

# Association factor analysis between osteoporosis with cerebral artery disease

## The STROBE study

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### Abstract

The purpose of this study was to determine the clinical association factors between osteoporosis and cerebral artery disease in Korean population. Two hundred nineteen postmenopausal women and men undergoing cerebral computed tomography angiography were enrolled in this study to evaluate the cerebral artery disease by cross-sectional study. Cerebral artery disease was diagnosed if there was narrowing of 50% higher diameter in one or more cerebral vessel artery or presence of vascular calcification. History of osteoporotic fracture was assessed using medical record, and radiographic data such as simple radiography, MRI, and bone scan. Bone mineral density was checked by dual-energy x-ray absorptiometry. We reviewed clinical characteristics in all patients and also performed subgroup analysis for total or extracranial/ intracranial cerebral artery disease group retrospectively. We performed statistical analysis by means of chi-square test or Fisher's exact test for categorical variables and Student's t-test or Wilcoxon's rank sum test for continuous variables. We also used univariate and multivariate logistic regression analyses were conducted to assess the factors associated with the prevalence of cerebral artery disease. A two-tailed p-value of less than 0.05 was considered as statistically significant. All statistical analyses were performed using R (version 3.1.3; The R Foundation for Statistical Computing, Vienna, Austria) and SPSS (version 14.0; SPSS, Inc, Chicago, Ill, USA). Of the 219 patients, 142 had cerebral artery disease. All vertebral fracture was observed in 29 (13.24%) patients. There was significant difference in hip fracture according to the presence or absence of cerebral artery disease. In logistic regression analysis, osteoporotic hip fracture was significantly associated with extracranial cerebral artery disease after adjusting for multiple risk factors. Females with osteoporotic hip fracture were associated with total calcified cerebral artery disease. Some clinical factors such as age, hypertension, and osteoporotic hip fracture, smoking history and anti-osteoporosis drug use were associated with cerebral artery disease.

**Abbreviations:** BMD = bone mineral density, CAD = cerebral artery disease, CI = confidence interval, OR = odds ratio.

**Keywords:** atherosclerosis, osteoporosis cerebral artery disease

## 1. Introduction

The World Health Organization (WHO) defines osteoporosis as a disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequential increase in fracture risk.<sup>[1]</sup> In the United States, Europe, and Japan, osteoporosis affects about 75 million people. Osteoporotic fractures (fragility fractures, low-trauma

fractures) are those occurring from a fall from a standing height or less, without major trauma such as a motor vehicle accident and osteoporosis causes about 9 million fractures annually worldwide, of which more than 4.5 million occur in the Americas and Europe.<sup>[2]</sup> Cerebrovascular disease refers to a group of conditions that affect the supply of blood to the brain, causing limited or no blood flow to the affected areas and is the most common life-threatening neurological event in the US.<sup>[2]</sup>

Osteoporosis and vascular atherosclerosis commonly occur in the elderly as important causes of mortality.<sup>[3,4]</sup> Generally, they are considered as independent disease associated with the aging process and managed medically and independently. However, several studies have reported that osteoporosis and vascular atherosclerosis are likely to be closely related to each other. Low bone density was reported to be an independent risk factor for death from cardiovascular disease in advanced age patients.<sup>[5,6]</sup> The prevalence of coronary heart disease and stroke in osteoporotic women is also increased. Furthermore, it has been reported that the presence of vertebral fractures is positively correlated with cardiovascular disease risk factors.<sup>[7]</sup>

Nevertheless, there are a few studies about the relations, several studies have reported that osteoporosis and cardiovascular atherosclerosis,<sup>[8-10]</sup> unfortunately, have determined the relationship between cerebral atherosclerosis and osteoporosis. Furthermore, correlation studies between cerebral artery disease (CAD) and osteoporotic in Korean population are rare. Therefore, we would like to determine the clinical association factors between osteoporosis and CAD in Korean population.

Editor: Bernhard Schaller.

Funding/support: This work was supported by the Soonchunhyang University Research Fund and Grant Form Kyunghgee University 2013 (KHU-0369).

The authors have no conflicts of interest to disclose.

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Medicine (2017) 96:9(e6164)

Received: 5 August 2016 / Received in final form: 24 January 2017 / Accepted: 27 January 2017

<http://dx.doi.org/10.1097/MD.00000000000006164>

## 2. Material and methods

This study was approved by the Institutional Review Board of our institute. We carried out a cross-sectional study among subjects who visited the out-patient's Department of Soonchunhyang University Hospital in Bucheon in the south of Korea from January 2010 to January 2015. A total of 246 consecutive healthy patients (postmenopausal women and men more than 45 years) undergoing cerebral computed tomography (CT) angiography and bone densitometry were enrolled. Among these patients, 27 were excluded based on the following exclusion criteria: chronic kidney disease (man with serum creatinine level of 1.5 mg/dL or higher, woman with creatinine level of 1.4 mg/dL or higher), history of steroid use for more than 3 months, chronic diseases affecting bone metabolism (eg, flow rheumatic arthritis and hyperparathyroidism), and history of cancer within the last 5 years.

Clinical and radiographic information was obtained through retrospective review of medical records and radiographs. Hypertension was defined as systolic blood pressure of 140 mm Hg or higher and diastolic blood pressure over 90 mm Hg or antihypertensive drugs. If a patient was not diagnosed as diabetes but taking oral hypoglycemic agents, the patient was considered as diabetic, if being diagnosed as diabetic based on the American Diabetes Association diagnostic criteria. Dyslipidemia was defined as running or taking cholesterol drugs with total cholesterol of 200 mg/dL or higher. Positive smoking history was defined if the patient was a current smoker. All patients underwent basic biochemical tests such as fasting plasma glucose, total cholesterol, aspartate aminotransferase, alanine aminotransferase, creatinine, etc. If a patient was suspected to have diabetes, glycated hemoglobin (HBA1c) level was measured.

The objective of this study was to determine the relationships between the osteoporosis-related parameters and CAD. The CAD as the dependent variable was divided into 2 types, extracranial and intracranial CADs and the osteoporosis-related parameters as the potential influential factor were bone mineral density (BMD), fracture of spine, hip, or other sites, and drug intake for osteoporosis. We considered the several parameters such as smoking history; underlying diseases including hypertension, diabetes mellitus, and hyperlipidemia; and laboratory markers as the potential confounders. CAD was diagnosed if there was narrowing of >50% diameter in 1 or more major cerebral vessel artery or the presence of vascular calcification. History of osteoporotic fracture was assessed using medical record, and radiographic data such as simple radiography, MRI, and bone scan. BMD was performed using dual-energy X-ray absorptiometry (DEXA) (Hologic QDR4500W, Hologic, Bedford, MA) at lumbar spine (L1-4) and femur neck. There were no missing values for the baseline characteristics and the outcomes of all 217 subjects included in the analyzed dataset.

Baseline characteristics of the study patients are summarized as mean and standard deviation (SD) for continuous variables and frequency (percentage, %) for categorical variables. Statistical differences in baseline characteristics between groups by the prevalence of CAD were evaluated by means of chi-square test or Fisher exact test for categorical variables and Student *t* test or Wilcoxon rank sum test for continuous variables. Before *t* test, Shapiro–Wilk test for normality and Levene homogeneity of variance test were conducted. To evaluate changes in baseline characteristics by the number of vessel disease, chi-square test for trend in proportion and linear regression were performed for categorical variables and continuous variables, respectively.

Univariate and multivariate logistic regression analyses were conducted to assess the factors associated with the prevalence of CAD. The odds ratios (ORs) for the chance of CAD prevalence were calculated. If a quantitative variable did not follow the normal distribution, it was log-transformed in the logistic regression and the regression coefficients were converted with the exponentiation. For multivariable logistic regression, the initial model included factors that showed significance based on likelihood ratio statistic of the univariable logistic regression and further refined by Akaike information criterion (AIC)-based backward selection. Multicollinearity of factors embedded in the multivariable model was evaluated by general variance inflation factor (GVIF). Goodness-of-fit of the final model was assessed by Hosmer–Lemeshow statistic and Nagelkerke  $R^2$ . The heterogeneity of association between factors and the prevalence of CAD according to cranial side (extracranial or intracranial) was assessed in subgroup analysis for sensitivity analysis.

A 2-tailed *P*-value of less than 0.05 was considered as statistically significant. All statistical analyses were performed using R (version 3.1.3; The R Foundation for Statistical Computing, Vienna, Austria) and SPSS (version 14.0; SPSS, Inc, Chicago, IL).

## 3. Results

Of the 219 patients in the study (mean age of  $68.66 \pm 11.39$  years), 77 (35.2%) patients had CAD. Vertebral fracture was observed in 29 (13.24%) patients. Hip fracture was found in 23 (10.5%) patients.

Demography of patients with or without CAD are summarized in Table 1. The mean age of the CAD group was significantly higher than that of the group without CAD (with CAD:  $72.23 \pm 10.82$  years, without CAD:  $66.73 \pm 11.25$  years,  $P < 0.001$ ). The prevalence of hypertension or total cholesterol concentration was also significantly different between the 2 groups (hypertension without CAD: 48.59%, hypertension with CAD: 67.53%,  $P = 0.011$ ; total cholesterol concentration without CAD:  $168.33 \pm 41.4$  mg/dL, total cholesterol concentration with CAD:  $153.16 \pm 41.47$  mg/dL,  $P = 0.021$ ). However, the 2 groups have comparable characteristics regarding diabetes, hyperlipidemia, and laboratory findings.

Although not statistically significant, the CAD group seemed to have less BMD of the spine and hip compared to the other group (spine BMD without CAD:  $-2.14 \pm 1.43$  g/cm<sup>2</sup>, spine BMD with CAD:  $-2.26 \pm 1.42$  g/cm<sup>2</sup>,  $P = 0.544$ ; hip BMD without CAD:  $-2.06 \pm 1.31$  g/cm<sup>2</sup>, hip BMD with CAD:  $-2.28 \pm 1.2$  g/cm<sup>2</sup>,  $P = 0.156$ ). In addition, the CAD group had higher prevalence of osteoporosis (63.64%) than the group without CAD (54.93%,  $P = 0.27$ ).

The number of CAD was increased markedly as patients were older ( $P$  for trend = 0.008). There were significant trends over the number of CAD toward increasing prevalence of hypertension and osteoporotic hip fracture (hypertension  $P$  for trend = 0.008; hip fracture  $P$  for trend = 0.011). The trend was independent of sex, other underlying diseases, other site-fracture (except to spine and hip fracture such as distal radius), and bone density (Table 2). Although the trend was not statistically significant, the prevalence of osteoporosis and spine fracture showed that an increasing trend as the number of CAD was increased.

To evaluate the risk factor for CAD, several candidate parameters were assessed in the total sample consisting of 77 CAD and 142 without CAD. All parameters were first tested by univariable logistic regression analysis. The following factors

**Table 1**  
**Characteristics of study subjects with or without cerebral artery disease.**

| Variable                      | No cerebral artery disease<br>(N = 142) | Cerebral artery disease<br>(N = 77) | Comparison<br>(P) |
|-------------------------------|---|-------------------------------------|-------------------|
| Demographic factor            |   |                                     |                   |
| Age, year                     | 66.73 ± 11.25                           | 72.23 ± 10.82                       | <0.001            |
| Sex                           | Male                                    | 24 (31.17)                          | 0.216             |
|                               | Female                                  | 53 (68.83)                          |                   |
| Smoking history               | 10 (7.04)                               | 11 (14.29)                          | 0.134             |
| Clinical factor               |   |                                     |                   |
| Hypertension                  | 69 (48.59)                              | 52 (67.53)                          | 0.011             |
| Diabetes mellitus             | 51 (35.92)                              | 31 (40.26)                          | 0.626             |
| Hyperlipidemia                | 35 (24.65)                              | 14 (18.18)                          | 0.354             |
| Fasting plasma glucose, mg/dL | 140.48 ± 64.96                          | 136.31 ± 61.02                      | 0.731             |
| Total cholesterol, mg/dL      | 168.33 ± 41.4                           | 153.16 ± 41.47                      | 0.021             |
| Creatinine, mg/dL             | 1.68 ± 8.77                             | 1.07 ± 0.63                         | 0.21              |
| HbA1c, %                      | 7.47 ± 1.39                             | 7.6 ± 1.8                           | 0.929             |
| AST, U/L                      | 26.92 ± 23.94                           | 24.01 ± 11.8                        | 0.849             |
| ALT, U/L                      | 22.62 ± 19.73                           | 17.7 ± 9.44                         | 0.206             |
| BMD-related factor            |   |                                     |                   |
| Drug for osteoporosis         | 46 (32.39)                              | 21 (27.27)                          | 0.528             |
| Spine BMD, g/cm <sup>2</sup>  | -2.14 ± 1.43                            | -2.26 ± 1.42                        | 0.544             |
| Hip BMD, g/cm <sup>2</sup>    | -2.06 ± 1.31                            | -2.28 ± 1.2                         | 0.156             |
| Osteoporosis                  | 78 (54.93)                              | 49 (63.64)                          | 0.27              |
| Fracture-related factor       |   |                                     |                   |
| Spine fracture                | 18 (12.68)                              | 11 (14.29)                          | 0.899             |
| Hip fracture                  | 9 (6.34)                                | 14 (18.18)                          | 0.012             |
| Other fracture                | 12 (8.45)                               | 3 (3.9)                             | 0.268             |

Values were presented as mean ± SD or count (%). P-values were computed by Chi-square test or Fisher exact test for categorical variables and Student t test or Mann-Whitney U test for continuous variables as appropriate. ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMD = bone mineral density, SD = standard deviation.

were found to be significant risk factors for CAD: age (OR = 1.05, 95% confidence interval [CI] = 1.02–1.08, P = 0.001), the presence of hypertension (OR = 2.2, 95% CI = 1.24–3.97, P = 0.008), total cholesterol (OR = 0.99, 95% CI = 0.98–1, P = 0.023), and the prevalence of hip fracture (OR = 3.28, 95% CI = 1.37–8.27, P = 0.009 by likelihood ratio statistic). Age and the prevalence of hypertension or hip fracture were positive related to CAD (Table 3).

The parameters tested by univariable analysis were next analyzed in a multivariable logistic regression analysis using AIC-based backward selection to drop insignificant terms from the model. This analysis resulted in a final model that included age, sex, hypertension, diabetes, hyperlipidemia, total cholesterol, the prevalence of osteoporosis, and osteoporotic hip fracture. The goodness-of-fit of the final model was assessed to be appropriate by Hosmer–Lemeshow statistic and Nagelkerke R<sup>2</sup>.

**Table 2**  
**Characteristics according to involving artery number of cerebral artery disease.**

| Variable                     | No cerebral artery disease<br>(N = 142) | 1 Vessel<br>(N = 34) | 2 Vessel<br>(N = 24) | ≥3 Vessel<br>(N = 19) | P for trend |
|------------------------------|---|----------------------|----------------------|-----------------------|-------------|
| Demographic factor           |   |                      |                      |                       |             |
| Age, year                    | 66.73 ± 11.25                           | 71.82 ± 10.53        | 72.46 ± 10.4         | 72.68 ± 12.33         | 0.008       |
| Sex                          | Male                                    | 9 (26.47)            | 9 (37.5)             | 6 (31.58)             | 0.137       |
|                              | Female                                  | 110 (77.46)          | 25 (73.53)           | 13 (68.42)            |             |
| Smoking history              | 10 (7.04)                               | 8 (23.53)            | 2 (8.33)             | 1 (5.26)              | 0.697       |
| Clinical factor              |   |                      |                      |                       |             |
| Hypertension                 | 69 (48.59)                              | 23 (67.65)           | 14 (58.33)           | 15 (78.95)            | 0.008       |
| Diabetes mellitus            | 51 (35.92)                              | 10 (29.41)           | 11 (45.83)           | 10 (52.63)            | 0.159       |
| Hyperlipidemia               | 35 (24.65)                              | 5 (14.71)            | 5 (20.83)            | 4 (21.05)             | 0.5         |
| BMD-related factor           |   |                      |                      |                       |             |
| Drug for osteoporosis        | 46 (32.39)                              | 7 (20.59)            | 8 (33.33)            | 6 (31.58)             | 0.821       |
| Spine BMD, g/cm <sup>2</sup> | -2.14 ± 1.43                            | -2.37 ± 1.49         | -2.19 ± 1.43         | -2.17 ± 1.34          | 0.874       |
| Hip BMD, g/cm <sup>2</sup>   | -2.06 ± 1.31                            | -2.1 ± 1.33          | -2.24 ± 1.16         | -2.68 ± 0.89          | 0.264       |
| Osteoporosis                 | 78 (54.93)                              | 19 (55.88)           | 16 (66.67)           | 14 (73.68)            | 0.085       |
| Fracture-related factor      |   |                      |                      |                       |             |
| Spine fracture               | 18 (12.68)                              | 3 (8.82)             | 4 (16.67)            | 4 (21.05)             | 0.353       |
| Hip fracture                 | 9 (6.34)                                | 4 (11.76)            | 8 (33.33)            | 2 (10.53)             | 0.011       |
| Other fracture*              | 12 (8.45)                               | 0 (0)                | 0 (0)                | 3 (15.79)             | 0.888       |

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMD = bone mineral density, SD = standard deviation.

\* Except to spine and hip fracture such as distal radius, values were presented as mean ± SD or count (%). P-values for trend were computed by Mantel–Haenszel test of trend and linear regression.

**Table 3****Logistic regression analysis with cerebral artery disease as a dependent variable.**

| Variable                       | Univariable |              |              | Multivariable |             |              |
|--------------------------------|-------------|--------------|--------------|---------------|-------------|--------------|
|                                | OR          | 95%CI        | P            | OR            | 95%CI       | P            |
| Age, year                      | 1.05        | (1.02–1.08)  | <b>0.001</b> | 1.04          | (1.01–1.08) | <b>0.016</b> |
| Female                         | 0.64        | (0.35–1.2)   | 0.164        | 0.82          | (0.38–1.8)  | 0.624        |
| Smoking history                | 2.2         | (0.88–5.54)  | 0.088        |               |             |              |
| Hypertension                   | 2.2         | (1.24–3.97)  | <b>0.008</b> | 1.69          | (0.82–3.51) | 0.157        |
| Diabetes mellitus              | 1.2         | (0.68–2.12)  | 0.526        | 1.04          | (0.5–2.17)  | 0.914        |
| Hyperlipidemia                 | 0.68        | (0.33–1.34)  | 0.275        | 1.06          | (0.44–2.58) | 0.894        |
| Fasting plasma glucose, mg/dL* | 1.02        | (0.59–1.86)  | 0.94         |               |             |              |
| Total cholesterol, mg/dL       | 0.99        | (0.98–1)     | <b>0.023</b> | 0.99          | (0.98–1)    | 0.165        |
| Creatinine, mg/dL*             | 1.26        | (0.67–2.49)  | 0.466        |               |             |              |
| HbA1c, %*                      | 1.29        | (0.08–21.63) | 0.858        |               |             |              |
| AST, U/L*                      | 0.79        | (0.39–1.52)  | 0.488        |               |             |              |
| ALT, U/L*                      | 0.6         | (0.36–0.99)  | 0.05         |               |             |              |
| Drug for Osteoporosis          | 0.78        | (0.42–1.43)  | 0.433        |               |             |              |
| Spine BMD, g/cm <sup>2</sup>   | 0.94        | (0.77–1.14)  | 0.542        |               |             |              |
| Hip BMD, g/cm <sup>2</sup>     | 0.87        | (0.69–1.09)  | 0.228        |               |             |              |
| Osteoporosis                   | 1.44        | (0.82–2.56)  | 0.213        | 0.88          | (0.41–1.89) | 0.751        |
| Spine fracture                 | 1.15        | (0.5–2.54)   | 0.737        |               |             |              |
| Hip fracture                   | 3.28        | (1.37–8.27)  | <b>0.009</b> | 1.43          | (0.44–4.63) | 0.549        |
| Other fracture                 | 0.44        | (0.1–1.44)   | 0.214        |               |             |              |
| Goodness-of-fit                |             |              |              |               |             |              |

Nagelkerke  $R^2 = 13.8\%$ H-L statistic = 3.75, DF = 8,  $P = 0.879$ 

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMD = bone mineral density, CI = confidence interval, DF = degree of freedom, H-L = Hosmer–Lemeshow, OR = odds ratio.

\* Natural logarithmic transformations were performed before analysis.

The adjusted ORs of age, hypertension, and hip fracture were 1.04 (95% CI = 1.01–1.08,  $P = 0.016$ ), 1.69 (95% CI = 0.82–3.51,  $P = 0.157$ ), and 1.43 (95% CI = 0.44–4.63,  $P = 0.549$ ), respectively. Although only age showed significant OR, the positive relation between these parameters and CAD was maintained. The OR of osteoporosis was changed from 1.44 (95% CI = 0.82–2.56,  $P = 0.213$ ) to 0.88 (95% CI = 0.41–1.89,  $P = 0.751$ ) after adjustment. All remained continuous variables in the final model generalized variance inflation factor (GVIF) of less than 5 (Table 3). Therefore, there was no multiple collinearity in this model.

In subgroup analysis, we assessed the effect of osteoporosis, bone density, and osteoporotic fracture on CAD according to the cranial side (extracranial vs intracranial). Two separated outcomes were analyzed in the way similar to that of total CAD as above.

For extracranial CAD, a similar pattern of results was observed as with total CAD. The unadjusted ORs of age, the prevalence of hypertension, and osteoporotic hip fracture in univariate logistic regression analyses were statistically significant (age: OR = 1.04, 95% CI = 1.02–1.07,  $P = 0.002$ ; hypertension: OR = 2.1, 95% CI = 1.15–3.9,  $P = 0.017$ ; and hip fracture: OR = 4.42, 95% CI = 1.83–11.21,  $P = 0.001$ ). However, the significance of OR of those factors in multivariate logistic regression analyses was different (age: OR = 1.03, 95% CI = 1–1.06,  $P = 0.079$ ; hypertension: OR = 1.44, 95% CI = 0.73–2.85,  $P = 0.298$ ; and hip fracture: OR = 3.05, 95% CI = 1.15–8.04,  $P = 0.024$ , Table 4). For intracranial CAD, an unadjusted OR of smoking history and antiosteoporosis drug use were statistically significant factors in univariate logistic regression analyses (smoking history: OR = 3.77, 95% CI = 1.23–10.53,  $P = 0.014$ ; use of drug for osteoporosis: OR = 0.28, 95% CI = 0.06–0.84,  $P = 0.043$ ). After adjustment for other factors, these significant relationships remained in multivariate logistic regression analyses for smoking history (OR: 4.55, 95% CI = 1.29–16.12,  $P = 0.019$ ) and for use of

antiosteoporotic drug (OR: 0.22, 95% CI = 0.06–0.83,  $P = 0.026$ , Table 5).

#### 4. Discussions

Osteoporosis and atherosclerosis are prevalent in the elderly. They have common clinical risk factors. Furthermore, shared pathophysiological factors of the 2 diseases, suggesting that the 2 diseases are closely related with 1 another.<sup>[11–14]</sup> However, the correlation between osteoporosis and atherosclerosis has not yet been clearly established in epidemiological or clinical studies. We would like to discuss association factor analysis between osteoporosis with CAD in this article. Unfortunately, these reports are rare and limited in scope. Therefore, we referred to relevant article such as association between osteoporosis and cardiovascular disease.<sup>[11]</sup>

Marcovitz et al<sup>[15]</sup> reported that osteoporosis in women is an independent risk of coronary artery disease even after adjusting for other risk factors such as high blood sugar, high blood pressure, and family history of cardiovascular disease. In a Multi-Ethnic Study of atherosclerosis, low BMD was associated with lower ankle-brachial index and intimal-medial thickness of extracranial internal carotid artery in men.<sup>[16]</sup> However, there are no association with intimal-medial thickness of common carotid artery in men.<sup>[11,16]</sup> The osteoporotic changes of the metacarpal bone was revealed to be associated with the progression of aortic calcification in women but not in men in the Framingham Heart Study.<sup>[16,17]</sup> Furthermore, a recent meta-analysis revealed that low BMD is associated with an increased stroke risk in women but not in men.<sup>[11]</sup> However, there were literatures showing different results. For example, Beer et al<sup>[8]</sup> found that low BMD is not associated with coronary heart disease done on 623 males. In our study, age, hypertension, high cholesterol, and the prevalence of hip fracture were found to be significant risk factors for CAD in univariate logistic regression analysis. In multivariate logistic

**Table 4**  
**Logistic regression analysis with extracranial cerebral artery disease as a dependent variable.**

| Variable                       | Univariable |              |              | Multivariable |             |              |
|--------------------------------|-------------|--------------|--------------|---------------|-------------|--------------|
|                                | OR          | 95%CI        | P            | OR            | 95%CI       | P            |
| Age, year                      | 1.04        | (1.02–1.07)  | <b>0.002</b> | 1.03          | (1–1.06)    | 0.079        |
| Female                         | 0.69        | (0.36–1.32)  | 0.253        | 0.64          | (0.31–1.34) | 0.238        |
| Smoking history                | 1.21        | (0.44–3.06)  | 0.7          |               |             |              |
| Hypertension                   | 2.1         | (1.15–3.9)   | <b>0.017</b> | 1.44          | (0.73–2.85) | 0.298        |
| Diabetes mellitus              | 1.28        | (0.7–2.31)   | 0.416        | 1.28          | (0.65–2.51) | 0.475        |
| Hyperlipidemia                 | 0.82        | (0.39–1.64)  | 0.584        | 0.96          | (0.44–2.07) | 0.912        |
| Fasting plasma glucose, mg/dL* | 1.22        | (0.68–2.39)  | 0.543        |               |             |              |
| Total cholesterol, mg/dL       | 0.99        | (0.99–1)     | 0.096        |               |             |              |
| Creatinine, mg/dL*             | 1.26        | (0.65–2.48)  | 0.467        |               |             |              |
| HbA1c, %*                      | 3.44        | (0.19–66.71) | 0.402        |               |             |              |
| AST, U/L*                      | 0.91        | (0.44–1.78)  | 0.794        |               |             |              |
| ALT, U/L*                      | 0.73        | (0.43–1.21)  | 0.228        |               |             |              |
| Drug for osteoporosis          | 1.01        | (0.53–1.88)  | 0.971        |               |             |              |
| Spine BMD, g/cm <sup>2</sup>   | 0.95        | (0.78–1.17)  | 0.649        |               |             |              |
| Hip BMD, g/cm <sup>2</sup>     | 0.8         | (0.63–1.02)  | 0.078        |               |             |              |
| Osteoporosis                   | 1.63        | (0.9–3.02)   | 0.113        | 1.15          | (0.55–2.4)  | 0.709        |
| Spine fracture                 | 1.29        | (0.55–2.9)   | 0.544        |               |             |              |
| Hip fracture                   | 4.42        | (1.83–11.21) | <b>0.001</b> | 3.05          | (1.15–8.04) | <b>0.024</b> |
| Other fracture                 | 0.57        | (0.13–1.88)  | 0.4          |               |             |              |
| Goodness-of-fit                |             |              |              |               |             |              |

Nagelkerke  $R^2 = 12.6\%$   
H-L statistic = 4.70, DF = 8,  $P = 0.789$

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMD = bone mineral density, CI = confidence interval, DF = degree of freedom, H-L = Hosmer–Lemeshow, OR = odds ratio.  
\* Natural logarithmic transformations were performed before analysis.

regression analysis, though, all associations except for that of age disappeared. However, the positive relationship was maintained. In subgroup analysis according to cranial side (extracranial vs intracranial), a similar pattern of results was observed for total cerebral and the extracranial cerebral artery group. In the intracranial CAD group, an unadjusted OR of smoking history

and antiosteoporosis drug use were found to be statistically significant risk factors.

Women with osteoporotic vertebral fractures had a higher risk of cardiovascular disease in a clinical study of osteoporosis.<sup>[7,14]</sup> Jørgensen et al<sup>[18]</sup> reported that patients with calcified plaque in the common carotid artery were at a high risk for nonvertebral

**Table 5**  
**Logistic regression analysis with intracranial cerebral artery disease as a dependent variable.**

| Variable                       | Univariable |              |              | Multivariable |              |              |
|--------------------------------|-------------|--------------|--------------|---------------|--------------|--------------|
|                                | OR          | 95%CI        | P            | OR            | 95%CI        | P            |
| Age, year                      | 1.03        | (0.99–1.07)  | 0.156        | 1.02          | (0.97–1.07)  | 0.412        |
| Female                         | 0.7         | (0.29–1.81)  | 0.435        | 0.94          | (0.3–2.9)    | 0.908        |
| Smoking history                | 3.77        | (1.23–10.53) | <b>0.014</b> | 4.55          | (1.29–16.12) | <b>0.019</b> |
| Hypertension                   | 1.84        | (0.78–4.69)  | 0.178        | 1.37          | (0.49–3.84)  | 0.546        |
| Diabetes mellitus              | 0.93        | (0.38–2.18)  | 0.874        | 0.82          | (0.3–2.27)   | 0.7          |
| Hyperlipidemia                 | 0.63        | (0.18–1.76)  | 0.42         | 0.73          | (0.21–2.51)  | 0.621        |
| Fasting plasma glucose, mg/dL* | 0.7         | (0.33–1.49)  | 0.293        |               |              |              |
| Total cholesterol, mg/dL       | 0.99        | (0.98–1)     | 0.119        |               |              |              |
| Creatinine, mg/dL*             | 1.21        | (0.44–2.51)  | 0.631        |               |              |              |
| HbA1c, %*                      | 0.05        | (0–4.96)     | 0.242        |               |              |              |
| AST, U/L*                      | 1.11        | (0.4–2.69)   | 0.826        |               |              |              |
| ALT (U/L)*                     | 0.9         | (0.43–1.83)  | 0.782        |               |              |              |
| Drug for osteoporosis          | 0.28        | (0.06–0.84)  | <b>0.043</b> | 0.22          | (0.06–0.83)  | <b>0.026</b> |
| Spine BMD, g/cm <sup>2</sup>   | 0.87        | (0.64–1.17)  | 0.376        |               |              |              |
| Hip BMD, g/cm <sup>2</sup>     | 0.9         | (0.63–1.25)  | 0.525        |               |              |              |
| Osteoporosis                   | 1.62        | (0.69–4.14)  | 0.285        | 2.55          | (0.83–7.9)   | 0.104        |
| Spine fracture                 | 1.29        | (0.35–3.73)  | 0.666        |               |              |              |
| Hip fracture                   | 1.19        | (0.26–3.83)  | 0.795        | 0.49          | (0.11–2.1)   | 0.335        |
| Other fracture                 | 1.21        | (0.18–4.76)  | 0.809        |               |              |              |
| Goodness-of-fit                |             |              |              |               |              |              |

Nagelkerke  $R^2 = 14.7\%$   
H-L statistic = 4.23, DF = 8,  $P = 0.836$

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMD = bone mineral density, CI = confidence interval, DF = degree of freedom, H-L = Hosmer–Lemeshow, OR = odds ratio.  
\* Natural logarithmic transformations were performed before analysis.



fractures. However, the risk of fractures in patients with echolucent plaque did not increase in a 6-year follow-up study of 2733 women.<sup>[14]</sup> Tanko et al<sup>[7]</sup> found postmenopausal women with osteoporosis are at an increased risk for cardiovascular events that is proportional to the severity of osteoporosis in Multiple Outcome of Raloxifene Evaluation Study. It was found that osteoporotic women had a 3.9-fold (95% CI, 2.0–7.7;  $P < 0.001$ ) increased risk for cardiovascular events compared with osteopenic patients.<sup>[7,19]</sup> The presence of at least 1 vertebral fracture had a 3.0-fold (95% CI, 1.8–5.1;  $P < 0.001$ ) increase in that risk in comparison of nonfracture.<sup>[7,19]</sup> Furthermore, cardiovascular risk was directly increased by the number and severity of baseline vertebral fractures.<sup>[7,19]</sup>

In our study, there was no correlation between vertebral fractures and cerebrovascular disease. However, the incidence of hip fractures was significantly higher in patients with cerebrovascular disease and in those with more atherosclerotic involvement in the cerebral artery.

There are some limitations in this study. First, the number of patients was relatively small compared to that in large-scale epidemiological studies. Also, because of the cross-sectional nature of our study, we could not estimate the effect size of the relationships. Thus, the practical formula of the sample size calculation was not adopted. Second, since this study was a cross-sectional study, it could only identify correlations. Third, additional markers of osteoporosis and skeletal health were not available.<sup>[16]</sup> Fourth, beta blockers, thiazide, and statins can affect BMD. However, this study did not assess patients' history of taking such drugs. Fifth, most patients were stroke-free adults who were worried about their health status that they paid sum of money for health check-up, which raised the possibility of a selection bias.

## 5. Conclusion

Some clinical factors such as age, hypertension, osteoporotic hip fracture, smoking history, and antiosteoporosis drug use were associated with CAD.

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