have fractures and deformities in the vertebral body, and a high incidence of trabecular microfracture with callus formation in spongyous bone. Therefore, a representative BMC could not be obtained with only one measurement of the 3rd vertebral lumbar body. Even a recent high-resolution method of dual-energy X-ray absorptiometry has some unavoidable limitations related to fractures and deformities. In order to examine the BMC of lumbar vertebrae in the elderly, it is necessary to establish a new standard method which avoids the unstable factors of bone deformities or fractures.

Clinical implications:
The incidence of posterior MAC is markedly higher than that of anterior MAC in the literature. Our study also showed that most cases were posterior MAC, some cases were anterior, and some cases were both anterior and posterior. In cases with both anterior and posterior MAC, severe cases seen as a circular C- or J-shape were few, and there was only one very severe case seen as a ring shape. A posterior fibrous ring suffers more strongly and more easily from pressure or stress loading, blood coagulation, and tissue degeneration by anatomical configuration than does an anterior fibrous ring. The above-mentioned migration phenomenon of calcium in elderly women may well affect the tissue change in fibrous ring caused by these mechanisms, and play a role in the high incidence of posterior MAC.

In this study, many patients with essential hypertension were included. In elderly patients, it is very difficult to exclude completely either current hypertension or a past history of it. There are many relationships between hypertension and intra- or extracellular calcium handling. Higher pressure or stress overloading in essential hypertension is one of many factors in the formation of MAC and AVC. However, essential hypertension may have no direct relationship to bone calcium metabolism. Thus, it is necessary to evaluate the relationships among hypertension, cellular calcium handling, bone calcium metabolism, and MAC or AVC formation.

Severe MAC and AVC are etiologic factors causing valvular heart disease and arrhythmia. Patients with both MAC and stenotic AVC have a high morbidity and mortality from cardiac events and thromboembolic strokes. In the near future with the aging population in Japan, prophylactic medicines for senile disease will be an important clinical goal. We expect that prophylactic therapy for osteoporosis will prevent mitral annular or aortic valve calcification.

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