Bone Mineral Density and Stroke

Michael E. Mussolino, MA; Jennifer H. Madans, PhD; R.F. Gillum, MD

Background and Purpose—We sought to assess the long-term predictive usefulness of bone mineral density (BMD) for stroke incidence and stroke mortality.

Methods—The First National Health and Nutrition Examination Survey data were obtained from a nationally representative sample of noninstitutionalized civilians. A cohort of 3402 white and black subjects 45 through 74 years of age at baseline (1971 to 1975) was observed through 1992. Hospital records and death certificates were used to identify a total of 416 new stroke cases.

Results—Results were evaluated to determine the relative risk (RR) for stroke per 1-SD decrease in BMD, after controlling for age at baseline, smoking status, alcohol consumption, history of diabetes, history of heart disease, education, body mass index, recreational physical activity, and blood pressure medication. In Cox proportional-hazards analyses, incidence of stroke was not associated with a decrease in BMD in any of the 3 race-sex groups: white men (RR, 1.01; 95% CI, 0.86 to 1.19; \( P=0.88 \)); white women (RR, 1.13; 95% CI, 0.93 to 1.38; \( P=0.21 \)), or blacks (RR, 0.93; 95% CI, 0.72 to 1.21; \( P=0.60 \)). No association between BMD and stroke mortality was found (RR, 1.03; 95% CI, 0.86 to 1.23; \( P=0.77 \)).

Conclusions—In a large national study, no significant associations of BMD and stroke incidence or mortality were found for whites or blacks. (Stroke. 2003;34:e20-e22.)

Key Words: bone density ■ cohort studies ■ stroke

A cohort study of elderly women reported significant associations of low bone mineral density (BMD) and stroke death and incidence over a 2-year follow-up.\(^1,\(^2\)\) The early posthoc mortality findings raised the possibility that, if confirmed, further studies of the association might lead to the discovery of a mechanism linking calcium metabolism with cerebrovascular disease or at least a useful risk marker. A relationship between BMD and stroke was observed in a case-control study in which female but not male stroke patients had lower BMD than population control subjects.\(^3\) A large, cross-sectional analysis of stroke prevalence and BMD using data from the Third National Health and Nutrition Examination Survey (NHANES) found no significant association of BMD and stroke in men.\(^4\) There was some indication of elevated prevalence in women with BMD <0.936 g/cm\(^2\), but no dose-response relationship was found. To further investigate the relationship between BMD and stroke incidence, we used data from the NHANES I Epidemiological Follow-up Study (NHEFS) to assess the association of phalangeal BMD with 20-year stroke incidence and mortality.

Subjects and Methods
The NHEFS is a longitudinal study of participants in NHANES I who were 25 to 74 years of age at the time of the survey in 1971 to 1975.\(^5\) The personal interviews and physical and laboratory examinations of NHANES I provided the BMD and other baseline data for the NHEFS. The ascertainment of subsequent stroke occurrence in this analysis was based on 4 waves of follow-up data collection during 1982 to 1984, 1986, 1987, and 1992. Data collected consisted of 4 interview surveys, healthcare facility medical records for the period between baseline and last follow-up, and death certificates for all decedents.

This analysis was restricted to white and black persons 45 to 74 years of age at baseline in NHANES I. Of the 4107 subjects in this group who had been randomly selected from the general sample to receive detailed examination, including a single bone density measurement, 112 (total, 2.7%) were lost to follow-up (no subject or proxy interview at any follow-up wave) or had no death certificate. Excluded from all analyses were 99 subjects (2.4%) who had a history of stroke at baseline and 494 subjects (12.0%) with unknown baseline history of heart disease, diabetes history, weight, height, smoking status, alcohol consumption, blood pressure medication, recreational physical activity, or educational attainment, leaving 3402 for analysis. The length of follow-up for stroke-free survivors ranged from 8.5 to 21.8 years (median, 18.5 years), with >50 000 total person-years of follow-up.

Incident stroke cases met at least 1 of the following criteria: (1) a death certificate with underlying or nonunderlying cause of death coded 431 to 434.9, 436, or 437.0 to 437.1 from the International Classification of Diseases, ninth revision (ICD-9), or (2) \( \geq \)1 hospital and/or nursing home stays during the follow-up period with any discharge diagnosis coded 431 to 434.9, 436, or 437.0 to 437.1 from the clinical modification of ICD-9 (see the Appendix, which is available online at http://stroke.ahajournals.org). The date of incidence was estimated as 1 of the following: date of first hospital admission with a stroke diagnosis or date of death for persons dying...
RRs* for Stroke Incidence According to Bone Mineral Density Measurement in Persons Aged 45–74 Years at Baseline: NHANES I Epidemiologic Follow-up Study

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>RR Adjusted†</th>
<th>Risk Adjusted†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>n</td>
<td>Age Adjusted (95% CI)</td>
</tr>
<tr>
<td>White men</td>
<td>178</td>
<td>1424</td>
<td>1.01 (0.86–1.19)</td>
</tr>
<tr>
<td>White women</td>
<td>167</td>
<td>1546</td>
<td>1.14 (0.94–1.37)</td>
</tr>
<tr>
<td>Blacks</td>
<td>71</td>
<td>432</td>
<td>0.92 (0.72–1.19)</td>
</tr>
</tbody>
</table>

*RRs and 95% CIs are based on a decrease of 1 SD in bone mineral density.
†Adjusted for baseline age, smoking status, alcohol consumption, history of diabetes, history of heart disease, education, body mass index, recreational physical activity, and blood pressure medication. Sex is included in age- and risk-adjusted models for blacks.

of stroke without any stroke hospital records. A total of 416 new stroke cases were identified.

Phalangeal BMD was determined from a baseline x-ray of the left hand by use of radiographic absorptiometry and reported in arbitrary units (AU). The radiographic absorptiometry process uses direct exposure (nonscreen) radiographs of the participant’s left hand alongside an aluminum alloy reference wedge, which are digitized by a high-resolution camera for computer analysis.6,7 Radiographic absorptiometry has been found to have excellent precision and accuracy (precision error: 1%; accuracy error: 4.8%) and to correlate well with other accepted methods of bone densitometry.8

Baseline age, smoking status, alcohol consumption, blood pressure medication use, educational attainment, and physical activity level were obtained by interview, and body mass index was calculated from measured height and weight. History of heart attack and diabetes was based on self-reported doctor’s diagnoses. Estimates of the risk of stroke for persons according to BMD derive from Cox proportional-hazards regression models computed with the PHREG procedure.9 Proportional-hazards assumptions were tested by methods using plots and time-dependent covariates.9 Separate analyses were carried out for white men, white women, and blacks. Small sample sizes did not permit sex-specific models for blacks. BMD was treated as a continuous variable, and estimates of risk of stroke were calculated for people with values of 1 SD below the mean compared with the mean. To assess the effect of complex survey design on the results, Cox proportional-hazards regression analyses were confirmed by use of the survival procedure in SUDAAN to incorporate the stratification, clustering, and sample weights.10

Results

No statistically significant differences in age-adjusted mean BMD at baseline with versus without stroke were found for white men (101.7 versus 101.1 AU, P=0.57), white women (95.8 versus 97.0 AU, P=0.29), and blacks (102.6 versus 100.1 AU, P=0.15). The number of incident cases of stroke by race and sex is shown in the Table. In stroke-free survivors, the length of follow-up averaged 18.7 years. In Cox proportional-hazards analyses, the incidence of stroke was not associated with a 1-SD decrease in BMD in any of the 3 race-sex groups (Table). No significant associations were found among white men (P=0.88), white women (P=0.21), or blacks (P=0.60). Results remained the same when the SAS-callable SUDAAN survival procedure was used to check for changes in stroke relative risk (RR) after using sampling weights. To exclude nonlinear associations, RR was estimated in a model with dummy variables for BMD tertiles for white women. With the first tertile serving as the reference group, the RR of stroke in the highest tertile was 0.75 (95% CI: 0.47 to 1.22, P=0.24) in multivariate analyses. In an analysis of BMD and stroke mortality (any mention on death certificate, n=169), the 3 race-sex groups were combined (controlling for sex and race in addition to other variables) because of the small number of deaths from stroke. No association between BMD and stroke mortality was found (RR, 1.03; 95% CI, 0.86 to 1.23; P=0.77).

Discussion

This article reports one of the few longitudinal studies of BMD and incidence of stroke and is the first to use a biracial cohort of women and men. No association of phalangeal BMD was found with the subsequent development of stroke. Controlling for baseline age and other potential confounding factors failed to alter this finding. (Unfortunately, BMD at proximal sites was not measured.) This is consistent with the fact that no satisfactory causal mechanism for the previously reported association of BMD and stroke incidence or death has been discovered.1–5 Low BMD may serve as a marker of other causes of stroke in some samples. For example, the possibility that both osteopenia and stroke may result from low relative lifetime exposure to estrogen in women or low vitamin D and its metabolites, which might affect vascular reactivity, has been raised.1,4 Osteoprotegerin, a cytokine that regulates osteoclastogenesis, was not found to be related to BMD or incidence of stroke in white women despite associations with hypertension and diabetes.11 A diet high in protein (acids) and salt but low in potassium might aggravate osteoporosis and increase risk of stroke.3,12 Essential hypertension may be associated with increased mobilization of calcium from bone.12 Stroke-prone spontaneously hypertensive rats have lower femoral BMD than Wistar-Kyoto control rats.13,14 However, treatment with antihypertensive agents prevented stroke but not decreased BMD.13 Thus, further in vitro and in vivo research is needed to determine whether a biological mechanism exists for an association of BMD with stroke incidence reported by others. It is important to exclude a causal association of BMD with stroke because, in clinical practice, finding low BMD in a woman may result in prescribing estrogen-replacement therapy, which itself may increase the risk of stroke.15

In summary, in a large national study, no significant associations of BMD and stroke incidence or mortality were found for whites or blacks.

References


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