Bone Mineral Density in Acute Stroke Patients
Low Bone Mineral Density May Predict First Stroke in Women

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Background and Purpose—Osteoporosis and stroke share several risk factors, including age, smoking, low physical activity, and hypertension. Thus, low bone mineral density (BMD) and high stroke risk may be related. We examined the relationship between BMD and acute stroke in noninstitutionalized men and women aged ≥60 years.

Methods—Sixty-three stroke patients (33 women and 30 men) and 188 control subjects from the general population were included. BMD was measured by using dual-energy x-ray absorptiometry at both proximal femurs. The measurements of the stroke patients were performed 6 days after the onset of stroke.

Results—The BMD at the femoral neck in the female stroke patients was 8% lower than in the control subjects (P = 0.007).

Conclusions—Female, but not male, stroke patients have lower BMD than population controls. Low BMD may predict stroke in women. (Stroke. 2001;32:47-51.)

Key Words: bone mineral density • osteoporosis • risk factors • stroke, acute

Osteoporosis and stroke share several risk factors, such as age, smoking, low level of physical activity, and hypertension.1–9 Low bone mineral density (BMD) and a high risk of stroke may thus be related, but studies on this relationship are sparse. Browner et al10,11 have shown that low BMD is significantly related to stroke mortality and stroke incidence in a female population, but no data are available for men. An examination of the association between BMD and stroke is of clinical importance for 2 reasons. First, if BMD is low in acute stroke patients, it may be an important explanatory factor for the increased risk of hip fracture in stroke patients.12,13 This risk factor will thus add to other known risk factors, such as the increased incidence of falls11–13 and the increased rate of bone loss.14–16 Second, low BMD may predict stroke.

The purpose of the present study was to examine the relationship between BMD and acute stroke in a case-control study among noninstitutionalized men and women aged ≥60 years.

Subjects and Methods

Cases
The stroke patients included in this study were identified from among all acute stroke patients aged ≥60 years from the municipality of Tromsø, Norway, consecutively admitted to The University Hospital in Tromsø from June 1, 1996, through August 31, 1997. This hospital is the only one in the area, and all persons with acute stroke from the municipality are admitted to this hospital.

Stroke was defined according to the definition of the World Health Organization, WHO.17 The diagnosis was based on a doctor’s clinical examination and an evaluation of all available information from the hospital medical records and was supported by anatomic cerebral changes on CT scans. A specialist in internal and geriatric medicine at the University Hospital (T.E.), blinded to the BMD measurements, validated all stroke diagnoses. Patients who had not been able to walk without personal support before the stroke and patients who were unable to answer simple questions, including informed consent, were excluded. Other exclusion criteria were history of previous stroke, unconsciousness and terminal illness, presence of osteosynthetic material in the femoral neck, and history of hip fracture.

Among a total of 125 stroke patients admitted to the hospital, 64 were eligible for the study and 63 agreed to participate. Five of them had intracerebral hemorrhages. Sixty-one patients (49%) were not eligible for the study because of death, unconsciousness, or severe disorientation during the first week after stroke (n = 30); previous strokes (n = 23); or a history of hip fracture or presence of osteosynthetic material in the femoral neck (n = 6). Two patients were not enrolled in the study because of femur amputation and cancer with metastasis to the bone.

Controls
The control subjects were randomly selected from the population register of Tromsø in 1998 and invited by letter to participate in the study. For each gender and 5-year age bracket, we invited more than...
twice the number of case patients in order to obtain a sufficient number. The letter of invitation contained information about the aim of the study, the criteria for exclusion (ie, hip fracture, presence of osteosynthetic material in the femoral neck, and stroke), and the fact that transportation to the hospital on the day of the examination would be provided if the attendees were unable to travel on their own.

Among the 404 invited possible control subjects, 197 (49%) agreed to be enrolled in the study. All of them had a medical record in the hospital, and to exclude possible unreported stroke these records were all reviewed by an experienced physician (T.E.). Six men and 3 women were found to have had a previous stroke and were thus excluded from the analysis.

Informed consent was obtained from all participants according to the Second Helsinki Declaration, and the Regional Committee for Medical Research Ethics approved the trial.

### Methods
All participants were interviewed about their alcohol and smoking habits: whether they were teetotalers, and whether they smoked currently or had smoked previously. The stroke patients were asked whether they had used assistive devices for walking before the stroke, and the control subjects were asked about current use of these devices. Body weight and height was mostly measured in a standing position, except for 27 of the stroke patients who had their height measured in a supine position, as they were unable to stand. The body mass index (BMI) was calculated as the weight (in kilograms) divided by the square of the height (in meters). Stroke severity was assessed by use of the Scandinavian Stroke Scale (SSS).18 –19 in the hospital, and to exclude possible unreported stroke these records were all reviewed by an experienced physician (T.E.). Six men and 3 women were found to have had a previous stroke and were thus excluded from the analysis.

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### Statistical Analysis
To test differences between the case and control groups, χ² test, the Fisher exact test or Student 2-sample t test was used. Statistical correlations between SSS and BMD were evaluated by using the Spearman rho (r).

For men and women separately, the control subjects were divided into quartiles with respect to the BMD values, and the case patients were categorized according to these quartiles. ORs for stroke in the different quartiles as well as with a 1-SD change in BMD were estimated by use of logistic regression analysis. Adjustments were done for potential confounders found to be related to the case-control status in one or both sexes with P≤0.1.

The data were analyzed with the Windows 7.5 version of the Statistical Package for the Social Sciences (SPSS, Inc).

### Results

#### Characteristics of the Cases and Their Controls

All the cases and all the controls were living in their own homes before the hospitalization or examination. The patients were measured a mean of 6 (SD 4) days after the stroke onset. There was no difference between the paretic and nonparetic side with respect to BMD, and this was also true for the 14 most severely affected stroke patients (SSS score 0; mean difference between the paretic and nonparetic leg 0.009 g/cm²; P=0.7).

Table 1 shows the characteristics of the cases and controls. Female stroke patients had a statistically significant 8% lower age-adjusted BMD of the femoral neck than the control men. In the analysis we used the mean values from the right and left side. All the measurements were done by 2 operators (L.J. and E.H.), and all the scans were analyzed by the same technician (L.W.). The interoperator precision (SD/mean) was 2.2%, tested by measuring BMD twice in 10 of the participants (mean age 67 years). The 2 measurements were done consecutively during the same day, with an interval of 2 to 3 minutes. Subjects were repositioned between each scan by the operators.

The longitudinal drift assessed with daily phantom measurements was <1%.

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observed. We concluded that no important effect of the adjustments was present at stroke onset, the severe bone loss thereafter 14–16 was associated with a 1.9-fold increase in stroke. Among women, no statistical significant relationship between BMD and stroke was found (Table 1 and 2).

In the present study we found that female stroke patients had lower BMD in the femoral neck than did population controls, a result consistent with those of Browner et al.10,11 They showed that low BMD in the calcaneus and proximal radius (but not in the distal radius) was associated with an increased stroke risk in women (RR 1.3 per SD decrease in BMD), whereas we found that the risk was somewhat higher. We measured BMD in the proximal femur, which is the most relevant region of interest to evaluate with respect to the risk of hip fracture,20–22 Consequently, if low BMD is already present at stroke onset, the severe bone loss thereafter14–16 puts the female stroke patients at a particularly high risk of hip fracture. The result of the present study, therefore, has considerable clinical implications regardless of what the causal relationship might be.

We did not find any relationship between stroke risk and low BMD in men; to our knowledge, this topic has not been studied previously. Although Johansson et al23 did show that BMD was a strong predictor of total mortality in men as well as women, the number of fatal stroke was too low to evaluate the relationship between BMD and stroke mortality.

Because of our study design, some bias cannot be excluded. First, the BMD in the patients was measured 6 days after stroke onset. In a previous longitudinal study, we showed that patients who were completely wheelchair-bound had a significant 3% BMD loss in the femoral neck on the paretic side and a nonsignificant 1% loss on the nonparetic side 2 months after stroke.14 The BMD difference of 8% between the female cases and their controls cannot, therefore, be explained by the bone loss that may have occurred between stroke onset and the BMD measurement 1 week later. Furthermore, there was no difference between the BMD values of the paretic and the nonparetic legs. This also indicates that no change in BMD had taken place before the measurement.

Second, there may be a bias connected to the enrolment of the control subjects. Only one eligible stroke patient refused to participate in the study, whereas 51% of the invited controls abstained, including an unknown number of individuals who were not eligible due to eg, previous stroke or hip fracture/osteosynthetic material in the femoral neck. The control subjects were told in the letter of invitation that they could participate in the study only if they had no history of stroke or hip fracture, but also that they could refuse to participate without giving any reason for this decision. Thus, we do not know the proportion of possible controls contacted who did not take part in the study due to the exclusion criteria or for other reasons. We did expect that a higher proportion of the control subjects were more likely to respond if they were ill and therefore wanted to participate in a medical research study. If so, the prevalence of risk factors may be overestimated and the BMD in the controls most probably underestimated. In particular, some female control subjects with known osteoporosis may have participated to have their BMD assessed, but as a consequence this would reduce the mean BMD in the control women and thus cannot explain our results. When we excluded women with

### Table 2. Unadjusted and Adjusted ORs for Stroke Among Women and Men According to Femoral Neck BMD Quartiles

| BMD Quartiles | Women | | | Men | | |
|---------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Cases, Controls, OR, Mean (95% CI) | Cases, Controls, OR, Mean (95% CI) | | | | |
| | | | | | |
| 1 | 19 | 26 | 4.8 (1.4–15.9) | 6.6 (1.8–24.8) | 6 | 21 | 0.9 (0.3–3.1) | 0.6 (0.1–2.3) |
| 2 | 6 | 25 | 1.6 (0.4–6.2) | 1.8 (0.4–7.4) | 6 | 22 | 0.9 (0.3–3.0) | 0.6 (0.2–2.4) |
| 3 | 4 | 24 | 1.1 (0.2–4.8) | 1.6 (0.3–7.5) | 11 | 22 | 1.6 (0.5–4.8) | 1.4 (0.4–4.7) |
| 4 | 4 | 26 | 1.00 | 1.00 | 7 | 22 | 1.00 | 1.00 |

**P for linear trend** 0.003 0.003 0.6 0.2

* BMD range for women: ≤0.707, 0.708–0.777, 0.778–0.873, ≥0.874; BMD range for men: ≤0.780, 0.781–0.884, 0.885–1.010, ≥1.011.
†Adjusted for BMI, alcohol drinking, previous myocardial infarction, and medication for hypertension.
known osteoporosis from our analysis, the difference in mean BMD in female stroke patients and controls was unchanged. We have also compared data from our control group with data from a population survey in Tromsø, which had a 77% response rate. The prevalence of risk factors in this group was similar to or even lower than that given for the control group in Table 1. Thus, the controls in our study were not a particular healthy group of people. In conclusion, we do not find it likely that selection bias can explain our findings.

The information about current use of medication and current and previous diseases were obtained from the medical records of the stroke patients, whereas the control subjects answered a questionnaire. This may have introduced response bias and hampered effective control for confounders. It is, nevertheless, reassuring that we found more people with previous myocardial infarction and more use of medication for hypertension among the stroke patients, although only the difference in use of medication for hypertension in women was statistically significant. Unfortunately, the information about some of the possible confounders (eg, physical activity, smoking, and alcohol) was not so detailed that residual confounding can be excluded. However, this is of major importance only if a causal relationship between low BMD and stroke is considered.

At present, it is unclear whether there is a cause-and-effect relationship between low BMD and high risk of stroke. Previous investigators have argued against a causal relation and suggested that low BMD is, rather, a marker of poor general health and aging. There is, however, several possible links between osteoporosis and stroke, because both conditions may be related to estrogen deficiency, diabetes, hypertension (and use of medication to treat hypertension), low level of physical activity, and smoking.  More over, high blood pressure, an established risk factor for stroke, has been associated with increased bone loss at the femoral neck in elderly women.

A salient finding in our study was the inverse relationship between BMD and stroke in women but not in men. This may indicate that estrogen deficiency may play an important part in this relationship. Estrogen replacement may reduce the risk of both stroke and osteoporosis, although the results are inconsistent. Because we considered the medical records of the cases (from which information about medication was extracted) to be unreliable with respect to information about use of estrogens, it was impossible to adjust for this medication. However, when persons known to use estrogen were excluded, the mean BMD value of the controls was essentially unchanged.

In conclusion, we found that female, but not male, stroke patients have lower BMD than population controls. Our results confirm the findings of previous studies about women and provide for the first time information about the relationship in men. We call for new studies to confirm or refute these findings, also because our study has limited statistical power. At present, it is unclear whether low BMD actually increases the risk of stroke or reflects poor health with both high stroke risk and low BMD. We believe that it is premature to reject a causal relationship; sometimes the biological understanding comes after the epidemiological finding. In any case, because female stroke patients have a low BMD (for whatever the reason), this emphasizes even more the need for an aggressive attitude in poststroke rehabilitation.

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References


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