Bone Mineral Density is an Independent Determinant of Left Ventricular Mass Index in the General Female Population

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ABSTRACT

Background and Objectives: Left ventricular hypertrophy (LVH) is a well known cardiovascular prognostic predictor. Osteoporosis has been suggested to be associated with cardiovascular disease. According to studies of primary hyperparathyroidism, a pathophysiological association between calcium metabolism and LVH has been suggested but is not yet fully understood. This study was performed to investigate the association between bone mineral density (BMD) and left ventricular mass index (LVMI) in a general population. Subjects and Methods: Data from 460 subjects among 543 subjects sampled from a general population in a rural area in Korea were analyzed. BMD, echocardiography, brachial-ankle pulse wave velocity (baPWV), carotid intima-media thickness (IMT) measurement as well as the measurements of blood pressure, blood chemistry and metabolic parameters were analyzed. BMD was measured using the Sahara Clinical Bone Sonometer (Hologic Inc., Mass., USA). Results: Age of the subjects was 59.4±12.4 years. Males were 42.2% (n=194). In a simple correlation analysis on female subjects, age and waist circumference showed negative correlation, and body mass index (BMI) showed positive correlation with BMD. However, only age showed negative correlation with BMD in male subjects. After adjusting baPWV and carotid IMT, we found that BMD was an independent determinant of LVMI in female subjects (β=-13.703, p=0.016), but not in male subjects (β=-1.235, p=0.841). Conclusion: BMD is a consistent and independent determining factor of LVMI, BMI and carotid IMT in postmenopausal women. (Korean Circ J 2010;40:573-580)

KEY WORDS: Bone density; Hypertrophy; Heart ventricles.

Introduction

Left ventricular hypertrophy (LVH) and increased left ventricular mass index (LVMI) are well known cardiovascular prognostic predictors. In patients with stable coronary heart disease, increased LVMI is independently associated with all-cause mortality and sudden or arrhythmic death, even in subjects with normal ejection fraction. Many factors such as blood pressure, circulatory volume load as well as age, body size and sex can influence left ventricular (LV) mass. Currently, osteoporosis has been suggested as another risk factor associated with cardiovascular disease. In addition, low bone mineral density (BMD) in postmenopausal women is associated with increase in cardiovascular mortality. According to studies in primary hyperparathyroidism, increased parathyroid hormone and serum calcium can affect cardiomyocytes, vascular endothelial cells and vascular smooth muscle cells. This could lead to hypertrophy of cardiomyocytes and vascular endothelial cell dysfunction, finally resulting in cardiac diastolic dysfunction and cardiac hypertrophy. Moreover, the causal relationship between low BMD and LVMI in postmenopausal women could be explained by hormonal changes, for example, decreased osteoprotegmin (OPG) levels in this population.
Although a pathophysiological association between calcium metabolism and LVH has been suggested, few epidemiologic studies have been performed. The objective of this study was to investigate the association between BMD and LVMI in a general population.

**Subjects and Methods**

**Study population**

A cross-sectional analysis was performed on a general population who lived in rural area, Korea from 2004 to 2005. A total of 543 subjects were sampled from the general population and informed consents were obtained from 502 subjects at study entry. Subjects were required to answer a questionnaire which included basic demographic, social economic information and past medical history. Lifestyle parameters including smoking, drinking, daily physical activity and dietary patterns were reviewed. Among these subjects, an echocardiography, carotid intima-media thickness (IMT), brachial-ankle pulse wave velocity (baPWV) and BMD were performed in 468 subjects. A complete physical examination including height, weight, waist circumference, heart rate and blood pressure was done and blood chemistry including fasting blood glucose (FBG) and lipid profile were analyzed. In total, 42 subjects were excluded due to incomplete data (n=34) and pre-existing cardiovascular disease (n=8). Subjects with hypertension or under treatment with antihypertensive medications (112 subjects, male 49%) and diabetes (34 subjects, male 41%) were included in the analysis. Finally, 460 subjects were included in the analysis.

**Echocardiography**

Two-dimensional and guided M-mode echocardiograms were performed on each subject by a single cardiologist using a commercially available machine (HP SONOS 2500; Hewlett Packard, USA) with a 2.5/2.0 MHz transducer. Measurements for M-mode guided calculations of LV mass were taken at or just below the tip of the mitral valve with a paper speed of 50 mm/sec. The LV internal end-diastolic dimension, end-systolic dimension (LVID), inter ventricular septal thickness (IVST) and posterior wall thickness (PWT) were measured on the leading edge, according to the guidelines of the American Society of Echocardiography. LV mass was calculated using the following equation: LV mass=\{1.04×(IVST+d+LVID+d)\}×0.92-0.6. LVMI was calculated using the following equation: LVMI=LV mass/height\^3.\(17)\(18)\)

Doppler echocardiographic recordings were performed by pulse-wave Doppler with the sample volume at the tips of the mitral valve in the apical four-chamber view and recorded at a paper speed of 100 mm/sec. Early (E) and late (A) diastolic peak velocities and deceleration time were determined, as previously reported.\(14)\)

**Bone mineral density**

BMD was measured by the Sahara Clinical Bone Sonometer (Hologic Inc., Waltham, MA, USA) which is a radiation-free, waterless, dry system. It consists of two unfocused transducers mounted coaxially on a motorized caliper. One transducer acts as transmitter and the other as receiver. The Sahara device measures both broadband ultrasound attenuation (BUA) and the speed of sound (SOS) at a fixed region of interest in the mid-calcaneus. BUA, expressed in decibel per megahertz (dB/MHz), is the slope of attenuation as a function of frequency as ultrasound waves pass the heel. SOS, expressed in meters per second (m/second), is the transit velocity of a high frequency sound wave through the heel. The results are combined to provide an estimate of heel BMD in units of grams per square centimeter, using the following equation:\(15)\)

\[
BMD=0.002592\times(BUA+SOS)-3.687\text{g/cm}^2
\]

**Brachial-ankle pulse wave velocity**

BaPWV was measured based on conventional methods with the use of automatic waveform analysis (VP-2000; Colin Medical Technology Co., Komaki, Japan) after resting in the supine position for at least 5 minutes following stabilization of the heart rate.\(10)\) baPWV between the bilateral brachial arteries and the ankle was measured by placing both arms and the ankle in a cuff, to which an oscillometric sensor was implanted. The mean of the left and right baPWV was used in the analysis.

**Carotid intima-media thickness**

The bilateral common carotid arteries (CCAs) were measured using the SA 9900 system (Medison Co. Korea) with a 7.5-MHz linear transducer. Scanning was performed at the far wall of the middle and distal CCAs using a lateral longitudinal projection. The authors decided on the measurement protocol according to previously published epidemiologic studies, and defined IMT at the CCA as the distance between the leading edge of lumen-intima interface and the leading edge of the media-adventitia interface.\(17)\(18)\) Five measurements were made on each side and the average measurement was used as the IMT. To avoid inter-observer variability, all measurements were performed by the same examiner who was unaware of subject characteristics. Intra-observer variability was already evaluated before including the data in this paper. To evaluate intra-observer variability, 20 subjects were randomly sampled and measurements were made twice on each subject. The correlation coefficient at the left bulb, left common carotid, right bulb and right common carotid area was 0.92, 0.90, 0.92 and 0.91, respectively.

**Statistical analysis**

Sex stratified analyses were conducted due to different characteristics. Independent t-test and chi-square test were performed to compare the general characteristics and clinical re-
sults with sex group. Pearson’s correlation and stepwise multiple regression analysis were used to identify significant determinants for BMD and LVMI. The criterion for entry into multiple regression analysis was $p<0.05$ while the removal criterion was $p=0.10$. A $p$ of less than 0.05 was considered statistically significant. Data were analyzed using Statistical Package for the Social Sciences (SPSS) 16.0 software (SPSS Inc., Chicago, IL, USA).

**Results**

**General characteristics of study subjects**

The demographic characteristics of the subjects are summarized in Table 1. The age of the subjects was $59.4\pm12.4$ years. 42.2% (n=194) were male. There was no statistical difference between the gender groups in age, waist circumference, systolic blood pressure (SBP) and diastolic blood pressure, pulse pressure and heart rate. However, significant differences in height, weight and body mass index (BMI) were noted. Although the total cholesterol and low density lipoprotein-cholesterol (LDL-C) levels were higher in female subjects, these profiles were within normal range in both sexes. The proportion of smokers was greater in male than in female subjects.

**Clinical characteristics of the subjects**

BMD, baPWV, carotid IMT and echocardiographic findings of the subjects are shown in Table 2. BMD, baPWV, carotid IMT in male subjects were higher than that of female subjects (BMD: $0.51\pm0.11$ g/cm$^2$ vs. $0.44\pm0.13$ g/cm$^2$, $p<0.001$, baPWV: $1,539.3\pm265.0$ cm/s vs. $1,490.2\pm273.9$ cm/s, $p<0.05$, carotid IMT: $0.65\pm0.18$ mm vs. $0.61\pm0.17$ mm, $p=0.03$). The LVMI of study subjects was $47.8\pm11.4$ g/m$^2$, and significant difference was not shown between male and female subjects ($47.1\pm10.7$ g/m$^2$ vs. $48.3\pm11.8$ g/m$^2$, $p=0.26$).

**Determinants of bone mineral density**

Among the clinical parameters, being female ($r=-0.288$, $p<0.001$), age ($r=-0.246$, $p<0.001$), waist circumference ($r=-0.083$, $p<0.05$), pulse pressure ($r=-0.129$, $p<0.01$) and LDL-C ($r=-0.187$, $p<0.001$) were negatively correlated with BMD. Current smokers showed negative correlation with BMD ($r=-0.140$, $p<0.001$). In male subjects, only age ($r=-0.121$, $p<0.05$) showed correlation with BMD, whereas in female subjects, age ($r=-0.356$, $p<0.001$), waist circumference ($r=-0.103$, $p<0.05$), SBP ($r=-0.126$, $p<0.05$), pulse pressure ($r=-0.209$, $p<0.001$), FBG ($r=-0.115$, $p<0.05$) and LDL-C ($r=-0.148$, $p<0.01$) showed negative correlation with the BMD. BMI was positively correlated with BMD ($r=0.149$, $p<0.01$). In the stepwise multiple regression analysis, sex ($\beta=-0.312$, $p<0.001$), age ($\beta=-0.182$, $p<0.001$), BMI ($\beta=0.382$, $p<0.001$), waist circumference ($\beta=-0.342$, $p<0.01$) and LDL-C ($\beta=-0.087$, $p<0.05$) were independent determinants of BMD. BMI, waist circumference as well as age were determinants of BMD in the female

**Table 1. Clinical characteristics of the population as a whole and divided into groups according to sex**

| Parameters          | Total (n=460) | Male (n=194) | Female (n=266) | p     |
|---------------------|---------------|--------------|----------------|-------|
| Age (years)         | 59.4±12.4     | 59.8±12.2    | 59.2±12.6      | 0.57  |
| Height (cm)         | 157.8±9.0     | 165.4±6.3    | 152.2±6.2      | <0.001|
| Weight (kg)         | 61.3±10.6     | 65.6±10.2    | 58.1±9.8       | <0.001|
| WC (cm)             | 87.9±9.0      | 87.1±8.1     | 88.4±9.6       | 0.12  |
| BMI (kg/m$^2$)      | 24.5±3.4      | 23.9±2.9     | 25.0±3.6       | <0.001|
| SBP (mmHg)          | 123.9±15.8    | 124.4±16.3   | 123.6±15.4     | 0.59  |
| DBP (mmHg)          | 80.3±9.3      | 80.7±9.6     | 80.0±9.1       | 0.42  |
| PPr (mmHg)          | 43.6±11.6     | 43.6±12.4    | 43.6±11.1      | 0.94  |
| HR (bpm)            | 67.9±9.4      | 67.1±9.7     | 68.4±9.1       | 0.16  |
| Blood chemistry (mg/dL) |             |              |                |       |
| FBG                 | 98.7±27.6     | 100.2±30.2   | 97.6±25.5      | 0.32  |
| TC                  | 186.9±38.0    | 177.7±36.3   | 193.7±37.8     | <0.001|
| TG                  | 147.0±87.6    | 151.3±90.9   | 143.8±85.1     | 0.37  |
| HDL-C               | 49.8±11.8     | 48.7±12.4    | 50.5±11.2      | 0.11  |
| LDL-C               | 100.4±32.9    | 91.1±32.3    | 107.2±31.8     | <0.001|
| Smoking, n (%)      | None          | 112 (57.7)   | 256 (96.2)     | <0.001|
| Smoker              | 82 (42.3)     | 10 (3.8)     |                |       |

Data are reported as means±SD, p by Chi-square test for smoking status. WC: waist circumference, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, FBG: fasting blood glucose, TC: total cholesterol, TG: triglyceride, HDL-C: high density lipoprotein-cholesterol, LDL-C: low density lipoprotein-cholesterol.
subjects (Table 3).

The relevance of left ventricular mass index and bone mineral density
Separate analyses were conducted for men and women due to their different general characteristics. BMD correlated with baPWV, carotid IMT and LVMI in female subjects (Table 4).

Table 2. Bone mineral density, carotid IMT, baPWV and echocardiographic findings of the population as a whole and divided into groups according to sex

| Parameter | Total (n=460) | Male (n=194) | Female (n=266) | p |
|-----------|---------------|--------------|----------------|---|
| BMD (g/cm²) | 0.47±0.13 | 0.51±0.11 | 0.44±0.13 | <0.001 |
| baPWV (cm/s) | 1.510.8±271.0 | 1.539.3±265.0 | 1.490.0±273.9 | 0.05 |
| Carotid IMT (mm) | 0.63±0.18 | 0.65±0.18 | 0.61±0.17 | 0.03 |

Echocardiography

| Parameter | Total (n=460) | Male (n=194) | Female (n=266) |
|-----------|---------------|--------------|----------------|
| IVSd (mm) | 10.3±1.4 | 10.7±1.4 | 10.0±1.4 | <0.001 |
| LVIDd (mm) | 48.3±4.5 | 50.3±4.1 | 46.8±4.2 | <0.001 |
| LVPWTd (mm) | 8.8±1.2 | 9.1±1.1 | 8.7±1.3 | <0.001 |
| IVSs (mm) | 14.0±1.9 | 14.6±1.8 | 13.5±1.8 | <0.001 |
| LVIDs (mm) | 29.2±4.3 | 31.1±4.0 | 27.8±3.9 | <0.001 |
| LVPWTs (mm) | 13.3±1.7 | 13.7±1.7 | 13.0±1.6 | <0.001 |
| AoD (mm) | 30.6±3.1 | 32.2±2.8 | 29.5±2.9 | <0.001 |
| LAD (mm) | 32.3±4.2 | 33.3±4.2 | 31.6±4.1 | <0.001 |
| E (cm/s) | 67.8±17.6 | 65.7±18.2 | 69.4±17.0 | 0.03 |
| A (cm/s) | 74.3±16.1 | 70.8±15.5 | 76.9±16.0 | <0.001 |
| DT (ms) | 201.1±35.2 | 203.9±38.2 | 199.0±32.8 | 0.15 |
| IVRT (ms) | 75.8±11.9 | 76.3±12.3 | 75.5±11.6 | 0.47 |
| LVMI (g/m²) | 47.8±11.4 | 47.1±10.7 | 48.3±11.8 | 0.26 |

Data are reported as mean±SD. BMD: bone mineral density, IMT: intima-media thickness, baPWV: brachial ankle pulse wave velocity, IVSds: interventricular septal thickness diastole, systole, LVIDds: left ventricular internal dimension diastole, systole, LVPWTds: left ventricular posterior wall thickness diastole, systole, AoD: aortic diameter, LAD: left atrial dimension, E: early diastolic peak velocity, A: late diastolic peak velocity, DT: deceleration time, IVRT: isovolumic relaxation time, LVMI: left ventricular mass index

Table 3. Pearson’s correlation coefficients between BMD and clinical parameters, and clinical predictors of BMD in stepwise multiple linear regression analysis

| Parameters | Total (n=460) | Male (n=194) | Female (n=266) |
|-----------|---------------|--------------|----------------|
| r | β | r | β | r | β |
| Sex | -0.288* | -0.312* | -0.121 | -0.092 | -0.356* | -0.248* |
| Age | -0.246* | -0.182* | 0.072 | 0.181 | 0.149* | 0.428* |
| WC | -0.083 | -0.342* | 0.003 | -0.186 | -0.103* | -0.376* |
| SBP | -0.051 | -0.025 | 0.034 | 0.001 | -0.126* | 0.036 |
| DBP | 0.075 | 0.022 | 0.016 | 0.078 | 0.040 | 0.021 |
| PPr | -0.129* | -0.050 | -0.037 | -0.016 | -0.209* | -0.104 |
| FBG | -0.040 | -0.021 | 0.018 | 0.005 | -0.114* | -0.043 |
| HDL | -0.041 | -0.017 | -0.034 | -0.042 | -0.011 | -0.010 |
| LDL | -0.187* | -0.083* | -0.093 | -0.084 | -0.148* | -0.062 |

Adjusted R² (%) | 19.5 | 20.3 | 20.1

*p<0.001, †p<0.01, ‡p<0.05. BMD: bone mineral density, BMI: body mass index, WC: waist circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure, PPr: pulse pressure, FBG: fasting blood glucose, HDL: high density lipoprotein, LDL: low density lipoprotein.
Table 4. Pearson’s correlation coefficients between BMD and LVMI, baPWV and carotid IMT in subjects

| Variables         | Total (n=460) | Male (n=194) | Female (n=266) |
|-------------------|--------------|--------------|----------------|
|                   | r   | p     | r   | p     | r   | p     |
| baPWV             | -0.195 | <0.001 | -0.094 | 0.191 | -0.318 | <0.001 |
| Carotid IMT       | -0.201 | <0.001 | -0.061 | 0.400 | -0.373 | <0.001 |
| LVMI (g/m²)       | -0.163 | <0.001 | -0.007 | 0.918 | -0.243 | <0.001 |

BMD: bone mineral density, baPWV: brachial ankle pulse wave velocity, IMT: intima-media thickness, LVMI: left ventricular mass index

The main finding of the study is that BMD is a consistent determinant of LVMI (β=−22.123, p<0.0001). In model 2, additional variables such as abdominal circumference, fasting glucose and lipid profile were included. In model 2, although BMD did not have an effect in males, BMD (β=−18.659, p=0.01) was an independent determinant for LVMI along with BMI and SBP in female subjects. In models 3 and 4, after adjusting the clinical parameters in model 2, the individual effects of arterial stiffness parameters such as baPWV and carotid IMT on LVMI were evaluated. Although baPWV was not related to LVMI, carotid IMT showed an independent effect on LVMI in both male and female subjects (β=10.262, p<0.001, β=21.456, p<0.0001, respectively). Finally, in model 5, the relationship between BMD and LVMI was evaluated, after adjusting not only previous clinical parameters noted above but also baPWV and carotid IMT. BMD did not have an effect in male subjects (β=−1.235, p=0.841). However, it was a negative determinant for LVMI in female subjects, along with BMI and carotid IMT (β=−13.703, p=0.016).

Discussion

The main finding of the study is that BMD is a consistent determinant of LVMI in postmenopausal female subjects. Furthermore, BMD is independent of BMI, blood pressure, chemistry profiles, and the parameters of arterial stiffness such as carotid IMT and baPWV in determining LVMI. This finding suggests that the pathophysiological concept derived from primary hyperparathyroidism can be applied to the relationship between BMD and LVMI in postmenopausal female patients. In primary hyperparathyroidism, increased serum calcium and osteoporosis could lead to hypertrophy of the cardiomyocytes and vascular endothelial cell dysfunction, finally resulting in cardiac diastolic dysfunction and cardiac hypertrophy. It is well known that LVMI is determined not only by hemodynamic factors, such as systolic blood pressure and arterial stiffness, but also by non-hemodynamic factors such as obesity. BMD is a non-hemodynamic factor and the interpretation of the relationship with LVMI could be confounded by many factors. For optimal adjustment of hemodynamic factors, we included baPWV and carotid IMT, which are stiffness parameters for peripheral or central arteries, respectively, in the multiple regression model. This was important because arterial stiffness may have clinical relevance in the age (59.4 ±12.4 years) of this study population.

In this study, BMD as a non-hemodynamic factor that showed correlation with LVMI in female subjects only (Table 4) (Fig. 1). According to the stepwise multiple linear regression analysis, BMD was a consistent and independent determinant for LVMI in female subjects (Table 6). These findings are comparable to that in previous studies, which reported that non-hemodynamic factors were more important in female subjects. Although more study is needed to clarify the causal relationship between low BMD and LVMI in postmenopausal women, hormonal changes in this population may be a possibility. For example, a change in hormones, including OPG in postmenopausal women, is involved in LV hypertrophy and vascular calcification as well as reduction in bone mass.

The relationship between BMD and baPWV or carotid IMT was also more definite in female subjects (Fig. 1). BMD was a greater determinant in cardiovascular change in female subjects, compared to male subjects. The difference between sexes may be explained by the following clinical characteristics: BMI was higher in female subjects (25.0±3.6 vs. 23.9±2.9, p<0.001), LDL was also higher (107.2±31.8 vs. 91.1±32.3, p<0.001) and BMD was lower compared to male subjects (0.44±31.8 vs. 0.51±0.11 g/cm², p<0.001). Generally, in subjects of this age group (59.4±12.4 years), BMD is lower in female compared to male subjects, and this could be due to differences in hormonal changes at this age.

According to the findings of our study, low BMD has harmful effects on the vascular structure and/or stiffness. Subsequently, increased arterial stiffness may contribute to LV hypertrophy. But considering that the effects of low BMD on LVH are independent, even after adjusting baPWV and carotid IMT, suggestive that low BMD could have direct influence on LV hypertrophy.

These results attribute to previous reports on the possibility of osteoporosis as a risk factor for cardiovascular disease. Moreover, osteopenia or osteoporosis and atherosclerotic vascular disease (coronary artery disease, ischemic stroke, or peripheral arterial disease) are common conditions in postmenopausal women. Osteoporosis and vascular calcification have been largely attributed to the aging process. However, recent studies have shown that arterial calcification is a highly
regulated process, with intriguing similarities to bone turnover that may be age-independent. In a previous study, low BMD was associated with increased risk of ischemic stroke, and was found to be a possible predictor for first stroke among older women. In another study, osteoporosis was linked to peripheral arterial disease independent of age and gender, and low BMD correlated with ankle-brachial indexes. In our study, we also found that in postmenopausal women, low BMD contributes to central and peripheral vascular stiffness, which are reflected by carotid IMT and baPWV.

Fig. 1. Correlation between bone mineral density (BMD) and brachial ankle pulse wave velocity (baPWV), carotid intima-media thickness (IMT) and left ventricular mass index (LVMI).
Table 5. Multivariate analysis of between LVMI and clinical parameters in male subjects

| Model | β     | p    | β     | p    | β     | p    | β     | p    | β     | p    |
|-------|-------|------|-------|------|-------|------|-------|------|-------|------|
| Age   | 0.145 | 0.018| 0.091 | 0.147| 0.110 | 0.092| 0.045 | 0.492| 0.064 | 0.339|
| Smoking | 1.101 | 0.454| 0.859 | 0.562| 0.950 | 0.520| 0.951 | 0.514| 1.038 | 0.477|
| BMI   | 1.012 | <0.0001| 1.188 | 0.019| 1.103 | 0.030| 1.122 | 0.024| 1.030 | 0.041|
| WC    | 0.015 | 0.930 | 0.038 | 0.829| 0.012 | 0.946| 0.034 | 0.846|       |      |
| SBP   | 0.194 | <0.0001| 0.319 | <0.0001| 0.365 | <0.0001| 0.295 | <0.0001| 0.347 | <0.0001|
| DBP   | -0.339 | 0.002 | -0.362 | 0.001 | -0.292 | 0.006 | -0.314 | 0.004|       |      |
| FBG   | 0.009 | 0.717 | 0.016 | 0.512| 0.004 | 0.877| 0.012 | 0.616|       |      |
| HDL-C | 0.019 | 0.759 | 0.023 | 0.699| 0.031 | 0.609| 0.036 | 0.547|       |      |
| LDL-C | -0.012 | 0.605 | -0.012 | 0.604| -0.029 | 0.217| -0.030 | 0.198|       |      |
| baPWV | -0.004 | 0.220 |       |      |       |      | -0.005 | 0.149|       |      |
| cIMT  |       |      | 10.262 | 0.018| 10.766 | 0.013|       |      |       |      |
| BMD   | -1.428 | 0.820 | -0.362 | 0.954|       |      | -1.235 | 0.841|       |      |
| Adjusted R² (%) | 18.9 | 23.4 | 24.0 | 25.7 | 26.6 |      |       |      |       |      |

LVMI: left ventricular mass index, BMI: body mass index, WC: waist circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure, FBG: fasting blood glucose, HDL-C: high density lipoprotein-cholesterol, LDL-C: low density lipoprotein-cholesterol, baPWV: brachial ankle pulse wave velocity, cIMT: carotid intima-media thickness, BMD: bone mineral density

Table 6. Multivariate analysis between LVMI and the clinical parameters in female subjects

| Model | β     | p    | β     | p    | β     | p    | β     | p    | β     | p    |
|-------|-------|------|-------|------|-------|------|-------|------|-------|------|
| Age   | 0.097 | 0.082| 0.073 | 0.204| 0.109 | 0.060| 0.045 | 0.423| 0.020 | 0.723|
| BMI   | 1.066 | <0.0001| 0.806 | 0.014| 0.627 | 0.068| 0.783 | 0.012| 0.949 | 0.005|
| WC    | 0.154 | 0.205 | 0.216 | 0.085| 0.140 | 0.231| 0.088 | 0.468|       |      |
| SBP   | 0.088 | 0.054 | 0.149 | 0.018| 0.145 | 0.041| 0.112 | 0.071| 0.105 | 0.122|
| DBP   | -0.181 | 0.095 | -0.204 | 0.066| -0.162 | 0.127| -0.148 | 0.160|       |      |
| FBG   | -0.008 | 0.750 | -0.006 | 0.817| -0.011 | 0.655| -0.013 | 0.604|       |      |
| HDL-C | -0.026 | 0.661 | -0.026 | 0.669| -0.017 | 0.764| -0.018 | 0.748|       |      |
| LDL-C | 0.022 | 0.309 | 0.027 | 0.229| 0.006 | 0.781| 0.005 | 0.823|       |      |
| baPWV | 0.003 | 0.421 |       |      |       |      | 0.000 | 0.913|       |      |
| cIMT  |       |      | 21.456 | <0.0001| 19.392 | 0.001|       |      |       |      |
| BMD   | -22.123 | <0.0001| -18.659 | 0.001|       |      | -13.703 | 0.016|       |      |
| Adjusted R² (%) | 20.9 | 23.0 | 26.9 | 28.5 |      |      |       |      |       |      |

LVMI: left ventricular mass index, BMI: body mass index, WC: waist circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure, FBG: fasting blood glucose, HDL-C: high density lipoprotein-cholesterol, LDL-C: low density lipoprotein-cholesterol, baPWV: brachial ankle pulse wave velocity, cIMT: carotid intima-media thickness, BMD: bone mineral density

WV, respectively. Moreover, we found that decrease in BMD has a weak, but definite contribution to increase in LVMI, leading to LVH even before osteoporosis sets place in postmenopausal women. From the standpoint of clinical relevance, the consistent relationship with relatively low strength between BMD, cardiac and vascular surrogates suggests that more evidence is needed for bone mineral metabolism to be generally accepted as a clinically valuable mechanism for cardiac and vascular health.

This study was a cross sectional analysis and BMD was measured by bone sonometer in the calcaneal bone, not the lumbar spine or femur neck, which limit result interpretation. For a hard endpoint on this subject, a large scale prospective study is warranted. However, this study gives us insights into the relationship between BMD and various cardiovascular parameters in postmenopausal female subjects. We found that BMD serves as a consistent and independent factor in determining LVMI, baPWV and carotid IMT in postmenopausal female subjects.

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REFERENCES

1) Levy D, Gharrosso RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med 1990;322:1561-6.

2) Verdecchia P, Schillaci G, Borgioni C, et al. Prognostic significance of serial changes in left ventricular mass in essential hypertension. Circulation 1998;97:48-54.

3) Turakhia MP, Schiller NB, Whookey MA. Prognostic significance of increased left ventricular mass index to mortality and sudden death in patients with stable coronary heart disease (from the Heart and Soul Study). Am J Cardiol 2008;102:1131-5.

4) Lim YH, Lee JU, Kim KS, et al. Association between inappropriate- ness of left ventricular mass and left ventricular diastolic dysfunction: a study using the tissue Doppler parameter. Echocardiography 2009;26:138-44.

5) de Simone G, Devereux RB, Daniels SR, Koren MJ, Meyer RA, Parmaghi JH. Effect of growth on variability of left ventricular mass: assessment of allometric indices in adults and children and their capacity to predict cardiovascular risk. J Am Coll Cardiol 1993;25:4106-2.

6) Marcovitz PA, Tran HH, Franklin BA, et al. Usefulness of bone mineral density to predict significant coronary artery disease. Am J Cardiol 2005;96:1019-6.

7) Nuss D, Aronow WS. Comparison of prevalence of atherosclerotic vascular disease in postmenopausal women with osteoporosis or osteopenia versus without osteoporosis or osteopenia. Am J Cardiol 2006;97:1427-8.

8) von der Recke P, Hansen MA, Hassager C. The association between low bone mass at the menopause and cardiovascular mortality. Am J Med 1999;106:273-8.

9) Samelson EJ, Kiel DP, Broe KE, et al. Metacarpal cortical area and risk of coronary heart disease: the Framingham Study. Am J Epidemiol 2004;159:589-95.

10) Andersson P, Rydberg E, Willenheimer R. Primary hyperparathyroidism and heart disease: a review. Eur Heart J 2004;25:1776-87.

11) Persy V, D’Haese P. Vascular calcification and bone disease: the calcification paradox. Trends Mol Med 2009:15:405-16.

12) Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 1986;57:438-9.

13) Shin J, Kim KS, Kim SK, et al. Influences of body size and cardiac workload on the left ventricular mass in healthy Korean adults with normal body weight and blood pressure. Korean Circ J 2005;35:335-40.

14) Sohn DW, Chot YJ, Ob BH, Lee MM, Lee YW. Estimation of left ventricular end-diastolic pressure with the difference in pulmonary venous and mitral A waves is limited when mitral E and A waves are overlapping. J Am Soc Echocardiogr 1999;12:106-12.

15) Frost Ml, Blake GM, Fogelman I. Quantitative ultrasound and bone mineral density are equally strongly associated with risk factors for osteoporosis. J Bone Miner Res 2001;16:406-16.

16) Kim YK, Lee MY, Rhee MY. A simple esocliometric measurement of pulse wave velocity: comparison with conventional tonometric measurement. Korean J Med 2004;67:597-606.

17) Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. Circulation 1997;96:1432-7.

18) Heiss G, Sharrett AR, Barnes R, Chambless LE, Szlko M, Alzola C. Carotid atherosclerosis measured by B-mode ultrasound in populations: associations with cardiovascular risk factors in the ARIC study. Am J Epidemiol 1991;134:250-6.

19) Krauser DG, Devereux RB. Ventricular hypertrophy and hypertension: prognostic elements and implications for management. Herz 2006;31:305-16.

20) Saitoh M, Nishimura H, Tanaka T, Kondo T. Gender-related differences in target organ damage in untreated patients with essential hypertension. Intern Med 2006;45:577-83.

21) Price PA, Jane HH, Buckley JR, Williamson MK. Osteoprotegerin inhibits artery calcification induced by warfarin and by vitamin D. Arterioscler Thromb Vasc Biol 2001;21:1610-6.

22) Collin-Osdoby P. Regulation of vascular calcification by osteocalcin regulatory factors RANKL and osteoprotegerin. Circ Res 2004;95:1046-57.

23) Bello N, Mosca L. Epidemiology of coronary heart disease in women. Prog Cardiovasc Dis 2004;46:287-95.

24) Feiglin VL, Lawes CM, Bennett DA, Anderson CS. Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. Lancet Neurol 2003;2:43-53.

25) Doherty TM, Asota K, Fitzpatrick LA, et al. Calcification in atherosclerosis: bone biology and chronic inflammation at the arterial crossroads. Proc Natl Acad Sci U S A 2003;100:11201-6.

26) Tintut Y, Demer LL. Recent advances in multifactorial regulation of vascular calcification. Curr Opin Lipidol 2001;12:553-60.

27) Brower WS, Pressman AR, Nevitt MC, Cauley JA, Cummings SR. Association between low bone density and stroke in elderly women: the study of osteoporotic fractures. Stroke 1993;24:940-6.

28) Jorgensen L, Engstad T, Jacobsen BK. Bone mineral density in acute stroke patients: low bone mineral density may predict first stroke in women. Stroke 2001;32:47-51.

29) Pennisi P, Signorelli SS, Riccobene S, et al. Low bone density and abnormal bone turnover in patients with atherosclerosis of peripheral vessels. Osteoporos Int 2004;15:389-95.

30) Vogt MT, Cauley JA, Kuller LH, Nevitt MC. Bone mineral density and blood flow to the lower extremities: the study of osteoporotic fractures. J Bone Miner Res 1997;12:283-9.