Bone mineral decrease in the leg with unilateral chronic occlusive arterial disease

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ABSTRACT

Objective. The links between osteoporosis and arteriosclerosis have been established by numerous epidemiological studies. Could arteriosclerosis induce bone mineral loss via ischemia or other pathological process? We carried out a comparative study of bone mineral density in both legs of patients with unilateral arterial disease of the lower limbs.

Methods. We studied 25 patients, 22 men and 3 women, whose mean age was 62.3 years (range 35-88 years). These patients had unilateral lower limb arterial disease of at least 3 months duration with a systolic index at least 50% lower on the affected than on the healthy side. Bone mineral content (BMC) and bone mineral densities (BMD) of the femoral neck, femur, tibia, foot and ankle of the affected and the unaffected legs were measured by dual x-ray absorptiometry (Lunar DPXL) and the results compared.

Results. Bone mineral density was significantly lower in the femur (-3.7%, p = 0.04), the foot and the ankle (-3%, p = 0.05) of the affected leg. There was a non-significant decrease in BMD of the whole femoral neck (-1.2%) and the trochanter (-4.4%, p = 0.08) on the affected side. Tibial bone mineral density was identical in both legs. Bone mineral content was lower on the affected side (-5.3%, p = 0.05) where- as fat mass and muscle mass were the same in both legs.

Conclusion. The ischemia resulting from arterial disease of the lower limbs appears to have a direct deleterious effect on bone mineralization.

Introduction

Numerous epidemiological studies have established the links between osteoporosis and arteriosclerosis. Browner et al. demonstrated in a cohort of women aged over 65 years that the bone mineral density (BMD) measured at the radius and calcaneum was a predictive factor of risk of death by stroke: a decrease of one standard deviation in calcaneal BMD increased the relative risk of stroke by 1.31 (1,2). In a previous study, we showed that in women aged over 75, operated for atraumatic fractures of the femoral neck, arterial disease of the lower limbs was more frequent than in women who had never had an osteoporotic fracture (3). Men with arteritis had lower spinal BMD than matched controls without vascular disease (4).

Are osteoporosis and arteriosclerosis linked because of common risk factors: sedentary lifestyle, tobacco consumption, early menopause? Can arteriosclerosis, through ischemia or other pathological processes, itself induce demineralization?

To answer this question, a cross-sectional study was performed to compare the bone mineral density (BMD) of each leg in patients with unilateral arterial disease of the lower limbs to see if BMD of the arteritic leg was decreased.

Patients and methods

Patients

We studied 25 patients, 22 men and 3 women, whose mean age was 62.3 years (range 35 - 88 years).

Inclusion criteria

Patients had stage II chronic occlusive arterial disease of the lower limbs, according to the criteria of Leriche. They had pain only on walking, giving a clinical picture of vascular claudication. Their arterial disease was unilateral, with pain in one leg only, and was of at least 3 months duration. The asymmetric nature of the arterial disease was confirmed by doppler measurement of the systolic indexes, the systolic index being 50% lower in the affected leg than in the unaffected leg.

Exclusion criteria

We excluded patients who had previously undergone vascular surgery or other revascularization procedures, or who had been treated with heparin or anti-vitamin K for more than 3 months. Other exclusion criteria were any disorder likely to modify bone mineralization: hyperthyroidism, hyperparathyroidism, corticosteroid treatment for more than 3 months, hypogonadism in men; previous treatment with calcitonin, bisphosphonates, fluoride salts, calcium or vitamin D, or oestrogens,
for more than 1 month; bony metastases, myeloma, bone dystrophy, Paget’s disease or any disease which had immobilized the patient for more than 2 months during the 5 years before the study; renal failure, serum creatinine above 200 μmol/l; or any metallic prosthesis of the lower limbs which could influence the measurement of bone density.

As healthy subjects, we studied BMD of the hip and BMC of 100 cross-matched subjects (8 men and 2 women) with a mean age of 61 ± 8 years (range 40 to 70). These patients had been referred for suspicion of osteoporosis but their BMD in the lumbar spine and femoral neck were in the normal range. They had no lower limb arteriopathy.

Methods

Measurement of bone mineralization

The patients and controls underwent investigations by dual x-ray absorptiometry (DEXA) using a Lunar DPX L, with measurement of whole body density (rapid scan mode) and of both femoral necks (medium scan mode). At the femoral necks, BMD of the total neck, Ward triangle and trochanter was determined. Regions of interest were determined manually from the whole body measurements and included the femurs, tibias, feet and ankles. Bone mineral content, muscle mass and fat mass were determined for each leg. The precision error between two BMD measurements obtained manually on the windows concerning the regions of interest in 10 patients with a 1-hour interval was 2% for the femur, 1% for the tibia and 3% for the foot and ankle. The precision error between two measurements of bone mineral content was 2.25% for each leg, 4% for muscle mass, and 4.5% for fat mass.

Evaluation of arterial disease

The duration of disease (DD) was determined by questioning the patient before inclusion in the protocol. The walking distance (WD) was determined by the treadmill test. The systolic indexes (SI) of the legs were calculated as the ratio of the arterial pressure of the posterior tibial arteries to the arterial pressure of the humeral artery, measured by doppler probe. A formula comprising these parameters was calculated for each patient: F = the systolic index of the affected leg (SIA) x walking distance (WD) / duration of disease (DD), i.e. F = SIA x WD / DD (5).

Statistical analysis

Bone mineral density and bone mineral content, both total and for each region of interest in the unaffected leg and the arteritic leg, were compared using Wilcoxon’s test for short matched series. Correlations between bone density measurements and the formula F were sought using Spearman’s test.

Results

Arterial disease of the lower limbs

Twenty-three of the 25 patients were smokers. Arteritic stenoses involved the primary or external iliac arteries in 16 patients, the superficial femoral artery in 7 patients and the iliac and femoral arteries in 2 patients. Arterial disease affected the right leg in 12 patients and the left leg in 13. Mean walking distance was 159 ± 24 m (range 45 – 550 m). The mean duration of leg pain attributed to arterial disease was 15 ± 9 months. The mean systolic index of the affected leg was 0.54 ± 0.13 and of the unaffected leg 0.86 ± 0.13.

Bone density measurements (Table I)

BMD was 0.909 ± 0.13 g/cm² at the femoral neck on the affected side compared with 0.921 ± 0.09 g/cm² at the unaffected femoral neck (p = 0.6). At the Ward triangle, BMD on the affected side was 0.734 ± 0.14 g/cm² compared with 0.747 ± 0.09 g/cm² on the unaffected side (p = 0.53). BMD of the affected trochanter was 0.820 ± 0.10 g/cm² and 0.864 ± 0.09 g/cm² on the unaffected side (p = 0.08). BMD of the affected femur was 1.320 ± 0.19 g/cm² compared with 1.356 ± 0.17 g/cm² in the unaffected femur (p = 0.04). In the affected tibia, BMD was 1.196 ± 0.16 g/cm² compared with 1.195 ± 0.16 g/cm² in the unaffected tibia (p = 0.89). BMD of the affected foot and ankle was 1.180 ± 0.23 g/cm² compared with 1.210 ± 0.18 g/cm² in the unaffected foot and ankle (p = 0.05). Bone mineral content was 514 ± 101 g on the unaffected side and 492 ± 84 g on the affected side (p = 0.05).

Distribution of muscle and fat was identical: muscle on the unaffected side 8384.5 ± 1660 g versus 8335.8 ± 1748 g on the affected side (p = 0.55), fat on the unaffected side 2.686 ± 788 g versus 2.675 ± 820 g on the affected side (p = 0.47).

Controls

There was no significant differences between the right and left legs in the control group: BMD at the right femoral neck: 0.912 ± 0.15, BMD at the left femoral neck: 0.910 ± 0.14 (p: 0.85); BMD at the right ward triangle: 0.750 ± 0.18, BMD at the left ward triangle: 0.760 ± 0.20 (p: 0.76); BMD at the right trochanter: 0.846 ± 0.12, BMD at the left trochanter: 0.840 ± 0.15 (p: 0.82); BMD at the right femur: 1.401 ± 0.21, BMD at the left femur: 1.392 ± 0.19 (p: 0.90); BMD at the right tibia: 1.200 ± 0.14, BMD at the

Table I. Densitometric findings in the leg with arterial disease compared with the unaffected leg.

<table>
<thead>
<tr>
<th>Total BMC</th>
<th>Neck BMC</th>
<th>Ward BMC</th>
<th>Troch BMC</th>
<th>Femur BMC</th>
<th>Tibia BMC</th>
<th>Foot BMC</th>
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<tr>
<td>g</td>
<td>g/cm²</td>
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<td>g/cm²</td>
<td>g/cm²</td>
<td>g/cm²</td>
<td>g/cm²</td>
</tr>
<tr>
<td>Affected leg</td>
<td>492 ± 84</td>
<td>0.909 ± 0.13</td>
<td>0.734 ± 0.14</td>
<td>0.820 ± 0.10</td>
<td>1.320 ± 0.19</td>
<td>1.196 ± 0.16</td>
</tr>
<tr>
<td>Unaffected leg</td>
<td>514 ± 101</td>
<td>0.921 ± 0.09</td>
<td>0.747 ± 0.09</td>
<td>0.864 ± 0.09</td>
<td>1.356 ± 0.17</td>
<td>1.195 ± 0.16</td>
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<tr>
<td>p</td>
<td>0.05</td>
<td>0.6</td>
<td>0.53</td>
<td>0.08</td>
<td>0.04</td>
<td>0.89</td>
</tr>
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</table>

BMD: bone mineral density; BMC: bone mineral content (BMC) of the femoral neck (neck), Ward triangle (Ward), the trochanter (troch), the femur, the tibia, the foot and the ankle (foot).
left tibia: 1.196 ± 0.17 (p = 0.92), BMD at the right foot and ankle: 1.192 ± 0.30, BMD at the left foot and ankle: 1.201 ± 0.24 (p = 0.78), BMC of right leg: 520 ± 80 g, BMC of the left leg: 525 ± 75 g (p = 0.79)

Correlations
No significant correlation was found between bone density measurements and the formula F (systolic index × walking distance / duration of disease): femoral neck BMD and F: $r = 0.3$ (p = 0.1), femoral BMD and F: $r = 0.13$ (p = 0.6), tibial BMD and F: $r = -0.2$ (p = 0.46), foot BMD and F: $r = 0.19$ (p = 0.41)

Discussion
Our patients with unilateral arterial disease had significantly decreased bone mineral density in the femur (-3.7%, p = 0.04) and foot and ankle (-3%, p = 0.05) of the affected leg. There was a non-significant decrease in total femoral neck BMD (-1.2%) and in trochanter BMD (-4.4%, p = 0.08). Tibial BMD was identical in both legs. Bone mineral content was significantly lower on the affected side (-5.3%, p=0.05) while fat and muscle mass were symmetrically distributed. These findings confirm those of our previous study, where in a smaller group of other patients (17 men) we demonstrated that the bone mineral content of the limb with arterial disease was lower than that of the affected limb: 495 ± 80 g versus 512 ± 76 g (6). In that cohort, we did not assess BMD in the various regions of the leg, as we were able to do in the present study.

Some authors have studied the dominant/non-dominant or right/left differences in bone mineral density of the femur. In non-arteritic subjects, no significant differences were detected in our control group, nor have any been reported in the literature (7-9).

There is an undoubted link between arteriosclerosis and osteoporosis: bone mineral density is a predictor of the risk for stroke or a coronary event (1,2). This link has been radiologically established as it has been shown that aortic or iliac calcification is frequent when vertebral osteoporosis with fractures is present (11,12). We ourselves have demonstrated that arteriosclerotic lesions were more frequent in the femoral head vasculature of patients with atraumatic fractures of the femoral neck than in arthritic femoral heads (13).

In the animal, it appears that degenerative vascular disorders can induce osteoporosis. Naito et al. (14), comparing spontaneously hypertensive and stroke-prone rats with control rats, found lower bone mineral density in the femurs of the hypertensive rats. Estrogen deficit after the menopause, a vector of osteoporosis, is also a vascular risk factor; coronary disease is more frequent after non-treated menopause in women (12).

However, does the relationship between arteriosclerosis and osteoporosis arise only from common risk factors: sedentary lifestyle, tobacco consumption, estrogen deficit?

A direct link between arteriosclerosis and osteoporosis by reduced vascular flow and intra-osseous ischemia is also a possibility. Bonnel had demonstrated that arterial ligation in the rabbit led to decreased strength of the bones of the limb concerned, with osteoporosis shown by histomorphometry (15). Scherman revealed decreased thickness of cortical bone and empty osteocyte cavities in the amputated tibias of patients with advanced arteritis (16).

Our study appears to confirm these findings. The bone mineral density of the leg with arterial disease (and thus subject to vascular ischemia) was decreased compared with that of the opposite leg. This decrease cannot be due to disuse, since although the pain of arterial claudication of course affects the arteritic leg, when the subject is forced to stop walking both limbs are concerned. The symmetry of fat and muscle mass in both legs also argues against such a mechanism.

Decreased bone density thus involves the femur, the foot and the ankle whereas theibia does not seem to be affected. We have no totally satisfying hypothesis to explain this result but we know that theibia comprises much cortical bone (17) and in cortical bone, bone remodelling is more quiescent than in trabecular bone. Moreover tibia is vascularised by the branches of the anterior tibial artery, less affected by arteriosclerosis than the posterior tibial artery (18).

We found no correlation between the bone mineral densities of the leg with arterial disease and the formula comprising duration of disease, walking distance and systolic indexes, but the pain which establishes the diagnosis of arterial disease of the lower limbs sometimes appears late and vascular occlusion probably precedes it. The true duration of the disease is thus difficult to determine. The systolic indexes do not give a true evaluation of blood flow as they depend also on the rigidity of the vascular walls. We considered quantifying arterial flow by electromagnetic methods and correlating it with BMD but this was not possible for technical reasons.

The decreases of BMD and BMC in the leg with arterial disease were moderate at around 3 to 5%, but if we consider that the disease had been progressing for a mean of only a year, the bone loss is similar to that induced by estrogen deficiency in the year after menopause.

Conclusion
The ischemia induced by arterial disease of the lower limbs appears to have a direct deleterious effect on bone mineralization, as the bone mineral content and mineral density of the femur, foot and ankle were decreased in the affected leg in patients with unilateral arterial disease.

References
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