Low Bone Mineral Density Is Related to Echogenic Carotid Artery Plaques: A Population-based Study

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In a 1994–1995 cross-sectional, population-based study of 2,543 men and 2,726 postmenopausal women aged 55–74 years in Tromsø, Norway, the authors assessed a possible relation between bone mineral density (BMD) and the prevalence of carotid artery plaques, with an emphasis on plaque morphology. BMD measurements of the forearm and ultrasonography of the carotid artery were performed. Study participants were divided into quartiles with respect to sex-specific BMD values. Prevalent plaques were categorized into four groups ranging from low echogenicity to high echogenicity. For echogenic plaques, a significant inverse correlation with BMD was found (p for linear trend = 0.007 after adjustment for age, sex, and cardiovascular risk factors). For predominantly echogenic plaques, a similar but weaker association was indicated (p = 0.08); for predominantly echolucent and echolucent plaques, no significant associations were observed (p ≥ 0.3). Subjects whose BMD values were in the highest quartile had a statistically significant lower risk of echogenic plaques than subjects whose BMD values were in the lowest quartile (odds ratio = 0.51, 95% confidence interval: 0.31, 0.83).

This study indicates that low bone mass is associated with an increased risk of echogenic calcified atherosclerotic plaques but not with a risk of echolucent plaques.

arteriosclerosis; bone density; calcification, physiologic; carotid arteries; ultrasonography

Abbreviations: BMD, bone mineral density; CI, confidence interval.

A possible relation between atherosclerosis and osteoporosis, two of the most prevalent chronic diseases in the Western world, is intriguing. Age is a major risk factor for both conditions. However, most (1–7), but not all (8–12) studies have indicated that, after adjustment for age, arterial calcification is associated with low bone mass. This finding suggests that for atherosclerosis and osteoporosis, there are other common etiologic factors.

Although the relation between bone mass and vascular calcification has been assessed in several studies (1–12), we know of none that has considered the association between bone mass and atherosclerotic plaques other than those harboring calcium deposits (e.g., lipid-rich plaques). Morphologic characteristics of carotid intraplaque structures may be evaluated with ultrasound. Plaques that only poorly reflect ultrasound (echolucent plaques) have a high content of lipid, necrotic debris, and/or hemorrhage, whereas plaques that strongly reflect ultrasound (echogenic plaques) have a higher content of dense fibrous tissue and calcified material. Studying the association between bone mineral density (BMD) and carotid plaques with different morphologies (fibrous, calcified plaques vs. lipid-rich plaques) may lead to a better understanding of the possible interrelation between osteoporosis and atherosclerosis and the etiology of both disease processes.

The purpose of this population-based study was to examine whether BMD is independently related to the prevalence of carotid plaques. Our specific emphasis was on plaque morphology in terms of echogenicity.

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MATERIALS AND METHODS

The Tromsø Study is an ongoing, population-based study of inhabitants of the municipality of Tromsø, Norway. The study has been approved by the Regional Committee for Medical Research Ethics, and all subjects have given informed consent.

In the fourth survey conducted in 1994–1995, all inhabitants aged 25 years or older were invited to a screening. The protocol was similar to that used in the previous surveys of this population (13) and included standardized measurements of, for example, height, body weight, blood pressure, and nonfasting serum lipids. Body mass index was calculated as weight divided by the square of height (kg/m²). Blood pressure was recorded before blood sampling in a separate, quiet room with only a nurse present. An automatic device (Dinamap Vital Signs Monitor 1846; Criticon, Inc., Tampa, Florida) was used. Serum total cholesterol was analyzed by enzymatic colorimetric methods with a commercial kit (CHOD-PAP; Boehringer-Mannheim, Mannheim, Germany), and serum high density lipoprotein cholesterol was measured after precipitation of lower density lipoprotein with manganese chloride (14).

The participants completed a self-administered questionnaire (included in the invitation) comprising questions about smoking habits, prevalent diabetes mellitus or angina pectoris, previous myocardial infarction or stroke (all yes/no), treatment for hypertension (never/previous/current), and physical activity. We defined persons as physically inactive if they reported that, during their leisure time, they were never so active that they sweated or were out or breath and that they had been lightly active only (not sweating or out of breath) for less than 3 hours per week during the past year. A second questionnaire handed out during the screening included more detailed questions about food habits, from which dietary intake of calcium and vitamin D was calculated (15), and about the use of drugs.

All attending subjects aged 55–74 years were invited to a second visit 4–12 weeks after the first. At the second visit, more extensive examinations were carried out, including BMD measurements and carotid artery ultrasonography. Personnel performing ultrasound and BMD measurements had no knowledge of the results of the other examinations, the questionnaires, or laboratory data. Parathyroid hormone levels were measured, as reported previously (16), by an Immulite intact parathyroid hormone assay (Diagnostic Products Corporation, Los Angeles, California) in a subgroup of 2,702 men and women. A total of 5,339 subjects (77 percent of the total population of Tromsø aged 55–74 years, and 85 percent of those in this age group who attended the first visit) had both their BMD measured and ultrasonography of the carotid arteries performed.

In the present cross-sectional analysis, we included all male subjects (n = 2,543) and all postmenopausal women aged 55–74 years (n = 2,726) for whom both BMD measurements and carotid artery ultrasonography were available. Women were defined as postmenopausal if they were aged 60 years or older or were aged 55–59 years and reported that they had stopped menstruating. Ten women aged 55–59 years who reported that they were still menstruating and 60 women who did not answer the question regarding postmenopausal status were excluded.

Bone densitometry measurements

BMD of the distal and ultradistal forearm was assessed by one of two single x-ray absorptiometry devices (DTX-100; Osteometer MediTech, Inc., Hawthorne, California) (17). The distal and ultradistal regions of interest were detected automatically. The distal site includes both the radius and the ulnae from the 8-mm point (the point at which the ulnae and the radius are separated by 8 mm) and 24 mm proximally. The ultradistal site includes only the radius and stretches from the 8-mm point up to the radial endpoint. For 99 percent of the subjects, BMD at the distal and ultradistal sites of the nondominant forearm was measured; however, for 1 percent of the subjects, the dominant forearm was measured because of plaster casts, wounds, and so forth, on the nondominant arm.

Quality control with respect to precision, long-term stability, detection, and correction of artifacts has been described in detail elsewhere (17, 18). We reviewed all scans to detect and correct possible artifacts, and we adjusted for systematic BMD differences between the two densitometers before analysis (17). A total of 111 subjects had repeated measurements. The median coefficients of variations for two scans performed 1 week apart by two different operators were 0.79 percent and 0.98 percent at the distal and ultradistal sites, respectively (18).

Ultrasonography of the carotid artery

Carotid atherosclerosis was assessed by use of high-resolution B-mode and color Doppler/pulsed-wave Doppler ultrasonography performed with an ultrasound scanner (Acuson 128-XP10 ART-upgraded; Acuson Corporation, Mountain View, California) equipped with a linear array transducer (19). We attempted to identify and record atherosclerotic plaques from six sites of the right carotid artery: the near and far walls of both the internal carotid, the bifurcation, and the common carotid as far downstream of the supraclavicular region as possible. A plaque was defined as a localized protrusion of the intimal part of the vessel wall into the lumen. Maximum plaque thickness was measured by using frozen B-mode images marked with electronic calipers whose readout was noted in tenths of a millimeter. If more than one plaque was present at one site, only the thickest one was included in the analysis. The extent of atherosclerosis was defined as the sum of the thickness (in millimeters) of all plaques present in the artery (from one to six plaques).

Plaque morphology in terms of echogenicity, defined as reflectance of the emitted ultrasound signal, was assessed by use of a visual analogue technique along a grey scale (19). Plaques that appeared black or almost black (such as fluent blood inside the vessel) were described as grade 1 (echolucent, low echogenic), whereas plaques that appeared white or close to white (echogenic), similar to the bright echo zone produced by the media-adventitia interface in the far wall of the carotid artery, were classified as grade 4. Grade 2 and 3 plaques were interpolated between grade 1 and grade 4 along
the black-white scale, the grade 2 plaques consisting of more echoluent than echogenic materials and the grade 3 plaques vice versa. If one single plaque was present and the echogenicity inside this plaque was heterogeneous, the dominant echogenicity determined the grading. When more than one plaque was present, echogenicity was graded by considering the overall plaque area. For 122 subjects, plaque morphology was defined as unclassifiable because of unsatisfactory image quality (19).

Ultrasoundography of the carotid artery was performed by three ultrasonographers. The between- and within-sonographer reproducibility of ultrasound assessment of plaque occurrence and thickness was estimated by repeated scanning of a random sample of 107 participants (19). The mean absolute differences between sonographers varied between 0.25 mm and 0.55 mm, and the coefficients of variation were between 17.9 percent and 22.4 percent. The mean absolute differences within sonographers varied between 0.28 mm and 0.36 mm, and the coefficients of variation were between 13.7 percent and 15.1 percent. The between- and within-sonographer agreement on plaque occurrence was satisfactory, with kappa values of 0.72 (95 percent confidence interval (CI): 0.60, 0.84) and 0.76 (95 percent CI: 0.63, 0.89), respectively. Agreement on classification of plaque echogenicity, determined by repeated reading of videotaped images of 119 randomly selected arteries with plaques, was also substantial, with kappa values of 0.73 (95 percent CI: 0.59, 0.87) and 0.69 (95 percent CI: 0.55, 0.83) between and within sonographers, respectively (19).

Statistical analysis

We included three different types of dependent variables in our analyses: whether or not a plaque was present, plaque morphology (graded 1–4 according to increasing echogenicity), and the extent of atherosclerosis (assessed by the sum of six plaque thicknesses in millimeters). Mean values of characteristics of subjects in different plaque groups were found after adjustment for sex and age by using analysis of covariance. Multiple linear regression analysis was performed to evaluate the impact of BMD (and multiple covariates) on the extent of atherosclerosis.

The subjects were divided into quartiles according to sex-specific BMD values. We estimated the odds ratios for the presence of plaque versus no plaque, echogenic plaque versus no plaque, predominantly echogenic plaque versus no plaque, predominantly echoluent plaque versus no plaque, and echoluent plaque versus no plaque in the different quartiles by using logistic regression analysis with adjustment for potential confounders. In all analyses of plaque echogenicity, the 122 subjects whose plaques were unclassifiable were excluded. In the other analyses, these subjects were included. Interaction terms with age were included in the models in separate analyses. For the subjects with plaques, the association between plaque echogenicity and BMD was also tested by cumulative ordinal logistic regression analysis, where plaque echogenicity (graded in categories from 1 to 4) was the dependent variable and BMD and several covariates were independent variables. The model deals with the odds ratio of being in a lower (i.e., more echoluent) category of the dependent variable relative to the higher categories. This was a joint analysis for several choices of case groups, and the comparison group included in each situation the subjects with plaques of higher echogenicity.

The possible confounding variables were all selected before the analyses were conducted. Age, sex, body mass index, blood pressure, serum total cholesterol, serum high density lipoprotein cholesterol, smoking, and physical inactivity were included in the main analysis because they are well-known risk factors for atherosclerosis. Age, sex, body mass index, smoking, and physical inactivity are also associated with BMD. Furthermore, BMD may be influenced by serum lipid levels (20–23) and diabetes (24). It has also been shown that high blood pressure predicts bone loss in women (25).

The data were analyzed by using the Windows 11.0 version of SPSS software (SPSS Inc., Chicago, Illinois) and the LOGISTIC procedure in the eighth version of the SAS software package (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Associations between BMD, plaque prevalence, and extent of atherosclerosis

Of the 5,269 persons included in the study, 2,326 had no plaques and 2,943 had at least one. Selected characteristics of the study group are presented in table 1. Significant differences between groups were found with respect to age, sex, body mass index, systolic blood pressure, level of serum total cholesterol, level of serum high density lipoprotein cholesterol, smoking status, prevalence of cardiovascular disease, and use of medication for hypertension. Furthermore, BMD at the distal and ultradistal sites of the forearm differed between the groups.

After adjustment for all relevant confounders, we found no significant linear association between distal forearm BMD and the presence of any plaque (table 2). Furthermore, no statistically significant relation was found between BMD and the extent of atherosclerosis, either among subjects with plaques in general (table 3) or between BMD and the extent of atherosclerosis within each of the four categories of echogenicity (p for linear trend over the quartiles = 0.3 for subjects with echogenic plaques, p for linear trend ≥ 0.8 in the three other groups, after adjustment for possible confounders; results not shown in tables).

Associations between BMD and prevalence of plaques of different echogenicity

Subjects whose distal forearm BMD values were in the highest quartile had a 49 percent lower risk of echogenic plaques than subjects whose BMD values were in the lowest quartile (p for linear trend = 0.007; table 4).

A nonlinear association may be suggested between BMD and plaques of high echogenicity (table 4), but a test for nonlinear effects was not statistically significant (p = 0.3). The results could reflect a high prevalence of echogenic plaques in subjects whose BMD is very low. However, when
we divided BMD into sex-specific deciles, we found a relatively high prevalence of echogenic plaques in all of the three lowest deciles (results not shown).

**Table 4** displays a systematic pattern: For echogenic plaques, a significant inverse correlation was found; for predominantly echogenic plaques, a similar, weaker associa-

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**Table 1.** Characteristics of subjects without carotid artery plaques and those with echogenic, predominantly echogenic, predominantly echolucent, echolucent, and unclassifiable plaques, the Tromsø Study, Norway, 1994–1995

<table>
<thead>
<tr>
<th>Without plaques (n = 2,326)</th>
<th>Echogenic (n = 174)</th>
<th>Predominantly echogenic (n = 1,592)</th>
<th>Predominantly echolucent (n = 937)</th>
<th>Echolucent (n = 118)</th>
<th>Unclassifiable (n = 122)</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (mean (SE))</td>
<td>62.3 (0.1)</td>
<td>65.8 (0.4)</td>
<td>65.3 (0.1)</td>
<td>64.3 (0.2)</td>
<td>63.4 (0.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>42</td>
<td>39</td>
<td>53</td>
<td>57</td>
<td>53</td>
<td>40</td>
</tr>
<tr>
<td>BMII in kg/m² (mean (SE))</td>
<td>26.2 (0.1)</td>
<td>26.3 (0.3)</td>
<td>26.1 (0.1)</td>
<td>26.1 (0.1)</td>
<td>26.0 (0.4)</td>
<td>0.9</td>
</tr>
<tr>
<td>Systolic blood pressure in mmHg (mean (SE))</td>
<td>140.9 (0.4)</td>
<td>145.3 (1.6)</td>
<td>145.0 (0.5)</td>
<td>144.4 (0.7)</td>
<td>141.8 (1.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure in mmHg (mean (SE))</td>
<td>81.0 (0.3)</td>
<td>82.0 (0.9)</td>
<td>81.6 (0.3)</td>
<td>81.1 (0.4)</td>
<td>80.7 (1.1)</td>
<td>82.3 (1.1)</td>
</tr>
<tr>
<td>Total serum cholesterol in mmol/liter (mean (SE))</td>
<td>6.70 (0.03)</td>
<td>6.96 (0.09)</td>
<td>7.04 (0.03)</td>
<td>6.92 (0.04)</td>
<td>7.09 (0.03)</td>
<td>6.93 (0.11)</td>
</tr>
<tr>
<td>Serum HDLII cholesterol in mmol/liter (mean (SE))</td>
<td>1.58 (0.01)</td>
<td>1.65 (0.03)</td>
<td>1.54 (0.01)</td>
<td>1.51 (0.01)</td>
<td>1.60 (0.04)</td>
<td>1.53 (0.04)</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>25</td>
<td>39</td>
<td>38</td>
<td>31</td>
<td>28</td>
<td>32</td>
</tr>
<tr>
<td>Physically inactive (%)</td>
<td>41</td>
<td>41</td>
<td>44</td>
<td>43</td>
<td>48</td>
<td>38</td>
</tr>
<tr>
<td>Cardiovascular disease (%)</td>
<td>Previous myocardial infarction</td>
<td>5</td>
<td>10</td>
<td>9</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>8</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>2</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Use of medication for hypertension (%)</td>
<td>Current</td>
<td>13</td>
<td>20</td>
<td>19</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Previous</td>
<td>4</td>
<td>9</td>
<td>6</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Bone mineral density in mg/cm² (mean (SE))</td>
<td>Without plaques</td>
<td>464.8 (1.3)</td>
<td>449.4 (4.7)</td>
<td>457.7 (1.6)</td>
<td>465.5 (2.0)</td>
<td>461.7 (5.7)</td>
</tr>
<tr>
<td></td>
<td>With plaques</td>
<td>363.5 (1.4)</td>
<td>346.9 (4.9)</td>
<td>357.5 (1.6)</td>
<td>364.8 (2.1)</td>
<td>360.4 (5.8)</td>
</tr>
<tr>
<td>p for trend</td>
<td>0.03</td>
<td>0.2</td>
<td>0.08</td>
<td>0.77</td>
<td>1.08</td>
<td></td>
</tr>
</tbody>
</table>

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**Table 2.** Odds ratios for carotid artery plaques according to quartiles of bone mineral density, the Tromsø Study, Norway, 1994–1995

<table>
<thead>
<tr>
<th>Quartile†</th>
<th>Total no. of subjects</th>
<th>Odds ratio</th>
<th>95% CI‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without plaques</td>
<td>With plaques</td>
<td>Adjusted for age and sex</td>
</tr>
<tr>
<td>1</td>
<td>475</td>
<td>848</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td>563</td>
<td>742</td>
<td>0.88</td>
</tr>
<tr>
<td>3</td>
<td>638</td>
<td>681</td>
<td>0.81</td>
</tr>
<tr>
<td>4</td>
<td>650</td>
<td>672</td>
<td>0.85</td>
</tr>
</tbody>
</table>

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† Adjusted for sex, age, systolic blood pressure, medication for hypertension (current and previous), serum total cholesterol, serum high density lipoprotein cholesterol, smoking, physical inactivity, cardiovascular disease (previous myocardial infarction or angina pectoris or stroke), and diabetes.
‡ CI, confidence interval.
tation was indicated. For predominantly echolucent and echolucent plaques, no connection was noted between BMD and plaque prevalence. The results hardly changed when information about parathyroid hormone levels (available for 51 percent of the subjects), or use of statins, or use of cod liver oil and vitamin D and calcium supplements (available for 81 percent of the subjects), or dietary intake of vitamin D and calcium (available for 41 percent of the subjects) was included in the regression models. For women, the point estimates did not change notably when the analyses were restricted to the 1,530 who reported that they had never used hormone replacement therapy (results not shown). Furthermore, adjustment for age at menopause did not influence the results.

In a separate cumulative ordinal logistic regression model with multivariate adjustment, which included only those subjects with plaques, we observed that, for each quartile increase in distal forearm BMD, the odds of being included in a category of lower plaque echogenicity increased by 13 percent (odds ratio = 1.13, 95 percent CI: 1.01, 1.22).

No significant interactions with age were found with regard to the associations between BMD and the prevalence of plaques in the overall data set (any plaque or plaques of different morphology, $p \geq 0.2$). In addition, there were no significant interactions with sex ($p \geq 0.5$), and analyzing the associations between BMD and plaque echogenicity in males and females separately gave essentially the same results as those presented in table 4. In particular, when data from men and women were merged, the adjusted odds ratio for echogenic plaques was 0.69 (95 percent CI: 0.54, 0.88) for each standard-deviation increase in BMD (99 mg/cm²), whereas for men it was 0.64 (95 percent CI: 0.44, 0.92) and

### TABLE 3. Adjusted mean extent of atherosclerosis* according to quartiles of bone mineral density,† the Tromsø Study, Norway, 1994–1995

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Mean in mm (standard error) adjusted for age and sex</th>
<th>Mean in mm (standard error) with further adjustment‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.29 (0.08)</td>
<td>3.27 (0.08)</td>
</tr>
<tr>
<td>2</td>
<td>3.23 (0.08)</td>
<td>3.23 (0.08)</td>
</tr>
<tr>
<td>3</td>
<td>3.07 (0.08)</td>
<td>3.07 (0.08)</td>
</tr>
<tr>
<td>4</td>
<td>3.22 (0.09)</td>
<td>3.24 (0.09)</td>
</tr>
</tbody>
</table>

$p$ for trend 0.4 0.5

* The sum of all measured thicknesses of plaques in a single carotid artery.


‡ Adjusted for age, sex, body mass index, systolic blood pressure, medication for hypertension (current and previous), serum total cholesterol, serum high density lipoprotein cholesterol, smoking, physical inactivity, cardiovascular disease (previous myocardial infarction or angina pectoris or stroke), and diabetes.
for women 0.73 (95 percent CI: 0.53, 1.00). We therefore present only the results of the pooled analyses in this paper.

Analyses of both the distal and ultradistal sites of the forearm were performed separately. However, because the results were similar, only the results for one site are presented.

**DISCUSSION**

In the present study, we found that the prevalence of echogenic carotid artery plaques was significantly related to low BMD, whereas no association was found between BMD and echolucent plaques. The present analyses extend previous studies by showing that the association between low bone mass and atherosclerosis most probably is limited to the development of fibrotic and calcified plaques.

To our knowledge, there is no previous study using the same design to compare our results with. However, the associations between BMD and echogenic plaques seem to be in line with the results of previous longitudinal studies showing that bone loss is positively related to progression of aortic calcification (3, 5), and they are also concordant with some of the cross-sectional examinations in which low bone mass was found to associate with arterial calcifications (1, 2, 4, 6, 7). However, others have indicated that aortic calcification and osteopenia are independent age-related processes (8–12). Subjects with echogenic plaques tend to be older than those with echolucent plaques (table 1), but, in the present study, we found that low BMD was related to the prevalence of echogenic plaques even after we adjusted for age and several other confounders. Nevertheless, residual confounding by factors for which we have failed to control could have influenced our findings. Another limitation of the present study is related to its cross-sectional design, implying that causal inferences cannot be drawn.

The present study has several strengths, including the large sample size for both sexes and a comprehensive analysis of BMD and plaque morphology. We used forearm single x-ray absorptiometry and B-mode ultrasound of the carotid arteries to assess BMD and atherosclerosis, respectively. Single x-ray absorptiometry is one of the most precise bone densitometry methods (18). Peripheral measurements, including those on the forearm, show a strong relation to later osteoporotic fractures (26); furthermore, their ability to predict any fracture in women is considered as good as that for other measurement sites (27). However, the study would have been strengthened if we had measured BMD at other body sites (e.g., the hip) as well. Ultrasound-assessed carotid atherosclerosis correlates with atherosclerosis in other arterial territories and is associated with clinical cardiovascular disease (28, 29). It reliably predicts the content of soft tissue and the amount of calcification in carotid plaques (30). In the present study, reproducibility of both ultrasound-assessed carotid atherosclerosis and the BMD measurements was good (17, 19), and the BMD scans were checked for artifacts, ensuring a low degree of misclassification with respect to exposure status. Nevertheless, unavoidable misclassification concerning both plaque echogenicity and BMD will probably lead to an underestimation of a true relation between the two.

Regions with more trabecular bone have been shown to be more metabolically active than regions with mostly cortical bone. Because the distal site of the forearm contains primarily cortical bone and the ultradistal site primarily trabecular bone (31), differences in the association with plaques and plaque types were not unlikely. If, for example, soft lipid-rich plaques develop into calcified fibrotic plaques over time and this process is accelerated in subjects with bone loss, the associations between BMD and echogenic plaques could have been reflected more strongly in more metabolically active regions of the skeleton, for example, the ultradistal site. However, in our study, the relations did not depend on which forearm site was measured.

Our study population consisted of subjects who were able to attend two visits at our research center, and those with osteoporosis, higher levels of cardiovascular risk factors, and cardiovascular disease may have been underrepresented (32–34). Fifteen percent of the participants who came to the first study screening either did not attend the second visit or did not have both BMD measurements and ultrasonography of the carotid arteries performed. Among these subjects, there were more current smokers and physically inactive persons; other cardiovascular risk factors differed only slightly (results not shown). However, because this group was rather small, the mean values of the risk factors for our study participants were very similar to those for the total group who attended the first screening. Only 10 percent of eligible persons in the Tromsø population were never examined. Thus, because of the high attendance rate, we find it unlikely that nonresponse seriously biased our findings.

Unfortunately, information on impaired vitamin K status, which may be associated with both atherosclerosis and BMD (35), was not available for this study. Moreover, secondary hyperparathyroidism, which can be induced by vitamin D deficiency in the elderly, may be associated with bone loss as well as soft-tissue calcium deposition (36). We had no information about the plasma 25-hydroxyvitamin D levels of our study subjects. However, in subgroups of the participants, adjustment for dietary intake of calcium and vitamin D, use of cod liver oil, use of calcium and vitamin D supplements, and parathyroid hormone levels did not influence our conclusions.

Studies conducted during the last decade support the possibility of a link between osteoporosis and atherosclerosis, and vascular calcification is increasingly seen as an active, organized process similar to that of osteogenesis. Several factors such as matrix Gla protein, osteocalcin, osteopontin, and collagen type I (all involved in the regulation of bone metabolism) have been shown also to be present in calcified atherosclerotic lesions (20–22).

Osteoprotegerin (a regulator of bone resorption) may play a role in the relation between osteoporosis and vascular calcification, but the nature of this possible link is unclear. Osteoprotegerin-deficient mice have been found to develop medial arterial calcification of the aorta and renal arteries as well as severe osteoporosis (37); in humans, elevated serum levels of osteoprotegerin are associated with the presence and severity of coronary artery disease (38, 39) and cardiovascular mortality (40). The presence of oxidized lipids may be another common factor explaining the apparent associa-
tion between atherosclerosis and low bone mass (20–23). Furthermore, several case-control studies have shown that statins, known to reduce serum cholesterol, may have a protective effect on BMD loss and fracture risk (41). However, a recent longitudinal study did not support the hypothesis that statins protect against early postmenopausal bone loss (42). In the present study, the association between echogenic plaques and BMD was essentially unchanged when we adjusted for use of statins.

We conclude that increasing BMD is related to a decreasing prevalence of echogenic plaque. Common factors other than age may underlie the pathogenesis of both arterial calcification and osteoporosis. Prospective studies on changes in BMD and plaque morphology are needed.

ACKNOWLEDGMENTS

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