Prevalence of osteoporosis in patients with acute coronary syndrome

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Summary
Objectives: To assess the relationship between osteoporosis and acute coronary syndrome.
Material and Methods: This study involved 163 patients aged between 39 and 79 years, with an average age of 62 years. Of these, 83 were patients with acute coronary syndrome (90% acute myocardial infarction; 10% unstable angina). The other 80 patients belonged to a control group without cardiovascular disease. Anthropometric measures were taken and densitometry carried out in both the lumbar spinal column and femoral neck. We considered a T-score < -2.5 DE as osteoporosis.
Results: No statistically significant differences were found regarding bone mineral density between the group of cases and the control group. Stratifying the data by osteoporotic disease, we observed that the prevalence is greater, to a statistically significant extent, in the group of patients with acute coronary syndrome. In analysing the data by sex, a greater prevalence of osteoporosis was found only in the group of women with acute coronary syndrome, the same relationship was not found in the group of men.
Conclusions: In our study we observed a greater prevalence of osteoporosis in patients with acute coronary syndrome.

Key words: Osteoporosis, Bone mineral density, Acute coronary syndrome.
Introduction
Atherosclerosis and osteoporosis are chronic degenerative diseases with a high incidence in the general population, representing two important health problems whose prevalence will increase with the average age of the population [1]. They are silent processes with high economic cost which are manifested through their complications, acute vascular accidents and osteoporotic fractures. Various epidemiological studies have shown an independent association of both processes with age [2].

Atherosclerosis, which appears in coronary disease, cerebro-vascular disease and peripheral arterial disease, is responsible for the majority of cardiovascular diseases. It is characterised by a chronic arterial inflammation caused, and exacerbated by disorders in the metabolism of lipids and other clearly identified risk factors [3]. A characteristic phenomenon of atherosclerosis is the calcification which is set in motion by an active process in which inflammatory cytokines and other mediators which regulate the phosphocalcic metabolism are involved [4]. These mechanisms can intervene in an opposing phenomenon which is, at the level of bone, characterised by a decrease in bone mineral content and changes in the micro-architecture which define osteoporosis. What is notable is the association of the two processes, which share mechanisms, but which have a different expression.

There are numerous studies which evaluate the relationship between cardiovascular diseases and osteoporosis. There are two different types of study, transversal and longitudinal, the latter being of greater interest. These studies usually use substitute markers to assess the association of the two processes, vascular calcification in atherosclerosis and bone mineral density in osteoporosis. Of greater value are those studies which use the presence of cardiovascular disease and fractures as makers for disease. Magnus et al. [5] using the NHANES III database found an independent and statistically significant relationship between previous myocardial infarction and low bone mass. The effect was observed only in men and was independent of age, race, alcohol consumption, physical exercise and body mass index. Also, in patients with cardiac failure of functional class II/III a lower bone mass, adjusted for age and sex, was found, compared to the control group [6]. Farhat et al. [7] observed that the volumetric BMD in the lumbar spinal column was decreased in individuals with cardiovascular disease, the effect being independent of age or of levels of inflammatory cytokines, IL-1 and II-6. This aspect has not been analysed in the Spanish population. The objective of this study is to assess the prevalence of osteoporosis in patients with acute coronary syndrome in our environment.

Material and methods
A case-controlled transversal study was carried out in the western health area of Valladolid. During the period 2001-2003 163 patients were analysed, 83 hospitalised by acute myocardial infarction and unstable angina, and 80 controls. Criteria for exclusion were the presence of alcoholism, neoplasia, hyper- or hypocalcemia and receipt of drug treatments which modify bone metabolism. In addition, in order to gather anthropometric data, densitometry was carried out on all patients in the four weeks prior to their inclusion. The control group was made up of individuals of the same age and sex without ischaemic cardiopathy. The densitometry was carried out in the lumbar spinal column (L2-L4) and femoral neck using a double photon densitometer (DXA, Lunar Corporation, Madison, Wisconsin, USA). The BMD (Bone Mineral Density) was expressed in g/m2 and determined the T-score, according to the reference values provided by the manufacturer of the densitometer. Patients with a T-score < -2.5 were considered to be osteoporotic.

The results are expressed as an average ± standard deviation. The comparison of averages was carried out through a student’s t test and the qualitative variables were compared using a chi-square test. The correlation between variables was found using Pearson’s r. The statistical programme used was SPSS (SPSS, Chicago, Ill; Base 11.4 for Windows).

Results
165 patients were studied, of which 83 had acute coronary syndrome and 80 were controls. The average age of the patients (61 ± 10 years) was less than that of the controls (64 ± 8 years) with those individuals with acute coronary syndrome being predominantly males. The characteristics of the cases and the controls are seen in Table 1.

There were no differences in the bone mineral density in the lumbar spinal column (1.136 ± 0.22 g/cm² vs 1.122 ± 0.16 g/cm², p= 0.457) and femoral neck (0.920 ± 0.15 g/cm² vs 0.933 ± 0.12 g/cm² p= 0.882). 31% of those patients with acute coronary syndrome were osteoporotic as against 14% in the control group, the difference being statistically significant, p= 0.017. In analysing by sex, in the women the difference remained significant (48% vs 17%, p= 0.007) while in the men it did not (21% vs 7%, p= 0.183) (Figures 1 and 2). There were 15 women with osteoporosis in the patients with acute coronary syndrome as opposed to 9 women in the control group. In the men, 11 patients presented with osteoporosis as opposed to 2 in the control group.

Discussion
The results of our study show that the patients with acute coronary syndrome had a greater prevalence of osteoporosis than in the control population, although only in the group of women is this statistically significant. Our results show some differences in relation to NHANES III. This study found a lower bone mass in the population with myocardial infarction and specifically in men. In our study we did not find differences in bone...
mass, although there were differences in the prevalence of osteoporosis, specifically in women. Our female patients were all postmenopausal, for which reason they probably had common factors which acted on both diseases. These could be genetic, vascular risk factors which exert a prejudicial effect on bone mass or physiopathological mechanisms shared by both entities.

Genetic factors play an important role in osteoporosis. Studies of twins and families have estimated that between 50% and 85% of bone mass is genetically determined. Ateriothrombotic cardiovascular diseases are multifactorial diseases with a significant genetic component. In both diseases the number of genes which are involved is large, with a small contribution from each of them.

The metabolic pathway Wnt-LPR is key to the formation of bone. Recently, a missense mutation in LPR6, which codes for a co-receptor, has been described in an Iranian family. Cysteine is substituted by arginine thus damaging the messaging of Wnt in vitro. These patients carry a major risk of coronary disease, of low bone mass and of osteoporotic fracture, suggesting that both diseases could be pleiotropic consequences of an alteration in the Wnt metabolic pathway.

The RANK/OPG system is the principal regulatory mechanism for bone resorption, polymorphisms which regulate osteoprotegerine (OPG) having been implicated in both processes. Polymorphisms within the promoter of the OPG gene (A163G and T245G) are detected most frequently in patients with vertebral fracture, while other polymorphisms located in the promoter T950C and in exon 1, G1181C, are associated with a high risk of ischaemic cardiopathy, especially in women and in men. In the Japanese population it has been observed that the allele A of the polymorphism G396A was more frequent in patients with ischaemic cardiopathy than in a control group, with an OR of 1.82 (p= 0.004).

All these data indicate a possible role for genetic mechanisms in the association between osteoporosis and cardiopathy, although the contribution of each one of these polymorphisms might be small.

### Table 1. Characteristics of the case-controls

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>61 ± 10</td>
<td>64 ± 8</td>
<td>0.044</td>
</tr>
<tr>
<td>Sex</td>
<td>31M, 52F</td>
<td>52M, 28F</td>
<td></td>
</tr>
<tr>
<td>BMD L2-L4 g/cm²</td>
<td>1.136 ± 0.22</td>
<td>1.122 ± 0.16</td>
<td>0.457</td>
</tr>
<tr>
<td>Femoral neck g/cm²</td>
<td>0.920 ± 0.15</td>
<td>0.933 ± 0.12</td>
<td>0.882</td>
</tr>
</tbody>
</table>

There are vascular risk factors which determine a high incidence of cardiovascular disease. These elements can have an influence on bone metabolism, reducing bone mass, facilitating the appearance of osteoporosis.

Tobacco is a risk factor for atherosclerosis. Its effects on bone metabolism have been little studied. In women it acts at the level of oestrogens, diminishing their levels and causing the loss of their protector role. In addition it produces a decrease in the blood levels of 25-hydrovitamin D which is not accompanied by raised levels of parathormone (PTH). These changes can provoke a decrease in BMD, which has been described predominantly in the lumbar region, of a dose-dependent form, although not all studies are in agreement on this.

The relationship between osteoporosis and hypertension is not clearly established, although numerous changes in the metabolism of calcium in patients with hypertension, which can cause a decrease in bone mass, have been described. Among these changes are included a decrease in ionic calcium, and an increase in calcuria and of urinary AMPc, raised levels of PTH and calcitriol and an increase in the intestinal absorption of calcium. Of these only hypercalcuria has been associated with a decrease in bone mass. Most of the studies did not find a relationship between levels of arterial tension and bone mineral density. In our population we found similar results, there being no greater risk of osteoporosis in the population with hypertension. However, in a retrospective study which included 998 patients with hip fracture the presence of hypertension did increase the risk of fracture (1.49 OR, 95 % CI 1.3-1.8). Homocysteine is one of the new markers for vascular risk which is associated with an increased risk of osteoporotic fracture. Prospective studies carried out in European and American populations show that raised levels of homocysteine are associated with a greater risk of fracture. However, not all studies obtain these results and those in which there has been an intervention to reduce blood levels of homocysteine have not seen a reduction in the number of fractures.

There are not many studies which relate plasmatic lipids, a substitute marker for atherosclerosis, with bone mineral density and/or osteoporot-
ic fracture. Broulik et al. showed that osteoporotic women had higher levels of cholesterol than the controls. Yamaguchi et al. found that LDL cholesterol was negatively related to BMD while HDL cholesterol was positively related. It was observed that those patients with low bone mass had higher concentrations of plasmatic lipids with a greater severity of vascular disease. In Asian population similar data have been obtained. Other studies have brought different results. The Framingham Osteoporosis Study did not show an association between cholesterol levels and the later appearance of osteoporosis. Nor did Tanko et al. find such a relationship in a study carried out in 340 postmenopausal women under 76 years of age. On the other hand, the influence of plasmatic lipids on peripheral bone mineral density in the diabetic population has not been demonstrated.

Similarly to that which happens with genetic factors, vascular risk factors can contribute to an increase in bone mass which appears in acute ischaemic cardiopathy, although not all studies are consistent on this. Recently there has been an attempt to evaluate the effect of a number of these factors, grouped as metabolic syndrome, on bone mass and osteoporotic fractures. The presence of metabolic syndrome is associated with higher bone mass but a greater risk of fractures.

Inflammation plays a central role in the appearance of atherosclerosis and its later development. Cells of the immune system are found in the initial phases of arteriosclerotic lesions, atheroma, and accelerate their later progression. The T lymphocytes are always present in the atherosclerotic lesions, predominantly the CD4 lymphocytes. These are capable of recognising antigens and differentiating (themselves from) type 1 helper cells (TH1). In their turn, the cytokines released by macrophages facilitate differentiation towards these cells. The TH1 cells go on to release specific cytokines, γ-interferon, interleukin-1 and tumour necrosis factor-alpha. In osteoporosis the activity of the osteoclasts can be modulated by the action of gamma interferon (INF-γ) acting on necrosis factor-receptor-associated factor 6 (TRAF-6). The same mechanisms which intervene in the stimulation of bone resorption and facilitate the decrease in bone mineral density also facilitate the progression of the atheromatous plaques.

The most frequently occurring osteoporosis is postmenopausal osteoporosis which is initiated by a fall in oestrogens. Their reduction then provokes a disequilibrium in the TH1/TH2 relationship with the predominance of TH1, in a similar way as that described in atherosclerosis. This is produced by an increase in local levels of IL-7 which then provoke an increase in concentrations of inflammatory cytokines, of RANKL and a decrease in TGF-β. This cytokine exerts a beneficial effect on the bone since it produces an increase in osteoblast activity and a decrease in their apoptosis. There are numerous similarities in the local mechanisms, of an inflammatory nature, which intervene in osteoporosis and in atherosclerosis. These mechanisms were evaluated by Farhat et al. in a broad study of patients with cardiovascular disease in which the effect of inflammatory cytokines (IL-6 and TNF-α) on bone mineral density were assessed. The patients presented higher levels of cytokines than the controls, but this bore no relationship to bone mineral density measured in a number of places. It should be taken into account that systemic levels of cytokines may not reflect that which occurs locally.

In conclusion, we can say that patients with acute coronary syndrome constitute a risk population for the appearance of osteoporosis, there being mechanisms which help us to explain this association.