Calcified Large Arteries, Osteoporosis & Acute Stroke: What is the Relationship?

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Abstract

Introduction: Atherosclerosis and osteoporosis are currently considered unrelated diseases. As age advances, osteoporosis is more frequently found in women than men; atherosclerosis is an illness predominantly affecting men [1]. A parallel relationship has been noted between spinal osteoporosis and aortic calcification due to atherosclerosis [2]. Osteoporosis and stroke share several risk factors, such as age, smoking, low level of physical activity, and hypertension [3]. Thus Low bone mineral density (BMD) and a high risk of stroke may thus be related, but studies on this relationship are sparse. Both bone and atherosclerotic arteries contain osteopontin, matrix gla protein, bone morphogenetic protein collagen I, osteonectin, Osteocalcin, nitric oxide, and matrix vesicles [4]. Atherosclerosis and osteoporosis both involve recruitment and differentiation of monocytic cells that differentiate into macrophage-foam cells in artery and osteoclasts in bone [5]. The artery wall contains cells capable of differentiation into osteoblasts, following the same stages of differentiation as occur in bone-derived osteoblasts, and ultimately producing bone mineral [6].

Objectives: To examined the relationship between Calcified large arteries, BMD and acute stroke in hospitalized patients aged > 60 years.

Methods: Seventy-five stroke patients (40 women and 35 men) in addition to sixty-five ages matched control group were included in the study. Careful family history, full clinical exam. Radiological examination for both lumbar & pelvic regions .Routine lab, Lipid profile investigations were done. The atherogenic index was calculated as the ratio of (total cholesterol-HDL cholesterol) to HDL cholesterol. Body mass index (BMI) was calculated for the entire studied group. BMD was measured by using dual-energy x-ray absorptiometry GE Healthcare Lunar Prodigy Primo. BMD measurements of the stroke patients were performed one week after the onset of stroke.

Results: There was a highly significant difference between the stroke patients and their controls as regards Total cholesterol, LDL, HDL and BMD. However in males; no difference was found between the stroke patients and their controls regarding BMD. As regards aortic calcifications, the noncalcified aorta was significantly higher in controls than stroke group. The advanced calcified aorta &moderate one was significantly higher among stoke group than controls, despite the mild aortic calcification show a non significant difference between both groups.

Conclusion: High Total cholesterol& LDL, but Low HDL& BMD in addition to aortic calcification whatever moderate or advanced may early predict stroke both in females and males. This may be an important explanation for the increased incidence of hip fracture in stroke patients.

Background: Atherosclerosis and osteoporosis are currently considered unrelated diseases. As age advances, osteoporosis is more frequently found in women than men; atherosclerosis is an illness predominantly affecting men [1]. A parallel relationship has been noted between spinal osteoporosis and aortic calcification due to atherosclerosis[1]. Osteoporosis and stroke share several risk factors, such as age, smoking, low level of physical activity, and hypertension [3]. Thus Low bone mineral density (BMD) and a high risk of stroke may thus be related, but studies on this relationship are sparse. Both bone and atherosclerotic arteries contain osteopontin, matrix gla protein, bone morphogenetic protein collagen I, osteonectin, Osteocalcin, nitric oxide, and matrix vesicles [4]. Atherosclerosis and osteoporosis both involve recruitment and differentiation of monocytic cells that differentiate into macrophage-foam cells in artery and osteoclasts in bone [5]. There are cells in the artery wall that can differentiate into bone forming cells, exactly as occur in bone-osteoblasts [6].
diabetics, more and more in end-stage renal disease [9]. Giachelli et al. [10] recognized hydroxyapatite and matrix vesicles in the vascular calcification and found similarities between artery and bone at the molecular level [10]. Bostrom and his colleague stated that atherosclerotic calcification occurs by the same molecular mechanism as embryonic bone formation [11]. Also they demonstrated expression of bone morphogenetic protein-2 in human calcified plaque [11,12].

Calcium deposits, consisting of the bone mineral apatite, are extremely common in atherosclerotic lesions and are associated with clinical complications such as myocardial infarction, impaired vascular tone, poor surgical outcome, and coronary insufficiency due to loss of aortic recoil [13]. The mechanism of vascular calcification is not yet established; however, some evidence implicates factors important in bone mineralization [14]. Such as matrix vesicles [15], BMP-2 [11], osteopontin [10], Osteocalcin [16], and collagen I [17], all of which have been identified in atherosclerotic plaque [18]. Subpopulations of aortic medial cells, termed calcifying vascular cells CVCs were identified, which spontaneously calcify in vitro and express osteoblast markers as alkaline phosphatase, osteopontin, Osteocalcin, osteonectin, and collagen I. This in vitro model was confirmed by Shioi and his colleague [19]. CVC calcified nodules express the bone/liver/kidney isoform of alkaline phosphatase, which is widely used as an early marker of osteoplastic differentiation [20]. Previous studies, using the alkaline phosphatase inhibitor levamisole, has shown its importance in the commitment of bone preosteoblasts to mineralization [21]. Alkaline phosphatase may also inactivate pyrophosphate, an inhibitor of hydroxyapatite formation [22] and it may have an intracellular function important in regulating cellular differentiation [23].

The role of LDL oxidation products and their accumulation in the vessel wall during atherosclerotic lesion formation is well established [24]. Since calcium deposits are found as early as the fatty streak stage [25], often in close association with lipids [26]. Further evidence for the possible role of lipids in calcification is the inhibition of calcification in delipidated heart valves [27]. MM-LDL is a potent atherogenic molecule with biologic activity in vitro and in vivo [28]. Osteoporotic loss of bone is attributed to abnormalities in the balance of bone remodeling; both increased bone resorption by osteoclasts and decreased bone formation by osteoblasts [29]. Since osteoporosis commonly coexists with atherosclerotic calcification [30]. Common factors may be responsible in the pathogenesis of both diseases [31].

Aim of the Work
To examine the relationship between calcified large arteries, bone mineral density and acute stroke in hospitalized patients aged ≥ 60 years.

Patients and Methods
Seventy-five stroke patients (40 women and 35 men) were admitted to AL-Hussein university hospital , their ages were ranged from 65-85 years with mean 77 ±(6), 75 ± [6] for both women and men respectively. Stroke was defined according to the definition of the WHO [32]. The diagnosis was based on a doctor’s clinical examination and was supported by cerebral CT changes without any knowledge about the bone mineral density of the patients. In addition to sixty-five ages matched control group that were randomly selected from the normal population were included in this study. Careful family history, full clinical & neurological examinations were performed for all of the studied groups.

Exclusion criteria: Patients who had not been able to walk without support before the stroke, Patients with history of previous stroke, unconsciousness and terminal illness, presence of osteolytic lesion, and history of hip fracture.

Radiological examination
Plain x-ray was done for both lumbar & pelvic regions.

a. Complete lipid profile in addition to routine laboratory investigations were done for all of the studied groups. The atherogenic index was calculated as the ratio of (total cholesterol-HDL cholesterol) / HDL cholesterol.

b. BMD was measured by usi using dual-energy x-ray absorptiometry GE Healthcare Lunar Prodigy Primo. BMD measurements of the stroke patients were performed within ten days after the onset of stroke to avoid the effect disuse on bone mineral density.

c. Body mass index (BMI) was calculated as the weight (in kilograms) divided by the square of the height (in meters).

Measurement of Aortic Calcification
Aortic calcification was diagnosed by radiographic detection of calcified deposits in the abdominal aorta. Lateral abdominal films from(T12-S1) were made (Figures 1-5). Aortic calcifications were considered present when linear densities were seen in an area parallel and anterior to the lumbar spine (L1-L4). The extent of calcification was scored according to the length of the involved area (1 -2 cm, 3 - 5 cm, 6 - 10 cm). The first class was considered as mild calcification, the second class as moderate and the third classes as advanced calcification. Progression of calcification was defined as the occurrence of new calcifications or enlargement of the calcified area present at baseline [35]. All films were examined by two independent professional radiologists without knowledge of the bone mineral density of the patients. If there were differences between them regarding readings, films were reviewed by both them simultaneously so as to reach consensus. The score that was agreed upon by both radiologists was recorded.
Results

There was a highly significant difference between the stroke patients and their controls as regards Total cholesterol, Triglycerides, LDL, HDL, and BMD. However in males; no difference was found between the stroke patients and their controls regarding BMD. As regards aortic calcifications, the calcified aorta was significantly higher in stroke than control group. The advanced & moderate calcified aorta were significantly higher among stroke group than controls, despite the mild aortic calcification show a non significant difference between both groups (Table 1). There is an indirect correlation between aortic calcifications and T-Score, while a direct correlation was present between serum cholesterol & the aortic calcifications (Table 2).

There was no difference between the paretic and nonparetic side with respect to BMD. Statistically BMD was significantly lower in females than in males within the stroke group also it was significantly lower in the entire stroke than control group. Where T-Score, was $-3.2\pm0.60.04$, $-2.7\pm0.60.04$, $-2.6\pm0.60.04$, $-2.4\pm0.60.04$, respectively with $P <0.01$. There was a significant indirect correlation between T. Score and age $P<0.05$. And a significant direct correlation between T. Score and BMI $P<0.01$ (Table 3).
### Table 1: Demographic data for all of the studied groups.

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
<th>P value</th>
<th>Patients</th>
<th>Controls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males (n=35)</td>
<td>Males (n=30)</td>
<td></td>
<td>Females (n=40)</td>
<td>Females (n=35)</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>67.09</td>
<td>65.90</td>
<td>&gt;0.05</td>
<td>65.08</td>
<td>64.36</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>BMI mean (SD)</td>
<td>26.23</td>
<td>27</td>
<td>&gt;0.05</td>
<td>26.96</td>
<td>25.06</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>197.78</td>
<td>115.25</td>
<td>&lt;0.01</td>
<td>163.35</td>
<td>120.58</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>79.14</td>
<td>47.06</td>
<td>&lt;0.04</td>
<td>78.66</td>
<td>66.67</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>LDL</td>
<td>142.22</td>
<td>96.45</td>
<td>&lt;0.05</td>
<td>153.35</td>
<td>120.71</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HDL</td>
<td>50.24</td>
<td>101.66</td>
<td>&lt;0.04</td>
<td>80.14</td>
<td>102.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>BMD mean (SD)</td>
<td>0.692</td>
<td>0.819</td>
<td>&gt;0.05</td>
<td>0.623</td>
<td>0.902</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>T-Score</td>
<td>-2.7</td>
<td>-2.3</td>
<td>&lt;0.05</td>
<td>-3.2</td>
<td>-2.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>No aortic Calcification</td>
<td>17</td>
<td>24</td>
<td>&lt;0.04</td>
<td>16</td>
<td>25</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Mild aortic Calcification</td>
<td>5</td>
<td>3</td>
<td>&lt;0.06</td>
<td>6</td>
<td>3</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Moderate aortic Calcification</td>
<td>6</td>
<td>2</td>
<td>&lt;0.03</td>
<td>8</td>
<td>4</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>Advanced aortic Calcification</td>
<td>7</td>
<td>1</td>
<td>&lt;0.01</td>
<td>10</td>
<td>3</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

### Table 2: Correlation between Aortic calcification & other variables.

<table>
<thead>
<tr>
<th>Measure</th>
<th>No (n=33)</th>
<th>Mild (n=11)</th>
<th>Moderate (n=14)</th>
<th>Advanced (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD</td>
<td>.531 ns</td>
<td>.755**</td>
<td>.700**</td>
<td>.660*</td>
</tr>
<tr>
<td></td>
<td>0.115</td>
<td>0.012</td>
<td>0.024</td>
<td>0.04</td>
</tr>
<tr>
<td>T-Score</td>
<td>.241 ns</td>
<td>.700**</td>
<td>.912**</td>
<td>-1.762**</td>
</tr>
<tr>
<td></td>
<td>0.050</td>
<td>0.024</td>
<td>-0.028</td>
<td>0.01</td>
</tr>
<tr>
<td>BMI</td>
<td>.0577</td>
<td>-1.522 ns</td>
<td>.867**</td>
<td>.565 ns</td>
</tr>
<tr>
<td></td>
<td>0.048</td>
<td>.122</td>
<td>0.001</td>
<td>0.089</td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>0.132</td>
<td>.672*</td>
<td>.628 ns</td>
<td>.912**</td>
</tr>
<tr>
<td></td>
<td>0.078</td>
<td>0.033</td>
<td>0.052</td>
<td>-0.072</td>
</tr>
</tbody>
</table>

### Table 3: Shows the correlation between T-score, age, BMI.

<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-Score and age</td>
<td>0.37</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>T-Score and height</td>
<td>0.28</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>T-Score and weight</td>
<td>0.58</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>T-Score and BMI</td>
<td>0.63</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

### Discussion

Atherosclerosis and osteoporosis are currently considered unrelated diseases. As age advances, osteoporosis is more frequently found in women than men; atherosclerosis is an illness predominantly affecting men [5]. A parallel relationship has been noted between spinal osteoporosis and aortic calcification due to atherosclerosis [2]. Osteoporosis and stroke share several risk factors, such as age, smoking, low level of physical activity, and hypertension [1]. Low bone mineral density (BMD) and a high risk of stroke may thus be related, but studies on this relationship are sparse. Examination of the association between BMD and stroke is of clinical importance for two reasons.

a. **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 [36].

b. **Second**: low BMD may predict stroke. Growing evidence links vascular disease and bone diseases [37]. The results of this study agreed with Barengolts and his colleagues who reported that patients with lower bone density and osteoporosis have higher lipid levels, more severe atherosclerosis, and have a greater risk of stroke [38]. Our findings also consistent with those of Banks et al who observed that osteoporosis is associated with both atherosclerosis and vascular calcification [30].

Von der Recke [39] stated that osteoporotic postmenopausal women are at significantly greater risk for cardiovascular disease than age-matched controls [39]. Although atherosclerotic vascular calcification occurs earlier in men than in women however osteoporosis more common in women than in men, these differences may be due to the higher peak bone mass in men and the multiple modulating effects of gonadal and steroidal
hormones. In addition, when osteoporosis afflicts women (postmenopausal), vascular calcification and atherosclerotic disease occur as often as in men [40]. Pinals et al. [5] stated that both atherosclerotic plaques and osteoporotic bone have monocytic cells that can differentiate into macrophage-foam cells in artery and osteoclasts in bone, [5].

Parhami et al. [6] reported that there are cells in the artery wall that can differentiate into bone forming cells, exactly as occur in bone-osteoblasts and ultimately producing bone mineral [6]. Postmenopausal women usually advised to receive daily calcium supplements as a prophylactic measure or additional to any anti osteoporotic medication whatever Osteoanabolic therapy as teriparatide or osteoclastic suppressors as bisphosphonates, implying that bone loss may occur as a result of insufficient dietary calcium. However, in many osteoporotic patients, the bone loss occurs at the same time of bone formation in the arterial walls. This paradox suggests that calcium supplement is not the only playing factor. Osteoporosis and calcification of the vascular walls can be found in rodents under three conditions: hyperlipidemia, osteoprogenitor deficiency and dietary essential fatty acids insufficiency [41]. In the present study we found that female stroke patients had lower BMD than the control group, a result consistent with those of Browner et al. [42] who showed that low BMD was associated with an increased stroke risk in women (RR 1.3 per SD decrease in BMD) [42], whereas we found that the risk was somewhat higher. Consequently, if low BMD is already present at stroke onset, the severe bone loss thereafter 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. In contrast to Michael et al. [43] who did not find any relationship between stroke risk and low BMD in men [43]; our study revealed an inverse relationship between Total cholesterol, LDL, Triglycerides and BMD among the male stroke patients. Also Johansson et al. [35] did show that BMD was a strong predictor of total mortality in males as well as females [35].

BMD measurements of the stroke patients were performed within ten days after the onset of stroke to avoid the effect disuse on bone mineral density. In contrast to Jørgensen et al. [44] who reported a significant BMD loss in the femoral neck of the affected side and a nonsignificant loss on the healthy side two months after stroke (3% versus 1%), our study showed that there was no difference between the parietal and nonparietal side with respect to BMD [44]. Johansson et al. [35] suggested that low BMD is, rather, a marker of poor general health and aging [35]. There are, however, several possible links between osteoporosis and stroke, because both conditions may be related to estrogen deficiency, diabetes, hypertension, low level of physical activity, and smoking [45]. Moreover, high blood pressure, an established risk factor for stroke, has been associated with increased bone loss at the femoral neck in elderly women [18,46].

**Conclusion**

High Total cholesterol & LDL, but Low HDL& BMD in addition to aortic calcification whatever moderate or advanced may early predict stroke both in females and males. This may be an important explanation for the increased incidence of hip fracture in stroke patients. In any case, because stroke patients have a low BMD (for whatever the reason), this emphasizes even more the need for a condensed attitude in poststroke rehabilitation.

**References**


